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Melatonin for Treatment of Sleep Disorders

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. This report was requested and funded by the National Center for Complementary and Alternative Medicine, National Institutes of Health (NIH). The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the healthcare system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to **epc@ahrq.gov.**

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Acknowledgments

We are grateful to members of the technical expert panel for providing input on the direction and scope of the review. We thank Dr. Richard Nahin, Dr. Nancy Pearson and the National Center for Complementary and Alternative Medicine, National Institutes of Health, as well as Ms. Margaret Coopey and the Agency for Healthcare Research and Quality for insight and recommendations. We are also grateful to Ms. Michelle Tubman, Dr. Mia Lang, Ms. Maria Ospina, Mr. Victor Juorio and Ms. Ellen Crumley for their contribution to the systematic review process.

Investigating authors acknowledge the following financial support: Dr. Sunita Vohra is supported by: Agency for Healthcare Research and Quality (USA); Canadian Institutes of Health Research; Change Foundation; Department of Pediatrics, Stollery Children's Hospital; Natural Health Products Directorate, Health Canada; Ontario Mental Health Foundation; Stollery Children's Hospital Foundation; The Hospital for Sick Children Foundation; and the University of Alberta. Dr. Glen Baker is supported by Canadian Institutes of Health Research, Canada Research Chairs Program and Zyprexa Research Foundation.

Structured Abstract

Context. Sleep disorders affect 50 to 70 million Americans, representing approximately 20 per cent of the population.

Objectives. To review the effectiveness of melatonin for the treatment of sleep disorders; the safety, pharmacology and mechanisms of action of exogenous melatonin; and the link between endogenous melatonin and circadian rhythms.

Primary Data Sources. Studies were selected from the following electronic databases: MEDLINE®, PreMEDLINE®, EMBASE®, PubMed®, CAB Health®, CINAHL®, AMED®, Cochrane Central Register of Controlled Trials®, Cochrane Complementary Medicine Field Registry®, Science Citation Index®, Biological Abstracts®, International Pharmaceutical Abstracts®, NLM Gateway®, OCLC papers First and Proceedings First®, TOXLINE®, Registry of Toxic Effects of Chemical Substances (RTECS) ®. Data were also obtained from register of ongoing trials.

Study Selection. Studies were selected for particular questions of the review according to pre-determined, question-specific inclusion criteria. Only English-language reports were included in the review.

Quality Assessment. The quality of studies was assessed using either the Jadad Scale for Quality Assessment of Randomized-Controlled Trials or the Downs and Black Checklist for Quality Assessment of Non-Randomized Controlled Trials. Allocation concealment in the randomized controlled trials was also assessed.

Data Analysis. ***Quantitative Analysis:*** Data were analyzed using a Random Effects Model. All results were reported with 95 per cent confidence intervals (95 per cent CI). Sources of heterogeneity were assessed using the I-squared statistic, and publication bias was assessed using the Funnel Plot approach, the Rank Correlation Test, the Graphical Test, and the Trim and Fill Method. ***Qualitative Analysis:*** Relevant information was summarized and synthesized.

Main Results. ***Effectiveness of Exogenous Melatonin:*** **People with a Primary Sleep Disorder:** Melatonin decreased sleep onset latency; it was decreased greatly in people with delayed sleep phase syndrome and marginally in patients with insomnia. There was no evidence that melatonin had an effect on sleep efficiency. The magnitude of the effect of melatonin on sleep onset latency in people with delayed sleep phase syndrome, but not in people suffering from insomnia, appears to be clinically significant. **People with a Secondary Sleep Disorder:** There was no evidence that melatonin had an effect on sleep onset latency, but it increased sleep efficiency. The magnitude of the effect of melatonin on sleep efficiency in people with secondary sleep disorders appears to be clinically insignificant. **People Suffering from Sleep Restriction:** There was no evidence that melatonin had an effect on sleep onset latency or sleep efficiency. ***Safety of Exogenous Melatonin:*** There was no evidence of adverse effects of melatonin with short-term use.

Main 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.

Contents

Flow Diagrams

Figures

Tables

Appendixes

The Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/melatntp.htm.

Agency for Healthcare Research and Quality

Evidence Report/Technology Assessment

Number 108

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.

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Evidence Report

Chapter 1. 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] Sleep disorders can also be associated with other conditions. For example, psychiatric conditions are the most common cause of insomnia and insomnia is often associated with subsequent development of a psychiatric disorder.[1] Similarly, many neurological conditions are strongly associated with sleep disorders, with prevalence of sleep disorders up to 80 percent in people with severe mental retardation.[1]

Sleep disorders place a tremendous burden on society due to their association with psychiatric disorders, negative impact on quality of life, safety, productivity and high health care utilization. The National Institutes of Health (NIH) has identified many areas of sleep disorder research that require greater attention, such as the neurobiology of sleep disorders, the effects of sleep disorders and deprivation on performance, and treatment of sleep disorders, including complementary and alternative therapy.

Generally, one of two approaches is used to treat sleep disorders. These approaches are designed to improve performance during waking hours by either improving the amount and quality of sleep, or improving alertness during waking hours. A range of therapies are employed for the treatment of sleep disorders, from behavioral therapy to light therapy to pharmacotherapy. Complementary and alternative therapy is increasingly utilized in the management of sleep disorders. Complementary and alternative medicine (CAM) may be defined as a broad area of healing resources distinct from those intrinsic to the politically dominant health system of a particular society at a given time.[4] This review will focus on the use of melatonin, a popular therapy within CAM, for the treatment of sleep disorders.

Classification of Sleep Disorders

Sleep disorders have been classified in various ways (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision [DSM-IV-TR]; International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM]; International Classification of Sleep Disorders [ICSD]). The most recent and detailed classification is the revised version of the International Classification of Sleep Disorders (1990), published by the American Academy of Sleep Medicine.[5] This document classifies sleep disorders according to four broad categories: dyssomnias, which are characterized by poor sleep; parasomnias, which are characterized by the occurrence of unusual events during sleep; sleep disorders associated with mental, neurological, or medical disorders; and proposed sleep disorders. Dyssomnias, disturbances of the normal sleep or rhythm pattern, are further subdivided into intrinsic (internally-caused), extrinsic (environmentally-caused) and circadian rhythm disorders. Circadian rhythm disorders may also

have an intrinsic cause, such as the inability to entrain the sleep-wake cycle to a 24-hour day in non-24-hour sleep wake syndrome, or an extrinsic cause in which the internal circadian apparatus is normal, but the demands of the external environment override it, such as in shift-work disorder or jet lag. Parasomnias involve dysfunctions occurring during sleep, such as nightmares, sleep paralysis or sleepwalking. Sleep disorders often occur in conjunction with mental disorders such as psychoses or mood and anxiety disorders; neurological disorders such as fatal familial insomnia, dementia, and Parkinsonism; and medical disorders such as chronic obstructive pulmonary disease and nocturnal cardiac ischemia (Table 1).[5]

Treatment of Sleep Disorders

The specific treatment used for a given sleep disorder depends on the type and etiology of the disorder.[6] Generally, the first line of treatment for sleep disorders involves improving sleep hygiene, which may consist of such strategies as strict adherence to a consistent routine seven days per week, a quiet and comfortable sleep environment, wind-down time before bed, stimulus control, avoidance of alcohol and caffeine before sleep and properly-timed exercise.[6] The American Academy of Sleep Medicine endorses the use of sleep hygiene and stimulus control, but other behavioral treatments, such as biofeedback, sleep restriction, relaxation training and cognitive therapy, may also be used.

Chronotherapy

Chronotherapy may be used for delayed or advanced sleep phase syndrome and usually involves application of a series of consecutive shifted 24-hour days, thus phase-delaying the sleep cycle three hours per sleep-wake cycle, until the desired bedtime is reached.[7] Light therapy may be used alone or in conjunction with chronotherapy and is often a treatment of choice for circadian rhythm disorders, since light is the principal synchronizer of circadian timing.[8] For delayed sleep phase syndrome, bright light exposure in the morning will lead to a phase advance, leading to an earlier time of rising,[9] while for advanced sleep phase syndrome, bright light exposure in the evening is effective in re-synchronizing the circadian rhythm.[10 11]

Light can shift the timing of the melatonin rhythm in a dose-response manner, with early night exposure resulting in phase delays and late night exposures resulting in phase advances. [12 13] Light can also suppress endogenous melatonin levels in a dose-response manner.[12]

Pharmacotherapy

Pharmacotherapy with sedative/hypnotic drugs is also widely used in the treatment of sleep disorders. Hypnotics promote drowsiness and facilitate the onset of sleep, while sedatives induce a calming effect. Ideally, a hypnotic should be rapidly absorbed into the bloodstream, display specific receptor binding, and induce sleep quickly, without causing side effects, buildup of tolerance, physical dependence, and respiratory or central nervous system depression.[14] However, no hypnotic is perfect. Benzodiazepines are the most commonly prescribed hypnotics and act on the inhibitory neurotransmitter receptors that are directly activated by the amino acid gamma-aminobutyric acid. Drugs of this class can be effective in treating transient insomnia and, due to anxiolytic as well as sedative/hypnotic properties, may be useful in the management of insomnia associated with select psychiatric disorders.[6] Although there are several chemical

classes of benzodiazepines, some benzodiazepines are metabolized in the body to N-desmethyldiazepam (nordiazepam), an active metabolite with a long elimination half-life and sedative effects. Unwanted effects of the benzodiazepines include daytime sedation, respiratory depression, dependence, and rebound insomnia.[6] Non-benzodiazepine hypnotics include zolpidem and zaleplon. Drugs of this class are more specific, display more rapid onset and shorter duration of action as well as fewer negative effects on memory and motor coordination, and are less likely to result in rebound insomnia, compared to benzodiazepines.[6] Antidepressants such as tricyclic antidepressants, trazodone and mirtazapine may also have sedative/hypnotic properties. Alternatives to traditional hypnotics include herbal and "natural" products such as St. John's Wort, valerian, kava kava, and melatonin.[15] These products have been reported to be effective, however, the methodological quality of studies on effectiveness of these products as well as their inconsistent findings, necessitate further research in this area.

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.[16] 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.[17-19] N-acetylserotonin is methylated via the enzyme hydroxyindole-o-methyltransferase to produce melatonin.[20] Approximately 90 percent of melatonin is cleared in a single passage through the liver. Microsomal enzymes of hepatic cells metabolize melatonin to 6-hydroxymelatonin.[20] The majority of the latter compound is subsequently conjugated with sulphate to produce 6-sulfoxymelatonin, while a smaller proportion is conjugated to glucuronide, prior to excretion in the urine. A small proportion of unmetabolized melatonin is also excreted in the urine.[20] Commercially available melatonin may be isolated from the pineal glands of beef cattle[21] or chemically synthesized.

Discovery and History of Melatonin

Melatonin was discovered as a result of the observation that bovine pineal extracts caused blanching of the skin of tadpoles when it was added to swimming water.[22] Aaron Lerner, an American dermatologist, isolated and characterized the hormone from beef pineal extracts in 1958, naming it melatonin based on its ability to lighten melanocytes.[23]

Melatonin is present in a number of organisms such as bacteria, algae, fungi, plants, insects and vertebrates, including humans.[24] Melatonin is also found in foodstuffs such as vegetables, fruits, rice, wheat and herbal medicines.[24]

Early research involving melatonin was conducted on animals and examined its effects on gonadal maturation and circadian systems. These early animal experiments provided evidence for chronobiologic and sleep-inducing effects of melatonin,[22] suggesting a role for this hormone in sleep and behavior in humans. The first experiments of melatonin on humans were conducted in the early 1970s, which provided evidence of a sleep inducing effect of melatonin in humans.[25] [26] The first study involving administration of chronic small doses of melatonin in human volunteers was conducted in 1984 and this study found that melatonin increased self-rated tiredness.[27] Sedative-hypnotic effects of melatonin were also noted in a study examining the behavioral effects of melatonin.[28] In 1984, melatonin was tested for its ability to alleviate the

symptoms of jet lag,[27] and this stimulated further trials of melatonin for the treatment of sleep disorders.

Physiology of Endogenous Melatonin

Melatonin secretion follows a circadian rhythm and is entrained to the light/dark cycle; light suppresses the production of melatonin, and with the onset of darkness, melatonin is produced and secreted from pinealocytes.[29] Light input is transmitted from the photic receptors in the retina through the retinohypothalamic tract to the suprachiasmatic nucleus (SCN), which is located in the anterior hypothalamus and functions as the central circadian pacemaker of the body.[30] During the dark period, the SCN stimulates the release of norepinephrine from the superior cervical ganglion; activation of pinealocyctes by norepinephrine results in production and release of melatonin.[31]

Melatonin is not stored in the pineal gland, but is secreted upon production. The hormone is likely secreted into the bloodstream before entering the cerebrospinal fluid (CSF) of the third ventricle, although it may also be secreted directly into cerebrospinal fluid.[32] Evidence for direct secretion of melatonin into CSF has been provided by findings that melatonin levels in CSF are substantially higher than in plasma.[33] Melatonin can also be measured in saliva, where levels are about 70 percent of plasma levels. The onset of melatonin secretion occurs at approximately 2200-2300 hours and maximal plasma concentrations occur at about 0300-0400 hours for a regular sleep cycle.[34] The offset of melatonin secretion occurs at approximately 0700-0900 hours.[34] The levels of metabolite in urine correlate positively with plasma levels of the hormone[29] and provide a non-invasive method of measuring melatonin levels in the body.[35]

Although melatonin is present in plasma of newborns, the circadian rhythm of melatonin does not exist at birth, but appears at 9-12 weeks of age and is fully established by 5-6 months of age.[35] Melatonin reaches high values at 1-3 years of age, with plasma levels peaking at approximately 250 pg/ml. Melatonin levels in plasma begin to decrease just prior to puberty to peak values of less than 100 pg/ml in adulthood.[36] There are, however, marked individual differences in the levels of melatonin that are produced by the pineal gland.[29]

Effects of Exogenous Melatonin

Melatonin has several effects on the body. It is best known as an entrainer of the circadian rhythm.[37] In mammals, removal of the pineal gland abolishes melatonin secretion.[19] Exogenous melatonin will cause a phase advance of the melatonin rhythm if given at dusk, and a phase delay if given in the morning.[38] The constant lag time between the onset of melatonin secretion and the onset of sleep suggests that exogenous melatonin could promote sleep.[39] Administration of exogenous melatonin to healthy volunteers has been shown to increase sleep propensity, reduce sleep onset latency and decrease REM sleep latency.[40]

The secretion of melatonin is also associated with the thermoregulatory cycle. The circadian rhythm of melatonin inversely correlates with the temperature rhythm in humans; melatonin levels in blood increase as core body temperature decreases.[41] Administration of pharmacologic, as opposed to physiologic, doses of exogenous melatonin, has been reported to cause a reduction in core body temperature.[42 43]

The secretion of melatonin secretion is also associated with the reproductive rhythm. In humans, melatonin secretion is inversely correlated with gonadal development; peak melatonin

levels fall just prior to the onset of puberty.[44] In addition, higher levels of plasma melatonin have been noted in women with amenorrhea.[45] Taken together, these findings suggest an inhibitory effect of melatonin on the reproductive rhythm.

Melatonin is also involved in immune function, and evidence suggests an immunoenhancing function for melatonin, via stimulation of natural killer cell activity, regulation of cytokine expression and inhibition of apoptosis in immune cells.[46] In support of such a function, high affinity melatonin receptors have been detected in human T lymphocytes.[47] Melatonin has also been shown to have oncostatic effects; it reduces tumor growth in animals and humans,[48 49] may reduce angiogenesis, protects DNA from mutation, and may also decrease tumor initiation.[29]

Melatonin Receptors

Melatonin has endocrine, autocrine and paracrine actions,[29] and some of these actions are receptor-mediated, while others are direct. There are three classes of melatonin receptors, MT1, MT2, and MT3.[50] In mammalian tissues, the distribution of melatonin receptors appears to be widespread.[29] The receptors are most consistently found in the SCN and the pars tuberalis of the adenophysis, although current research suggests that few tissues are devoid of melatonin receptors.[29] MT1 receptors are high affinity receptors that fall into the G-protein coupled receptor superfamily, and binding of melatonin to these receptors results in inhibition of adenylate cyclase activity in target cells.[51] There are two subgroups of the ML1 receptors, ML1a receptors and ML1b receptors.[52] The ML1 receptors are likely involved in regulation of retinal function, circadian rhythms and reproduction.[31] The ML2 receptors are low affinity receptors that are coupled to phosphoinositol hydrolysis.[31] Activation of MT3 receptors inhibits leukotriene B4-induced leukocyte adhesion and decreases intraocular pressure.[50]

Sleep Disorders and Melatonin

Clinical Trials of Melatonin for Sleep Disorders

The circadian phase modulating effects of melatonin point to its potential use in the treatment of circadian rhythm disorders, while the hypnotic/soporific effects of melatonin suggest its potential use in the treatment of insomnia. The use of melatonin in the elderly is considered a potential treatment for sleep disturbances in this population. Similarly, sleep disorders secondary to other medical conditions, such as depression or neurological disorders, may involve circadian rhythm abnormality, and thus could be mitigated by melatonin. A number of randomized controlled trials have been conducted to examine the effect of melatonin in the treatment of various types of insomnia[53-58] such as sleep maintenance insomnia,[37] terminal insomnia,[57] sleep onset insomnia,[59] psychophysiological insomnia[60] as well as circadian rhythm disorders such as time zone change (jet lag) syndrome,[61-65] shift work sleep disorder,[66-70] delayed sleep phase syndrome,[71-75] and non-24-hour sleep wake disorder (associated with blindness).[73 76 77] Randomized controlled trials have also been conducted to examine the effect of melatonin in the treatment of sleep disorders secondary to neurological conditions such as dementia,[78] Alzheimer's syndrome,[79] Rett syndrome,[80] tuberous sclerosis[81] and various other developmental disabilities[82] as well as disorders secondary to psychiatric conditions such as depression, bipolar disorder[83] and seasonal affective disorder.[84 85] Many case studies have also been conducted, particularly in children, on the use of melatonin for sleep difficulties secondary to neurological

syndromes such as Rett syndrome,[86] Smith-Magenis syndrome,[87] Angelman syndrome,[88] autism[82] and epilepsy.[83] Randomized controlled trials have also been conducted to examine the effect of melatonin in the treatment of parasomnias and REM sleep behavior disorder.[89]

Formulation and Dosage of Melatonin Used in Clinical Trials

The trials on melatonin for the treatment of sleep disorders vary in the formulation, timing of administration, frequency and duration of melatonin administration. The providers of melatonin for the various clinical trials on melatonin are diverse; Nestle, Sigma, Neurim, and Regis formulations are common providers. Melatonin products vary from fast-release to sustained release formulations. The formulation of melatonin used in the treatment of sleep disorders may have an effect on sleep outcomes, for example, in one trial, constant-release melatonin improved sleep quality in elderly insomniacs,[90] but in another trial, fast-release melatonin did not improve sleep quality in elderly insomniacs.[91] By far the most common method of melatonin administration is orally by capsule; the capsule usually consists of melatonin and lactose in a gelatin capsule. However, melatonin has also been administered by a sublingual tablet route, in patch format, and has also been tested intravenously. Commercially available agents are even more variable; melatonin products available include capsule, tablet (oral or sublingual), lozenge, liquid or spray forms. In trials of melatonin, the hormone has been administered orally or by transbuccal patch in dosages between 0.1 and 10 mg. The duration of melatonin administration in these trials varied from a single, one-time dose of melatonin[92] to multiple doses of melatonin administered for several months.[86] In most studies, melatonin is administered thirty minutes to two hours before usual bedtime or desired sleep time. The sleep outcomes analyzed in these studies include such measures as sleep onset latency, total sleep time, sleep duration, quality of sleep, number of awakenings, wake time after sleep onset, sleep efficiency as well as alertness, mood and performance. Some of these studies have found a positive effect of melatonin on these outcomes in people with sleep disorders, whereas some have shown no benefit of melatonin administration, that is, no improvement in sleep quality.

Adverse Effects of Melatonin

Compared to some pharmacological treatments for sleep disorders, melatonin has a very short half-life and its effects are short-lived.[93] There have been some side effects of melatonin reported, such as drowsiness and headache.[65 94 95] In general, most trials have not reported any hangover effects of melatonin, although some trials have reported adverse effects of melatonin on performance.[96] Melatonin administration in epileptic children has been associated with increased seizure activity.[97] Melatonin has also been associated with deterioration of mood in depression,[83 98] and has been reported to be associated with development of autoimmune hepatitis in one case.[99]

Systematic Reviews on the Use of Melatonin for the Treatment of Sleep Disorders

A small number of systematic reviews have been conducted on the use of melatonin for the treatment of sleep disorders. One systematic review of the effectiveness of melatonin in the treatment of jet lag, which included ten randomized controlled trials with a total of 953 patients, found melatonin to be effective in decreasing subjective ratings of symptoms of jet lag.[100] The timing of melatonin administration was found to be important for positive effects of the hormone; melatonin must be taken close to the target bedtime at the destination in order to alleviate the symptoms of jet lag. A second systematic review on the effect of melatonin in the treatment of elderly insomniacs found that the administration of exogenous melatonin reduced sleep onset latency and improved sleep quality, as measured by increased sleep efficiency and total sleep time, in elderly people with insomnia, who were characterized with benzodiazepine use and low circulating levels of melatonin.[101] This review included six small randomized controlled trials with 95 patients. In another review of the effectiveness of melatonin in the treatment of sleep disorders,[102] evidence was provided that melatonin may have modest effectiveness in treating insomnia, jet lag, and sleep disorders in neurologically impaired patients. This study was based on four trials involving the use of melatonin for the treatment of jet lag, two trials involving the use of melatonin for the treatment of shift work disorder and six trials of melatonin for the treatment of insomnia, all of which were indexed in MEDLINE®. Finally, a review of the effectiveness of melatonin in treating children with neurodevelopmental disability and severe sleep problems found very little good quality evidence for the effectiveness of melatonin in this population, due to small study sizes and difficulties with objective assessments of outcomes, and the authors proposed that melatonin may be more effective in the treatment of sleep onset difficulties rather than fragmented sleep or early morning awakening.[103] This review included six trials and the report highlighted a lack of significant evidence for the long-term safety of melatonin; one of the included studies reported a notable increase in seizures with melatonin administration.[97]

Although a few systematic reviews have been conducted on the use of melatonin for the treatment of sleep disorders, many focus on the treatment of a particular category of sleep disorders in a specific population. In this systematic review, we broaden the focus to include a review of 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.

Melatonin Safety and Legal Status

Melatonin has sometimes been considered a “safe” substance, since it has been shown to have low toxicity in animal studies[104] and to result in minor and infrequent adverse events in humans (see above). However, its safety has not, in fact, been definitively established; the safety of melatonin products is still under review and these products are regulated differently in various

countries. Rigorous safety evaluations of melatonin in humans have not been conducted and clear standards have not been developed for the quality of melatonin formulations.

Status in the United States

Currently, melatonin falls under the Food and Drug Administration's (FDA's) Dietary Supplement Health and Education Act[105] in the category "other dietary supplements". Melatonin is not considered a drug, since it is a naturally occurring substance[106] and it is designated "generally recognized as safe" (GRAS). Recognizing the lack of a common framework for evaluating the safety of dietary supplements, the Institute of Medicine Food and Nutrition Board has proposed a framework accompanied by six prototype monographs for the evaluation of various dietary supplements, including melatonin.[107]

Status in Canada

The Natural Health Products Directorate (NHP) of Health Canada has been re-evaluating natural health products such as melatonin. New NHP regulations have come into effect as of January 1st, 2004, which permit natural health products to be sold in Canada if they meet specific licensing, manufacturing, labelling, and safety standards. Melatonin is now available for sale in Canada.[108]

Status in Europe

In the European Union, melatonin is not considered as a foodstuff but rather a medicine or hormone. It is available by prescription only.[109]

Status in Australia

Melatonin is an unregistered good under the Therapeutic Goods administration. However, it can be imported for use under the Personal Import Scheme with a prescription.[110]

Objectives of the Review

The primary objective of this Evidence Report is to provide the details of a comprehensive literature review and synthesis of evidence on the use of melatonin for the treatment of sleep disorders, including not only the safety and effectiveness of melatonin for the treatment of sleep disorders, but also, the pharmacology of exogenous melatonin as well as the physiology of endogenous melatonin. Specifically, we sought to synthesize evidence related to four topic areas, including the physiology and pharmacology of melatonin; the populations that would benefit most from melatonin treatment; the effectiveness of melatonin treatment; and the safety of melatonin treatment.

Questions of the Review

The specific questions addressed in this Evidence Report are as follows:

Topic Area 1: Physiology and Pharmacology of Melatonin

1. What are the various formulations of melatonin? How are the formulations different in terms of content and quality as well as safety and effectiveness? What is the clinical importance of any observed differences?
2. What is the pharmacology of exogenous melatonin (including pharmacokinetics and pharmacodynamics)? How is it absorbed, distributed, metabolized and excreted? What blood levels are achieved? Does it penetrate the blood/brain barrier?
3. What is the evidence linking endogenous melatonin to sleep cycles?
4. What are the basic mechanisms by which melatonin produces sleepiness?
5. What is the effect of exogenous melatonin on sleep latency, sleep efficiency, and REM latency in normal sleepers?
6. How is endogenous melatonin involved in circadian rhythms?

Topic Area 2: Population at Risk

7. Which sleep disorders would be most effectively managed by treatment with melatonin?
8. Which populations, based on gender, age, ethnicity, genetic factors and co-morbid conditions, would benefit most from treatment with melatonin?

Topic Area 3: Effectiveness of Melatonin

9. What is the effect of exogenous melatonin on people with sleep disorders?
10. What is the appropriate dosage/duration of melatonin for the treatment of sleep disorders? Does the appropriate dosage depend on patients' gender, age, and/or ethnicity?
11. What is the timing of melatonin administration during the sleep/wake cycle that would produce optimum treatment effects?

Topic Area 4: Safety of Melatonin

12. What are the adverse effects of short and long-term use of exogenous melatonin?
13. How do the benefits and harms of exogenous melatonin vary based on dose, timing of administration, and patient factors such as gender, age and ethnicity?
14. How do the benefits and harms of melatonin compare to those of other approved pharmacological treatments for sleep disorders?

Flow Diagram 1: Analytic Framework

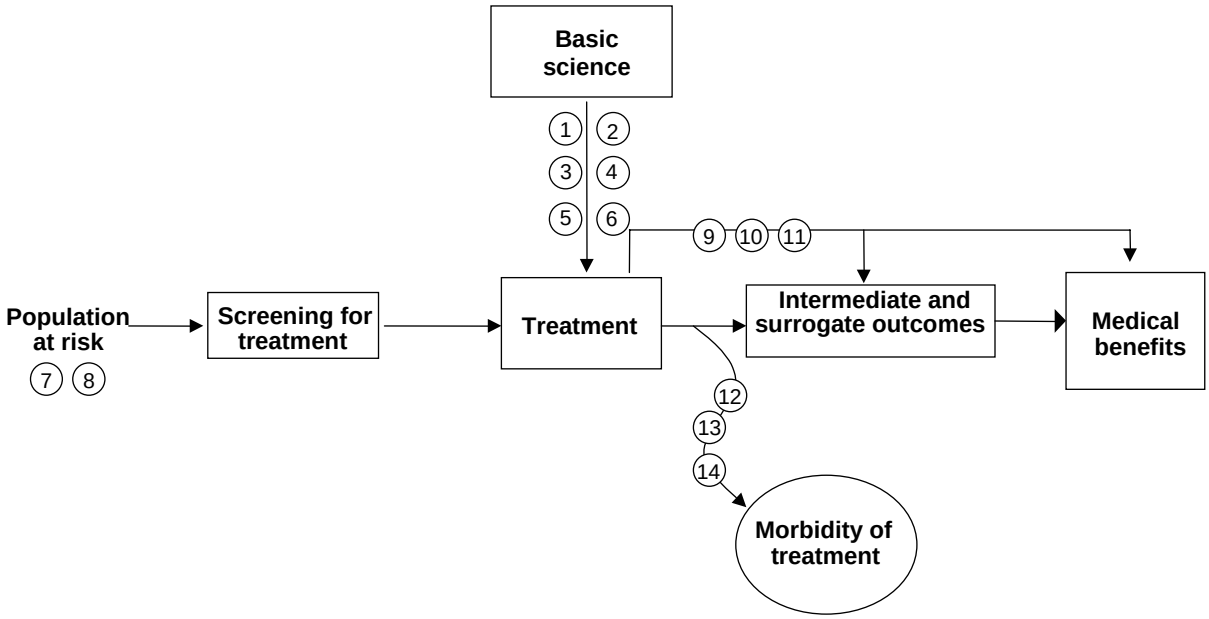


Table 1: Classification of Sleep Disorders according to ICSD

Dyssomnias			
Intrinsic Sleep Disorders	Extrinsic Sleep Disorders	Circadian Rhythm Sleep Disorders	
Parasomnias			
Arousal disorders	Sleep-wake transitional disorders	Parasomnias usually associated with REM sleep	Other parasomnias
Sleep disorders associated with mental, neurologic, and other medical disorders			
Associated with mental disorders	Associated with neurological disorders	Associated with other medical disorders	
Proposed Sleep Disorders			
Short sleeper	Long sleeper	Subwakefulness syndrome	Fragmentary myoclonus
Sleep hyperhidrosis	Menstrual-associated sleep disorder	Pregnancy-associated sleep disorder	Terrifying hypnagogic hallucinations
		Sleep choking syndrome	
Sleep-related neurogenic tachypnea	Sleep-related laryngospasm		

Abbreviations: ICSD = International Classification of Sleep Disorders

Chapter 2. Methods

Research Team

The research team designated to this Task Order was selected to represent the diverse areas of expertise required to properly elucidate the topic of the review and has both basic and clinical science expertise. The areas of expertise encompassed by the research team include melatonin and pineal cell biology, sleep, complementary and alternative medicine (CAM), neurochemistry, pharmacology, physiology, as well as systematic review methodology. The research team consists of a Core Research Team, which has been involved in the day-to-day operations required to fulfill the Task Order, as well as a Technical Expert Panel (TEP), which has functioned in an advisory capacity. The Core Team consists of two Task Order Leaders with expertise in clinical pharmacology, clinical epidemiology, pediatrics and CAM (Dr. Sunita Vohra) and pharmacology/neurochemistry (Dr. Glen Baker); the Evidence-based Practice Centre (EPC) Director (Dr. Terry Klassen), Associate Director (Dr. Brian Rowe) and Administrative Director (Ms. Lisa Hartling) with expertise in systematic review methodology; and a Project Manager (Dr. Nina Buscemi) and Staff. The Core Team has met on a regular basis to plan the approach for fulfilling the Task Order and to ensure that project activities were conducted in an appropriate and timely manner.

The TEP is multi-disciplinary in nature and has provided the breadth of expertise required to produce a comprehensive Evidence Report on the use of melatonin for the treatment of sleep disorders. During the course of the project, a total of 15 individuals have joined the TEP. Members of the TEP have been consulted during the course of the project, as required, for specific input and guidance, according their particular area of expertise. See **Appendix D**[*] for affiliations and areas of expertise of TEP members.

In addition to the individuals mentioned above, the Core Research Team maintained regular communication and dialogue with representatives of the National Center of Complementary and Alternative Medicine (NCCAM) as well as the Task Order Officer of the Agency for Healthcare Research and Quality (AHRQ).

Methods for the Systematic Review

Overview

The methods of the University of Alberta Evidence-based Practice Centre (UAEPC) were used to conduct a systematic review and synthesis of evidence relevant to the questions of the review. A number of steps were followed in producing this Evidence Report:

- Comprehensive Search
- Development of Inclusion Criteria
- Study Selection
- Assessment of Study Quality

[*] **The Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/melatntp.htm.**

- Data Extraction
- Data Analysis

Comprehensive Search

As a first step, a number of biomedical databases were searched. Given the subject area of the review, there was a possibility that these databases would not provide accurate representation of the breadth of research in this area. Thus, our intention was to conduct preliminary searches of these databases, assess publication bias, and if it were found across studies relevant to the questions of the review pertaining to the effectiveness of melatonin in the treatment of sleep disorders, we would expand our search accordingly. Table 2 outlines the electronic databases that were searched and Table 3 outlines the keywords and subject headings that were used in the searches. See **Appendix A**[*] for a detailed description of the search strategy.

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. In addition to these initial searches, similar searches of MEDLINE® and EMBASE were conducted periodically for more recently published studies that were potentially relevant to the review.

In addition to the electronic searches described above, the reference lists of a random sample of reports, encompassing half of all studies included in the review, were reviewed. The reference lists of narrative and systematic reviews related to melatonin and sleep disorders were also reviewed. We also reviewed the reference list of a Health Canada document on the use of melatonin for the treatment of various disorders as well the reference list of a document from Natural Standard Research Collaboration on the use of melatonin for the treatment of sleep disorders. Lastly, we hand-searched Associated Professional Sleep Society (APSS) Abstracts of 1999 to 2003.

As mentioned above, searches were limited to English-language reports. We sought to avoid the inclusion of non-English language reports in the review, unless deemed necessary, as a means of containing resource requirements for this review, which was already large in scope. The Core Team, in consultation with NCCAM and AHRQ, devised a strategy for inclusion of non-English language reports in the review. Our approach was to evaluate the presence of publication bias across studies relevant to the question of the review pertaining to the effectiveness of melatonin in the treatment of sleep disorders. If publication bias were found, we would expand our search to include non-English language data. We would also expand our search to include non-mainstream data sources. Publication bias refers to a bias in the literature whereby the publication of research is dependent upon the results of research. In Western medical journals, this phenomenon is reflected in the fact that results indicating no effect of an intervention are less likely to be published.[111] The problem is reversed for CAM-related research, such that studies with negative results are more likely to be published in mainstream Western medical journals (e.g. "MEDLINE®"), and CAM studies with positive results are

[*] **The Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/melatntp.htm.**

more likely to be published in smaller journals that may not be accessible on usual search engines.[112] Thus, it was necessary to assess this bias across studies related to the effectiveness of melatonin included in this review. We considered the use of non-English language reports and expansion of data sources only for the latter question of the review, since this question related to the main thesis of the report.

Development of Inclusion Criteria

Specific inclusion criteria were developed for each question of the review. In general, only controlled clinical trials were included for each 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 pre-determined outcomes relevant to that question. Only English-language reports were included in the review.

Question-Specific Inclusion Criteria

What are the various formulations of melatonin? How are the formulations different in terms of content, quality as well as safety and effectiveness?

A study was considered relevant to the portion of this question that pertains to the differences in the safety of various formulations of melatonin if it met inclusion criteria for the question relating to the safety of melatonin, and the formulation of melatonin used in the study was specified in the report. A study was considered relevant to all other portions of this question if it met inclusion criteria for the question relating to the effectiveness of melatonin, and the formulation of melatonin used in the study was specified in the report.

What is the pharmacology of exogenous melatonin, including pharmacokinetics and pharmacodynamics? How is it absorbed, distributed, metabolized and excreted? What blood levels are achieved? What is its half-life? Does it penetrate the blood-brain barrier?

A study was considered relevant to this question of the review if it met the following inclusion criteria:

- it involved human participants
- melatonin was administered to a group of participants

- at least one of the following outcomes was assessed in participants' serum/plasma/blood within hours of melatonin administration and a value was ascribed to it in the text of the report:
  - half-life of melatonin ($t_{1/2}$)
  - time to reach peak concentration of melatonin (T_{max})
  - peak concentration of melatonin (C_{max})
  - area under the melatonin versus time curve (AUC)

What is the evidence linking endogenous melatonin to sleep cycles?

A study was considered relevant to this question of the review if it met the following inclusion criteria:

- it was a controlled clinical trial
- it involved human participants
- it involved an intervention that altered either endogenous melatonin or the sleep cycle, such as manipulation of light/dark exposure or manipulation of the sleep schedule, respectively. If the intervention involved light administration, a lower intensity light condition was required as a control. If the intervention involved manipulation of the sleep schedule, a normal sleep schedule condition was required as a control.
- it involved only one intervention; a constant routine was not considered a secondary intervention if it was applied to both the experimental and control groups.
- it assessed the levels of melatonin and/or the phase of the melatonin rhythm in participants' blood, urine, saliva or cerebrospinal fluid in the case where the intervention altered the sleep cycle, or it assessed an aspect of participants' sleep cycle in the case where the intervention altered endogenous melatonin.

What are the basic mechanisms by which melatonin produces sleepiness?

Initially, a study was considered relevant to this question of the review if it met the following inclusion criteria:

- it involved human participants
- it involved administration of exogenous melatonin or an intervention that manipulated endogenous melatonin levels
- it characterized a mechanism by which alterations in endogenous melatonin levels affect sleep propensity

Given the lack of studies that met these inclusion criteria, the latter criteria were revised. A study was considered relevant to this question of the review if it met the inclusion criteria of the question relating to the effectiveness of melatonin in normal sleepers or the question relating to the effectiveness of melatonin in people with a sleep disorder, and the report provided a proposed mechanism by which melatonin produces sleepiness based on findings of the study.

What is the effect of exogenous melatonin on sleep latency, sleep efficiency and REM latency in normal sleepers?

A study was considered relevant to this question of the review if it met the following inclusion criteria:

- it was a controlled clinical trial
- it involved participants that did not have a sleep disorder
- melatonin was administered to a group of participants and placebo was administered to a group of participants
- at least one of the following outcomes was assessed:
- sleep onset latency
- sleep efficiency
- REM latency

How is endogenous melatonin involved in circadian rhythms?

The scope of this question was limited to an analysis of how endogenous melatonin is involved in the temperature rhythm. A study was considered relevant to this question of the review if it met the following inclusion criteria:

- it was a controlled clinical trial
- it involved human participants
- it involved an intervention that altered endogenous melatonin or the temperature rhythm, such as manipulation of light/dark exposure or temperature exposure, respectively. If the intervention involved light administration, a lower intensity light condition was required as a control. If the intervention involved manipulation of the temperature rhythm, a normal temperature condition was required as a control.
- it involved only one intervention; a constant routine was not considered a secondary intervention if it was applied to both the experimental and control groups.
- it assessed the levels of melatonin and/or the phase of the melatonin rhythm in participants' blood, urine, saliva or cerebrospinal fluid in the case where the intervention altered the temperature rhythm, or it assessed an aspect of participants' temperature rhythm in the case where the intervention altered endogenous melatonin.

What is the effect of exogenous melatonin on people with sleep disorders?

A study was considered relevant to this question of the review if it met the following inclusion criteria:

- it was a randomized controlled clinical trial
- it involved human participants who suffer from a sleep disorder and this condition was explicitly mentioned in the report
- melatonin was administered to a group of participants and placebo was administered to a group of participants
- at least one of the following outcomes was assessed:
  - sleep onset latency
  - sleep efficiency
  - sleep quality

- wakefulness after sleep onset
- total sleep time
- percent time in REM sleep

Which sleep disorders would be most effectively managed by treatment with melatonin? Which populations based on gender, age, ethnicity, genetic factors and co-morbid conditions, would benefit most from treatment with melatonin?

What is the appropriate dosage/duration of melatonin for the treatment of sleep disorders? Does the appropriate dosage depend on patients' gender, age, and/or ethnicity? What is the timing of melatonin administration during the sleep/wake cycle that would produce optimal treatment effects?

A study was considered relevant to these questions of the review if it met the inclusion criteria for the question relating to the effectiveness of melatonin in people with sleep disorders, and the report provided the information necessary for the study to be incorporated into a subgroup analysis related to at least one variable specified in the question.

What are the adverse effects of short and long-term use of exogenous melatonin?

A study was considered relevant to this question of the review if it met the following inclusion criteria:

- it included human participants
- melatonin was administered to a group of participants and placebo was administered to a group of participants
- it reported on adverse events and/or adverse effects of the interventions

For this question of the review, short-term melatonin use was defined as less than three months duration and long-term melatonin use was defined as three months or greater duration.

How do the benefits and harms of exogenous melatonin vary based on dose, timing of administration, and patient factors such as gender, age and ethnicity?

A study was considered relevant to this question of the review if it met the inclusion criteria for the question relating to the safety of melatonin, and the report provided the information necessary for the study to be incorporated into a subgroup analysis related to at least one variable specified in the question.

How do the benefits and harms of melatonin compare to those of other approved pharmacological treatments for sleep disorders?

A study was considered relevant to this question of the review if it met the inclusion criteria for the question relating to the effectiveness of melatonin in normal sleepers and the question relating to the effectiveness of melatonin in people with sleep disorders, except that melatonin and another pharmacological treatment for sleep disorders, instead of placebo, were administered to groups of participants.

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 key 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 pre-determined inclusion criteria for each key 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[113] was used to assess the quality of studies relevant to this question. The Jadad Scale assigns studies a quality score of zero to five, with a score of five indicating high quality. The scale assesses the components of randomization, blinding and reporting of dropouts and withdrawals. To our knowledge, neither this scale nor any other has been validated for the quality assessment of crossover trials. However, this scale has been validated for the quality assessment of randomized-controlled trials, and thus, was considered an appropriate quality assessment tool for this review. The concealment of allocation in the randomized-controlled trials was assessed as "adequate", "inadequate" and "unclear".[114] 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[115] was used to assess the quality of studies relevant to these questions. This checklist is partially validated and assesses a number of design components including reporting, internal and external validity, and the statistical power of a study to detect a clinically important difference. 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. See **Appendix B**[*] for Quality Assessment Forms.

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

[*] **The Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/melatntp.htm.**

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 pre-determined, question-specific outcomes.

Additional information that was extracted from reports included the name of the first author of the report and year of publication of the report; the country where the study took place; the source of funding for the study; authors' objectives and conclusions; 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 completion. Disagreements between reviewers were resolved by discussion and consensus. See **Appendix B**[*] for the Data Extraction Form.

Data Analysis

Table 4 outlines the keywords associated with the questions of the review and the type of analysis that was applied to data relevant to these questions. Data relevant to questions relating to the pharmacology of melatonin, the link between endogenous melatonin and the sleep and temperature rhythms, the mechanism of action of melatonin and the benefits and harms of melatonin compared to other pharmacological treatments for sleep disorders were analyzed qualitatively. All components of the question relating to the formulation of melatonin, except for the portion pertaining to the differences in the safety and effectiveness of melatonin formulations, were analyzed qualitatively. Data relevant to questions relating to the effectiveness, safety, and appropriate timing and duration of melatonin treatment were analyzed quantitatively.

Quantitative Analysis

For all continuous outcomes (e.g. sleep onset latency, sleep efficiency) studies were combined using a Weighted Mean Difference (WMD) with the exception of sleep quality where studies were combined using a Standardized Mean Difference (SMD). Due to the large number of studies with a crossover design, the Inverse Variance Method[116] was used to weight the studies. An effectiveness estimate with corresponding 95 percent confidence interval was computed for each outcome.

We were usually able to calculate the effectiveness estimates for each study exactly (i.e. weighted mean difference, standardized mean difference, risk difference), but occasionally, estimates had to be made by extracting from graphs or using medians. Standard errors of the differences were calculated exactly from available data (i.e. individual patient data or exact p-values) whenever possible. For studies with a parallel design, this calculation was usually accomplished with the standard formula for variance of difference of independent variables: $var(A-B) = var(A) + var(B)$. For studies with a crossover design, the standard error was estimated using the formula for variance of difference of dependant variables: $var(A-B) = var(A) + var(B) - 2\rho(var(A)var(B))^{1/2}$ and using a correlation estimate of 0.5. In cases where this calculation could not be done, standard errors were estimated using conservative p-values (i.e.

[*] **The Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/melatntp.htm.**

$p < 0.05$), inter-quartile ranges, and extracting from graphs. As a last resort, an average of standard deviations of other studies was used to impute standard deviations of a study.

For studies with a parallel design, change from baseline data was used if available, otherwise final data were used. For studies with a crossover design, final data were always used.

When continuous data were presented for multiple conditions, which we wished to combine, a new mean and standard deviation were computed. If the study had a parallel design, the new mean and standard deviation could be computed exactly using the formula:

$$\bar{y} = \frac{1}{g}\sum \bar{x}_i \qquad s_{\bar{y}} = \sqrt{\frac{\sum[(n_i - 1)s_i^2 + n_i \bar{x}_i^2] - N\bar{y}^2}{N-1}}$$

where $\bar{y}$ is the mean of the newly formed combined arm, g is the number of groups combined, $\bar{x}_i$ are the means of each group (i may take the value of 1 through g), s_y is the standard deviation of the newly formed combined arm, n_i are the sample sizes of each group, s_i are the standard deviations of each group and N is the total new sample size (the sum of the n_i). If the study had a crossover design, we treated the data as we would a repeated measures experiment. The formula for the mean was the same, but the following formula was used for the standard deviation with the within subject correlation (ρ) being estimated as 0.5.

$$s_{\bar{y}} = \frac{\sqrt{\sum s_i^2 + \sum_{i<j} 2\rho_{ij} s_i s_j}}{g}$$

Dichotomous outcomes (i.e. safety outcomes) were combined using a Risk Difference with corresponding 95 percent confidence interval. Many studies stated that there were no reported adverse events. These were included in the analysis, but a sensitivity analysis excluding them was also performed, since the lack of reporting on adverse events does not necessarily indicate that they did not occur in the study.

All meta-analyses were performed using a Random Effects Model. Bailey[117] suggests that the Random Effects Model is more appropriate when making recommendations for management and treatment of the next given patient. Fixed effects were considered in a sensitivity analysis.

All estimates of effectiveness (weighted mean differences, standardized mean differences, and risk differences) were assessed for heterogeneity using the I-squared statistic.[118] Based on this statistic, heterogeneity for each outcome was classified as negligible ($I^2 = 0$ percent), minimal ($I^2 < 20$ percent), moderate (20 percent $< I^2 <$ 50 percent), or substantial ($I^2 > 50$ percent). For our primary outcomes, heterogeneity was explored in subgroup analyses using a number of variables. These variables were: age, gender, ethnicity, use of concurrent medication, formulation, dosage, duration of study, method of measurement, study design, and study quality. For patients with sleep disorders, we also examined type of disorder and allocation concealment, while for subjects with normal sleep patterns, we also examined patient description, time of sleep, and use of multiple sleep onset techniques. Deeks' chi-square statistic[119] was used to test for significant heterogeneity reduction in partitioned subgroups.

We tested for publication bias visually using the Funnel Plot and quantitatively using the Rank Correlation Test,[120] the Graphical Test,[121] and the Trim and Fill Method.[122]

Qualitative Analysis

What are the various formulations of melatonin? How are the formulations different in terms of content, quality as well as safety and effectiveness? What is the clinical importance of any observed differences?

In order to obtain more detailed information regarding the content and quality of the melatonin formulations that were used in the studies relevant to this question of the review, the corresponding authors of these studies were contacted and asked to respond to a short questionnaire. The following is a list of questions that were posed:

1. What are the constituents of the formulation and the relative proportion of each constituent?
2. Was the melatonin component natural or synthetic and what was the purity of this component?
3. Do you have information on the pharmacology of this formulation in humans?

The information provided by corresponding authors was used to supplement information that was provided in the report of these studies. It was used to answer the portion of the question regarding the differences in the content and quality of melatonin formulations that have been used in relevant studies.

What is the pharmacology of exogenous melatonin, including pharmacokinetics and pharmacodynamics? How is it absorbed, distributed, metabolized, excreted? What blood levels are achieved? What is its half-life? Does it penetrate the blood brain barrier?

A detailed Evidence Table was created outlining the design details and results of studies relevant to this question of the review. The results of the studies were also summarized in a Summary Table. The key elements of these tables were summarised.

What is the evidence linking endogenous melatonin to sleep cycles? AND How is endogenous melatonin involved in circadian rhythms?

The studies relevant to these questions of the review were categorized according to details of study design. First, studies were categorized according the type of intervention that was employed; in the case of the question relating to the link between endogenous melatonin and the sleep cycle, these interventions were either alterations in lighting, alterations in the sleep schedule or exposure to another intervention that altered either endogenous melatonin or the sleep cycle; in the case of the question relating to the link between endogenous melatonin and the temperature rhythm, these interventions were either alterations in lighting or temperature. The studies were further subdivided into studies involving participants with or without a sleep disorder or with a disorder other than a sleep disorder. Each of these categories of studies was further categorized according to timing of the intervention. The analysis of data pertaining to these sub-categories of studies began with a summary of the conditions of the intervention and characteristics of the population and continued with a synthesis of the results of each study as they pertain to the question being addressed.

What are the basic mechanisms by which melatonin produces sleepiness?

The studies relevant to this question of the review were categorized as involving participants with or without a sleep disorder and further grouped according to the proposed mechanism by which melatonin produces sleepiness. The findings upon which the proposed mechanisms were based were described for each category of studies.

How do the benefits and harms of melatonin compare to those of other approved pharmacological treatments for sleep disorders?

The studies relevant to this question of the review were categorized as involving participants with or without a sleep disorder and the effects of melatonin and another pharmacological treatment for sleep disorders were compared in terms of their effects on one or more of the following outcomes: sleep onset latency, sleep efficiency, sleep quality, wakefulness after sleep onset, total sleep time and percent time in REM sleep. The adverse events accompanying both treatments were also compared.

Table 2: Biomedical Databases Searched

Database	Platform	Dates of Search
MEDLINE®	Ovid	1966 to June, Week 3, 2003
PreMEDLINE	Ovid	June 30 and July 4, 2003
EMBASE	Ovid	1988 to Week 26, 2003
PubMed®	N/A	July 9, 2002
CAB Health	SilverPlatter version 4.3	July 8, 2003
CINAHL®	Ovid	1982 to June Week 4, 2003
Cochrane Central Register of Controlled Trials	Ovid	3rd Quarter, 2003
Science Citation Index	ISI Web of Knowledge	July 4, 2003
Biological Abstracts	SilverPlatter version 4.3	July 4, 2003
International Pharmaceutical Abstracts	OVID	1970 to August, 2003
NLM® Gateway	http://gateway.nlm.nih.gov/gw/Cmd	August 13, 2003
OCLC Papers First and Proceedings First	OCLC FirstSearch	July 11, 2003
TOXLINE	CSA Internet Database Service	July 4, 2003

Table 3: Keywords and Subject Headings used in Searches

melatonin	restless legs syndrome
melatonine	nocturnal eating (drinking) syndrome
5-methoxy-N-acetyltryptamine	time-zone change syndrome
N-(2-(5-methoxy-1H-indol-3-yl)ethyl)acetamide	Jet lag
N-acetyl-5-methoxytryptamine	parasomnias
3-(2-acetamidoethyl)-5-methoxyindole	confusional arousals
Acetamide, N-(2-(5-methoxy-1H-indol-3-yl)ethyl)-(9CI)	rhythmic movement disorder
Acetamide, N-(2-(5-methoxyindol-3-yl)ethyl)-, N-(2-(5-methoxyindol-3-eyl)ethyl)acetamide, CAS Reg No: 73-31-4	nocturnal leg cramps
luzindole	nightmares
sleep	nocturnal paroxysmal dystonia
sleep disorders	sudden unexplained nocturnal death syndrome
dyssomnias	snoring
insomnia	congenital central hypoventilation syndrome
narcolepsy	sudden infant death syndrome
hypersomnia	subwakefulness syndrome
central alveolar hypoventilation syndrome	fragmentary myoclonus
periodic limb movement disorder	terrifying hypnagogic hallucinations
circadian	

Table 4: Questions of the Review and Type of Analysis Applied to Data Relevant to these Questions

Questions	Type of Analysis Applied to Data Relevant to Question
Formulations of melatonin	Qualitative and Quantitative
Pharmacology of melatonin	Qualitative
Endogenous melatonin and the sleep cycle	Qualitative
Mechanism of action of melatonin	Qualitative
Effect of melatonin on normal sleepers	Quantitative
Endogenous melatonin and circadian rhythms	Qualitative
Effectiveness of melatonin among types of sleep disorders	Quantitative
Effectiveness of melatonin among types of populations	Quantitative
Effect of melatonin on people with sleep disorders	Quantitative
Appropriate dosage of melatonin for treatment of sleep disorders	Quantitative
Appropriate timing of melatonin administration for treatment of sleep disorders	Quantitative
Adverse effects of melatonin	Quantitative
Adverse effects of melatonin as a function of dose, timing, and patient factors	Quantitative
Melatonin and other pharmacological treatments for sleep disorders	Qualitative

Chapter 3. Results

Literature Review

The database searches yielded 1884 references of potentially relevant articles. An initial screening of titles and abstracts of articles identified from database searches, as well as from hand-searching, yielded 935 studies to which specific inclusion criteria were applied. Of these 935 studies, 796 studies were excluded from the review and 139 studies were included in the review. Of the 796 studies that were excluded from the review, the majority were excluded because they were reviews (n=328). Other reasons for exclusion included inappropriate study topic (n=36), design (n=272), population (n=7), intervention (n=21) and outcomes (n=101). Three studies were not included in the review because of inadequate reporting. The reports of 25 studies were unobtainable at the time of this writing and two were realized upon completion of the final report. The rate of disagreement for study inclusion was approximately 20 percent. These disagreements were usually due to oversight of particular details of study design, and were easily resolved with discussion. In many cases, a given study was relevant to more than one question of the review (Flow Diagram 2). Table 5 outlines the number of studies relevant to each question of the review and the type of analysis that was applied to data relevant to these questions.

Results of Quantitative Analysis

What is the effect of exogenous melatonin on sleep latency, sleep efficiency, and REM latency in healthy people?

Twenty-one studies were relevant to this question of the review. The quality of these studies was assessed using the Downs and Black Checklist.[115] The overall quality of studies ranged from 11 to 25 on a 29-point scale; most studies had a score between 16 and 20; four studies had a score between 10 and 15;[78 123-125] and one study had a score of 25.[126] The quality of reporting ranged from 4 to 11 on an 11-point scale; most studies had a score between seven and nine, three studies had a score between four and six[78 124 125] and two studies had a score of 10 or 11.[126 127] The external validity of studies ranged from zero to three on a three-point scale; most studies had a score of zero, five studies had a score of one[124 127-130] and one study had a score of three.[126] The internal validity of studies ranged from seven to 11 on a 13-point scale; approximately half of the studies had a score of 10 or 11; five studies had a score of nine;[78 127 131-133] and six studies had a score of seven or eight.[123-125 134-136] None of the studies reported a power calculation for the primary outcome and, therefore, it was unclear whether the study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5 percent. In general, these studies were of relatively low quality. Although all studies involved a placebo control, many studies did not involve random allocation of participants to interventions. For studies in which participants were randomly allocated to intervention groups, it was often unclear whether allocation concealment was maintained or whether participants were blinded as to the intervention they received. See Evidence Table C-1

for a description of design characteristics and overall quality scores of studies relevant to this question of the review.

The following three outcomes were examined with respect to effectiveness of melatonin in normal sleepers, the first two being the primary outcomes:

- **Sleep Onset Latency**: Defined as the amount of time between the subject laying down to sleep and the onset of stage one sleep.
- **Sleep Efficiency**: Defined as the amount of time the subject spent asleep expressed as a percentage of the total time spent in bed.
- **REM Latency:** Defined as the amount of time required to begin REM sleep after sleep onset.

Sleep Onset Latency

Primary Analysis

There were a total of twenty studies with data on sleep onset latency for normal sleepers. The combined estimate comparing melatonin to placebo showed that melatonin caused a statistically significantly reduction in sleep onset latency (weighted mean difference (WMD): -3.9 minutes (min.); 95 percent confidence interval (CI): -5.3 min, -2.6 min). This effect appears to be clinically insignificant. Heterogeneity among the studies was moderate (I^2: 47.1 percent). Nineteen of the twenty studies had a point estimate that favoured melatonin (Figure 3-1).

Subgroup and Sensitivity Analyses

The results of all the subgroup and sensitivity analyses are summarized in Table 6. Subgroups that could not be analyzed for sleep onset latency included age (all studies involved adult participants), ethnicity (not specified in any study), and formulation of melatonin (all studies used fast-release melatonin).

As can be seen from Table 6, none of the subgroups produced markedly different results from those obtained from the primary analysis. All of the subgroup point estimates favoured melatonin and this result was significant in most cases; the only exceptions were cases with only a small number of studies. Four of the partitions showed a significant Deeks' chi-square value, indicating that heterogeneity was significantly reduced by the partition. Method of measurement of sleep outcomes and timing of melatonin administration had the largest effect. Method of measurement of sleep outcomes showed the questionnaire group to have a larger effect than the other methods, but this could be due to the smaller sample size of only two studies. For all other subgroup analyses, the subgroups had overlapping confidence intervals.

Using the Fixed Effects Model instead of the Random Effects Model tightened the confidence interval but did not greatly change the point estimate (WMD: -3.2; 95 percent CI: -4.0, -2.5).

Assessment of Publication Bias

There was evidence of asymmetry in the funnel plot, indicating possible publication bias (Figure 3-2). In the numerical tests, the results of Egger's Graphical Test showed a p-value that was borderline significance, indicating possible bias (p-value: 0.049). Begg's Test (Kendall's S=-39 giving a p-value of 0.217 for 20 studies) and Duvall's Trim and Fill Test did not indicate publication bias.

Sleep Efficiency

Primary Analysis

There were a total of thirteen studies with data on sleep efficiency for normal sleepers. A statistically significant increase in sleep efficiency with melatonin was calculated when comparing melatonin to placebo (WMD: 2.3 percent; 95 percent CI: 0.7 percent, 3.9 percent). This effect appears to be clinically insignificant. Heterogeneity among the studies was substantial (I^2: 53.9 percent). Eleven of the thirteen studies showed a point estimate indicating increased sleep efficiency with melatonin, one study indicated neutrality between melatonin and placebo, and one study indicated increased sleep efficiency with placebo (Figure 3-3).

Subgroup and Sensitivity Analyses

The same subgroups that were analysed for sleep onset latency were also analysed for this outcome except for the use of the multiple sleep onset latency test (there were no studies employing this test) and study design (all studies had a crossover design). The results are summarized in Table 7.

While most of the subgroups produced estimates there were not markedly different from the primary analysis, some differences are noteworthy. The most striking difference was in time of sleep; the efficiency effect of melatonin was much more prominent in the daytime sleepers. Timing of melatonin administration was the only partitioned result that showed a significant reduction in heterogeneity, but the confidence intervals of the two groups overlapped.

Using the Fixed Effects Model in place of the Random Effects Model gave a slightly lower effectiveness estimate of sleep efficiency but remained significant (WMD: 1.38; 95 percent CI: 0.5, 2.3).

Assessment of Publication Bias

All four tests of asymmetry indicated the possible presence of publication bias (Figure 3-4). The funnel plot showed a marked asymmetry that was confirmed by both Begg's Rank Correlation Test (Kendall's S=41—with 13 studies giving a continuity corrected p-value of 0.014) and Egger's Regression Test (bias p-value of 0.005). Duval's Trim and Fill Algorithm added 5 studies to the analysis and gave a modified estimate that was not significant (WMD: 0.9; 95 percent CI: -0.8, 2.7).

REM Latency

Primary Analysis

Eleven studies had data on REM latency for normal sleepers. The point estimate showed that REM latency was slightly higher with melatonin but the difference was not significant (WMD: 2.6 min.; 95 percent CI: -4.1 min, 9.2 min). Heterogeneity among the studies was substantial (I^2: 55.2 percent). Six of the 11 studies had a point estimate that showed an increase in REM latency for melatonin, while five studies showed a decrease (Figure 3-5).

Sensitivity and Subgroup Analysis

The subgroups analysed for REM latency in normal sleepers were the same as those analysed for sleep onset latency with the exception of method of measurement (all studies used

polysomnography to measure sleep outcomes) and study design (all studies had a crossover design). The results are summarized in Table 8.

All of the subgroup point estimates, except one, showed a non-significant difference in REM latency between melatonin and placebo; the 1-3 mg dosage subgroup, showed increased REM latency compared to both higher and lower doses. Although three of the partitioned subgroups indicated significant reduction in heterogeneity, besides the group already mentioned, there was no indication that REM latency is affected by melatonin.

The point estimate using the Fixed Effects Model in place of the Random Effects Model favoured placebo rather than melatonin, but was not statistically significant (WMD: -0.4, 95 percent CI: -3.9, 3.1).

Assessment of Publication Bias

While a visual inspection of the funnel plot seems to indicate some minor asymmetries (Figure 3-6), there was no evidence of publication bias in any of the quantitative tests. Begg's Test (Kendall's S=2; with 11 studies this is a p-value of 0.938), Egger's Test (bias p-value: 0.257) and Duval's Trim and Fill test (no studies added) did not give any indication of any asymmetry in the funnel plot.

What is the effect of exogenous melatonin on people with sleep disorders?

Thirty randomized controlled trials were relevant to this question. The quality of relevant studies was assessed using the Jadad Scale.[113] The overall quality scores ranged from two to five on a five-point scale. Three studies had a quality score of two,[125 137 138] eight studies had a quality score of three,[66 70 80 132 139-142] 12 studies had a quality score of four[54 60 63 69 71 73 74 81 82 90 131 135] and seven studies had a quality score of five.[57 61 67 68 78 91 143] It was unclear whether there was adequate concealment of treatment allocation in all studies except six.[67-69 78 90 143] All studies were described as randomized and double-blind and a description of withdrawals and dropouts was provided in all reports except six.[80 125 137-139 141] The method of randomization was described and was appropriate in nine studies,[57 61 63 67 68 78 91 135 143] while the method of randomization was not described in all other studies. All reports except 11[60 63 66 70 125 132 135 137 138 140 142] provided a description of an appropriate method of double-blinding; the method of double-blinding was not described in all other reports. These studies differed from studies involving normal sleepers mentioned above in that participants were randomized to intervention groups. However, other aspects of study design such as allocation concealment and blinding were similar to studies involving normal sleepers. See Evidence Table C-2 for a description of design characteristics and overall quality scores of studies relevant to this question of the review.

The following six outcomes were examined with respect to effectiveness of melatonin in people with sleep disorders, the first two being the primary outcomes:

- **Sleep Onset Latency**: Defined as the amount of time between the subject laying down to sleep, and the onset of stage 1 sleep.
- **Sleep Efficiency**: Defined as the amount of time the subject spent asleep as a percentage of the total time spent in bed.
- **Sleep Quality**: Defined as the overall quality of sleep attained. This outcome was measured differently across studies and was thus combined using a Standardized Mean Difference.

- **Wakefulness After Sleep Onset (WASO)**: This is the amount of time spent awake in bed following the first attainment of stage one sleep.
- **Total Sleep Time**: Defined as the total time spent asleep while in bed.
- **Percentage Time in REM Sleep**: Defined as the total time spent in REM sleep as a percentage of total sleep time.

People with a Primary Sleep Disorder

Sleep Onset Latency

Primary Analysis. There were 12 studies that examined sleep onset latency in patients with a primary sleep disorder. The combined weighted mean difference (WMD) of the studies showed that those in the melatonin group had a statistically significant shorter sleep onset latency period than those in the placebo group (WMD: -10.7 min.; 95 percent CI: -17.6 min., -3.7 min.), although there was substantial heterogeneity among the studies (I^2: 81.5 percent). This effect appears to be clinically insignificant. Nine of the 12 studies showed a difference that favoured melatonin (Figure 3-7). These results are based on trials of four weeks or less in duration.

Sensitivity and Subgroup Analysis. Table 9 summarizes the results of the subgroup and sensitivity analyses of sleep onset latency in patients with a primary sleep disorder. Subdivision by gender was not possible as all studies were mixed gender. Only two studies specified ethnicity—both were Caucasian. For use of concurrent medications, all but two studies either did not specify or had a mixture of patients on and off medications. For dosage, three studies used multiple doses and were included in two or more groups, while two studies were excluded since they did not specify dosage.

Many of these sub groupings significantly reduced heterogeneity despite retaining a substantial heterogeneity statistic in at least one subgroup. The one subgroup that is noteworthy is that of primary diagnosis, which substantially reduced the heterogeneity and is the only sub grouping that gave results with non-overlapping confidence intervals. This variable appears to explain much of the heterogeneity in the primary analysis.

Using the Fixed Effects Model rather than Random Effects Model greatly changes the results of the primary analysis as well as the conclusion. One study[91] received nearly 92 percent of the weight and the new difference was not significant (WMD = -0.32; 95 percent CI –1.3, 0.6).

Assessment of Publication Bias. Assessment of publication bias for sleep onset latency of patients with primary sleep disorders was performed. No obvious asymmetry was evident in the funnel plot (Figure 3-8). Begg's test gave a Kendal's score of S=6—with 12 studies, this constitutes a continuity corrected p-value of 0.732 indicating no publication bias. Performing Duval's Trim and Fill Method, no studies were added to the meta-analysis, and the final results were identical to the primary analysis. The only test that showed any indication of publication bias was Egger's Graphical test, which had a p-value of 0.027 on the bias of the funnel plot.

Sleep Efficiency

Primary Analysis. Nine trials were included in the analysis of sleep efficiency for people with primary sleep disorders. Although the WMD did favour melatonin, the difference was not significant (WMD: 1.5 percent; 95 percent CI: -0.7 percent, 3.6 percent) and the heterogeneity among the studies was substantial (I^2: 62.8 percent). Six out of the nine studies showed a point estimate that favoured melatonin (Figure 3-9). These results are based on trials of four weeks or less in duration.

Sensitivity and Subgroup Analysis. Table 10 summarizes the results of the subgroup analysis of sleep efficiency in patients with a primary sleep disorder. Subdivision by gender and ethnicity was not possible since all studies were of mixed gender and none of the studies specified ethnicity. For use of concurrent medications, all studies either did not specify or had a mixture of patients on and off medications. For subdivision by dosage, three studies used multiple doses and were in multiple groups; one study was excluded, as it did not specify dosage.

The only sub-grouping that is noteworthy is that of allocation concealment. Removing the study by Garfinkel et al.,[90] which was considered to have adequate allocation concealment, removed the vast majority of the heterogeneity from the analysis and the result based on this study was significant. This finding is likely due to chance, since allocation concealment has been associated with smaller, rather than larger, effect sizes.[114] The remaining eight studies showed no effect. The only other sub grouping that significantly reduced heterogeneity was age, but the resulting confidence intervals were non-overlapping and non-significant.

If we use a fixed effects model instead of a random effects model in our analysis, our point estimate decreases slightly and our confidence interval tightens, but the result is still non-significant (WMD: 0.8; 95 percent CI: -0.3, 1.8).

Assessment of Publication Bias. The funnel plot showed some asymmetry (Figure 3-10), however all other tests did not indicate publication bias. Begg's test gave a Kendal's score of S=7—with nine studies, this constitutes a continuity corrected p-value of 0.529. Egger's Graphical Test had a p-value of 0.441 on the bias of the funnel plot. Finally, Duval's Trim and Fill Method had no studies added to the meta-analysis, and the final results were identical to the primary analysis.

Sleep Quality

Sleep quality for patients with a primary sleep disorder was recorded in only two studies[57 140] and measured on different scales. The results were combined using a Standardized Mean Difference (SMD); this outcome is slightly more difficult to interpret since it appears in units of standard deviation. The SMD favoured melatonin over placebo, but the result was not significant (SMD: 0.5; 95 percent CI: -0.1, 1.1). Heterogeneity between the two studies was negligible (I^2: 0 percent). Both studies had a point estimate that favoured melatonin.

Wakefulness After Sleep Onset

WASO was reported in five studies involving administration of melatonin to individuals with primary sleep disorders. Combining them with a WMD showed virtually no difference between placebo and melatonin (WMD: -1.4 min.; 95 percent CI: -21.8 min., 19.0 min.). The heterogeneity among the studies was substantial (I^2: 84.0 percent). Three of the studies had point estimates that favoured placebo, one study had a point estimate that favoured neither melatonin nor placebo, and one study had a point estimate that favoured melatonin.

Total Sleep Time

Eleven studies had data on total sleep time for patients with a primary sleep disorder. Their combined estimate comparing total sleep time between placebo and melatonin using a WMD favoured melatonin but was not significant (WMD: 4.0 min.; 95 percent CI: -10.5 min., 18.5 min.). The studies showed substantial heterogeneity (I^2: 67.6 percent). Only five of the 11 studies had a point estimate that favoured melatonin.

Percentage Time Spent in REM Sleep

Three studies involving melatonin administration to individuals suffering from a primary sleep disorder reported on percentage time spent in REM sleep. Using a WMD to combine the studies gave an estimate that marginally favoured melatonin but was not significant (WMD: 0.4 min.; 95 percent CI: -1.2 min., 2.0 min.). Heterogeneity in the estimate was negligible (I^2: 0 percent). Two of the three studies had a point estimate that favoured melatonin.

People with a Secondary Sleep Disorder

Sleep Onset Latency

Primary Analysis. There were six trials involving melatonin administration to individuals with a secondary sleep disorder that reported on sleep onset latency. Their combined estimate favoured melatonin but was non-significant (WMD: -13.2 min.; 95 percent CI: -27.3 min., 0.9 min.). Heterogeneity among the studies was substantial (I^2: 79.2 percent) due primarily to one study[132] that had a very small standard deviation and an estimate very different from the other five studies. This study had a point estimate that favoured placebo, while the other five studies had point estimates that favoured melatonin (Figure 3-11). These results are based on trials of four weeks or less in duration.

*Sensitivity and Subgroup Analysis. T*able 11 summarizes the results of the subgroup and sensitivity analyses of sleep onset latency for patients with a secondary sleep disorder. Subgroups not analysed below were ethnicity (not specified in any study), concurrent medications (all patients taking additional medications in all studies), and Jadad score (same for all studies). For gender, all study populations were mixed except for a study by McArthur et al.,[80] which was all female. For dosage, only four studies are listed since one study did not specify dosage,[82] and another gave varying doses based on weight.[80] Primary disorder was different for all studies except for two studies that both examined patients with schizophrenia.[131] [132]

One study by Shamir et al.[132] completely dictated the results of the subgroup analysis. Subgroups that omitted this study, showed a significant result in favour of melatonin with negligible heterogeneity, while subgroups that did include this study were non-significant with substantial heterogeneity. The two sub groupings in which this study stood alone do not shed much light on the reason for the difference. The Shamir et al. study[132] was the only study that used polysomnography to measure sleep outcomes and also the only study that was considered to have adequate allocation concealment.

Using the Fixed Effects Method instead of the Random Effects Method drastically changed the results due to the vast majority of the weight being assigned to the study by Shamir et al.[132] The point estimate for sleep onset latency favoured placebo and was non-significant (WMD: 3.0; 95 percent CI: -0.1, 6.1).

Assessment of Publication Bias. With only six studies analysing sleep onset latency in patients with a secondary sleep disorder, the number of studies was deemed too few to do any meaningful tests for publication bias.

Sleep Efficiency

Primary Analysis. There were six trials for which data were available for comparing melatonin to placebo in sleep efficiency. The WMD of the six studies showed a statistically significant effect that favoured melatonin (WMD: 1.9 percent; 95 percent CI: 0.5 percent, 3.3

percent). This effect appears to be clinically insignificant. Heterogeneity among the studies was negligible (I^2: 0 percent). Five of the six studies had point estimates that favoured melatonin while one study had a point estimate that favoured neither melatonin nor placebo (Figure 3-12). These results are based on trials of four weeks or less in duration.

Sensitivity and Subgroup Analysis. Table 12 summarizes the results of the subgroup analysis of sleep efficiency on patients with a secondary sleep disorder. Subgroups that were not possible were gender, ethnicity, timing, and Jadad score. Only three studies could be classified by use of concurrent medications (others were mixed or not specified). For dosage, one study was excluded since it gave varying doses based on weight and another gave multiple doses and was included in multiple categories. Primary disorder was different for all studies except for two studies that both examined patients with schizophrenia.

The only study that did not show a positive effect for sleep efficiency used polysomnography instead of actigraphy as its method to measure sleep outcomes. The two studies considered to have adequate allocation concealment had the lowest sleep efficiency estimates. However, the differences were not enough to significantly reduce heterogeneity in either of the subgroups.

Due to the negligible amount of heterogeneity, using the Fixed Effects Model instead of the Random Effects Model did not change the estimate in the primary analysis. The WMD and confidence interval were identical.

Assessment of Publication Bias. With only six included studies analysing sleep efficiency in patients with a secondary sleep disorder, the number of studies was deemed too few to do any meaningful tests for publication bias.

Sleep Quality

There were no studies involving individuals with a secondary sleep disorder that examined sleep quality.

Wakefulness After Sleep Onset

Three studies involving individuals with secondary sleep disorders had data on WASO. The combined estimate showed a difference between melatonin and placebo that favoured melatonin but the difference was non-significant (WMD: -6.3 min.; 95 percent CI: -16.6 min, 3.9 min.). Heterogeneity among the studies was moderate (I^2: 35.3 percent). Two of the three studies had a point estimate that favoured melatonin.

Total Sleep Time

There were a total of nine studies that analyzed total sleep time for patients with secondary sleep disorders. The studies showed a combined estimate that significantly favoured melatonin (WMD: 15.6 min.; 95 percent CI: 7.2 min., 24.0 min.). Heterogeneity was negligible (I^2: 0 percent). Eight out of the nine studies had a point estimate that favoured melatonin.

Percentage Time in REM Sleep

There was only one study involving individuals with a secondary sleep disorder that provided data on percent time spent in REM sleep. The WMD favoured placebo but was not significant (WMD: -1.5 percent; 95 percent CI: -4.4 percent, 1.4 percent).

People Suffering from Sleep Restriction

Sleep Onset Latency

Primary Analysis. There were a total of nine studies that provided data on sleep onset latency for patients suffering from sleep restriction. Despite a tight confidence interval, the nine studies did not show a significant effect for melatonin on sleep onset latency (WMD: -1.0 min.; 95 percent CI: -2.3 min., 0.3 min.). Heterogeneity among the studies was minimal (I^2: 4.0 percent). Six of the nine studies had a point estimate that favoured melatonin (Figure 3-13).

Sensitivity and Subgroup Analyses. Many of the planned subgroup analyses of sleep onset latency in patients suffering from sleep restriction could not be performed. The subgroups include gender (all studies involved both males and females and did not provide a breakdown by gender), age (subjects' age was similar across studies), ethnicity (not specified in any study), timing (all patients took melatonin before bed), and duration (the duration of melatonin administration was similar across studies). The results of the subgroup analyses that could be performed are summarized in Table 13. Note that only two studies could be classified in terms of concurrent medication use.

Using the Fixed Effect Model in place of the Random Effects Model does not change the conclusions. The point estimate and confidence interval (WMD: -1.0; 95 percent CI: -2.1, 0.1) are comparable to the random effects estimate.

Assessment of Publication Bias. The funnel plot showed no obvious signs of asymmetry (Figure 3-14). There were also no indications of publication bias by any of the tests conducted. Begg's Test gives a Kendall's score of –10, which gives a continuity corrected p-value of 0.348 with nine studies. Egger's Test has a p-value of 0.479 on the bias of the funnel plot. Duval's Trim and Fill Method added no new studies and thus had the same effectiveness estimate.

Sleep Efficiency

Primary Analysis. Data on sleep efficiency were available for only five studies that examined patients suffering from sleep restriction. The combined estimate of the studies showed no significant difference between melatonin and placebo with respect to sleep efficiency (WMD: 0.5 percent; 95 percent CI: -0.6 percent, 1.6 percent). Heterogeneity among the studies was moderate (I^2: 20.9 percent). Four of the five studies had point estimates that favoured melatonin (Figure 3-15).

Sensitivity and Subgroup Analyses. Many subgroup analyses could not be performed, including gender (all studies involved both males and females and did not provide a breakdown by gender), age (subjects' age was similar across studies), ethnicity (not specified in any study), timing (all patients took melatonin before bed), duration (the duration of melatonin administration was similar across studies), use of concurrent medication (not stated in any of the studies) and dosage (different across studies). The partitions that could be performed are outlined in Table 14.

Interestingly, all four subdivisions above gave negligible heterogeneity in all of their respective subgroups, although it was never a significant reduction in overall heterogeneity.

Using the Fixed Effects Model in place of the Random Effects Model to obtain the estimate of sleep efficiency for patients suffering from sleep restriction did not differ substantially from the primary analysis. The effectiveness estimate slightly favoured melatonin but was non-significant (WMD: 0.2; 95 percent CI: -0.6, 0.9).

Assessment of Publication Bias. There were an insufficient number of studies that involved subjects suffering from sleep restriction that examined sleep efficiency to justify performing tests for publication bias.

Sleep Quality

Five studies contained data on sleep quality. The standardized mean difference showed an effectiveness estimate that favoured melatonin but was not significant (SMD: 0.24; 95 percent CI: -0.17, 0.64). Heterogeneity among the studies was substantial (I^2: 58.5 percent). Four out of the five studies had a point estimate that favoured melatonin.

Wakefulness After Sleep Onset

Two studies involving individuals suffering from sleep restriction provided data on WASO. Their combined estimate favoured melatonin but was not significant (WMD: -10.4 min; 95 percent CI: -21.0, 0.2). Heterogeneity between the studies was negligible (I^2: 0 percent). Both studies' point estimates favoured melatonin.

Total Sleep Time

Seven studies involving patients suffering from sleep restriction compared total sleep time between placebo and melatonin; a significant effect that favoured melatonin was observed among the seven studies (WMD: 18.2 min; 95 percent CI: 8.1 min, 28.3 min). Heterogeneity among the studies was negligible (I^2: 0 percent). Five of the seven studies showed a point estimate that favoured melatonin, one study had a point estimate that neither favoured melatonin or placebo, and one study had a point estimate that favoured placebo.

Percentage Time in REM Sleep

Only one study[138] presented data on percentage time spent in REM sleep. The effectiveness estimate favoured placebo and was non-significant (WMD: -3.6 percent; 95 percent CI: -7.3, 0.1).

Which sleep disorders would be most effectively managed by treatment with melatonin?

As can be seen by the results above, the effect of melatonin on the various sleep disorders varies by outcome.

Sleep Onset Latency

For patients with primary sleep disorders, there was too much statistical heterogeneity among the studies to make a valid conclusion about the effect of melatonin on sleep onset latency in a broad sense. However, the heterogeneity largely disappears when we subdivide by type of sleep disorder. We then find that sleep onset latency is reduced substantially (by nearly 39 minutes) by melatonin in patients with delayed sleep phase syndrome, and marginally (by about 4 minutes) in patients with insomnia. Both results are statistically significant, however, the effect of melatonin on sleep onset latency in people with insomnia appears to be clinically insignificant. The reduced heterogeneity lends support to these conclusions.

The results for patients with secondary sleep disorders are also unclear as there was too much statistical heterogeneity in the data to make a firm conclusion. The removal of the study by Shamir et al.[132] would lead to conclusions that melatonin significantly reduces sleep onset

latency, but there are no grounds for its exclusion as it is clinically similar to the other studies in all aspects except for method of measurement and a clear method of allocation concealment. Thus, we can give no real statement as to the effect of melatonin on sleep onset latency for these patients.

Sleep onset latency did not significantly change with melatonin in patients suffering from sleep restriction. This conclusion does not change when we analyze the data by type of sleep restriction (i.e. jet lag or shift work).

Sleep Efficiency

There was no significant difference in sleep efficiency between patients with a primary sleep disorder taking either melatonin or placebo. Unlike sleep onset latency, sleep efficiency did not change when we partitioned the studies into sleep phase syndrome patients and patients with insomnia. With heterogeneity substantial in both cases, we can say that there is no evidence that sleep efficiency is changed by melatonin in these patients.

Melatonin had the strongest effect on sleep efficiency among patients with secondary sleep disorders; our results show a statistically significant increase in sleep efficiency with melatonin (about 1.9 percent), however, this effect appears to be clinically insignificant.

There was no effect of melatonin on sleep efficiency in patients suffering from sleep restriction.

Other Outcomes

There was no evidence that melatonin affects sleep quality, wakefulness after sleep onset (WASO), or percentage time spent in REM sleep for any of the three sleep disorder groups.

There is evidence that total sleep time is increased with melatonin in individuals suffering from a secondary sleep disorder and those suffering from sleep restriction. There was, however, no evidence of any change in total sleep time in patients with primary sleep disorders.

Which populations based on gender, age, ethnicity, and co-morbid conditions would benefit most from treatment with melatonin?

Gender

No information could be obtained regarding the effect of melatonin on sleep disorder patients by gender. All studies but one were a mixed population and a breakdown of data by gender was not available in any of them. The one exception[80] was an all female study of children with Rett syndrome and the results of this one study were non-significant with respect to both sleep onset latency and sleep efficiency.

Age

For patients with primary sleep disorders, there is some evidence that sleep onset latency is reduced more in children (up to 17 years) than in adults (18-65 years) or elderly patients (greater than 65 years). The one study involving children showed a significant reduction in sleep onset latency with melatonin while the studies involving adults and the elderly did not show this overall reduction, despite the presence of studies showing a highly significant reduction of sleep onset latency in this latter category. In terms of sleep efficiency, however, both the studies involving adults and the elderly showed non-significant differences between melatonin and placebo (there were no studies involving children that examined sleep efficiency).

There is no evidence that sleep onset latency is reduced more in children than in adults in studies involving individuals with secondary sleep disorders; none of the studies involving elderly with secondary sleep disorders examined sleep onset latency. Although the three studies involving children showed a significant reduction in sleep onset latency while the three studies involving adults did not, the confidence intervals are fully overlapping. In terms of sleep efficiency, there was no evidence of any differences among the three groups. Although the two studies involving elderly subjects showed a significant difference, they actually had the smallest point estimate. Similar to sleep onset latency, the three confidence intervals are fully overlapping.

No comparisons could be made by age for patients suffering from sleep restriction since all studies examined adult subjects.

Ethnicity

Ethnicity was generally not mentioned in any of the studies. Only two studies stated that their patients were all Caucasian. These two studies both involved individuals with primary sleep disorders and did show a significant reduction in sleep onset latency.

Co-Morbid Conditions

Regarding the studies involving subjects with secondary sleep disorders, the only co-morbid condition reported in more than one study was schizophrenia, which was present in two studies.[131 132] The other studies involved patients with different conditions: Rett syndrome,[80] tuberous sclerosis,[81] developmental disabilities,[82] depression,[125] dementia,[78] and Alzheimer's disease;[135] the first three studies involved children, the study by Serfaty et al. [125] involved adults, while the last two studies involved the elderly (the two studies by Shamir involved adults). Based on these other differences, it is difficult to discern the effects of melatonin solely by co-morbid condition. We can say that the study that involved children with tuberous sclerosis did show a significant reduction in sleep onset latency with melatonin (WMD: -23.4 min; 95 percent CI: --45.2, -1.6) and the study that involved elderly patients with Alzheimer's showed a significant increase in sleep efficiency with melatonin (WMD: 2.0 percent; 95 percent CI: 0.1, 3.9). It is difficult, however, to draw any conclusions from these results.

What is the appropriate dosage/duration of administration of melatonin for the treatment of sleep disorders? Does the appropriate dosage depend on patients' gender, age, and/or ethnicity?

Dosage

We categorized dosage according to the following levels: <1 mg, 1-3 mg, 4-5 mg, 6-10 mg, >10 mg. Among patients with a primary sleep disorder, there was no obvious effect of dose on the outcome of sleep onset latency or sleep efficiency. The point estimate of difference in sleep onset latency increased in magnitude with increasing dosage, while the point estimate of sleep efficiency decreased in magnitude with increasing dosage, but all confidence intervals for both outcomes were overlapping and non-significant.

The breakdown by dosage for patients with a secondary sleep disorder is also inconclusive; all confidence intervals were overlapping and non-significant for both sleep onset latency and sleep efficiency. With only two dosage groups for each outcome, no trends were detectable.

The breakdown of the studies involving sleep restriction also showed no discernable effect of dosage; all confidence intervals were overlapping and non-significant and no trend was detectable. There was no evidence of a dose effect on sleep onset latency or sleep efficiency for subjects suffering from sleep restriction.

A further subdivision by age, gender, or ethnicity was not possible in any of the sleep disorder subgroups due to lack of data.

Duration of Administration

When studies involving sleep disorders were subdivided by duration of administration (i.e., <1 week, 1-2 weeks, 3-4 weeks), there was no apparent melatonin effect with respect to either sleep onset latency or sleep efficiency. The results were generally the same (i.e. overlapping confidence intervals) regardless of the duration.

There were no data for subjects suffering from sleep restriction, as all studies were approximately the same duration.

What is the timing of melatonin administration during the sleep/wake cycle that would produce optimal treatment effects?

Without exception, every sleep disorder study administered melatonin to its patients just before they went to bed. As a result there is no information on effect of timing of melatonin administration.

How do different formulations of melatonin differ with respect to effectiveness?

There was insufficient information on melatonin formulations in the sleep disorder studies to allow us to do any subgroup analysis by formulation.

What are the adverse effects of short and long-term use of melatonin?

Thirty-four studies were relevant to this question of the review. The overall quality of these studies was assessed using the Downs and Black Checklist.[115] The overall quality of studies ranged from 12 to 26 on a 29-point scale; one study had a score of 12,[144] 13 studies had a score between 16 and 20,[27 60 61 63-65 81 92 94 124 145-147] 19 studies had a score between 21 and 25[54 66 68 69 71 74 76 78 80 82 90 95 129 130 143 148-151] and one study had a score of 26.[67] The quality of reporting ranged from five to 11 on an 11-point scale; two studies had a score of five or six,[63 144] 15 studies had a score between seven and nine[27 61 64-66 68 76 80-82 92 94 145-147] and 17 studies had a score between 10 and 11.[54 60 67 69 71 74 78 90 95 124 129 130 143 148-151] The external validity of studies ranged from zero to three; most studies had a score of one, eight studies had a score of two,[63 66 74 80 82 130 145 151] four studies had a score of three,[54 67 90 143] and six studies had a score of zero.[78 94 95 146 147 149] The quality of internal validity ranged from five to 12 on a 13-point scale; most studies had a score between nine and 11; one study had a score of five,[144] one study had a score of eight,[27] one study had a score of 10,[151] and two studies had a score of 12.[54 130] A power calculation for the primary outcome was reported for eight studies;[66-68 76 78 82 143 150] four of these had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5 percent,[66-68 150] while four others did not.[76 78 82 143] A power calculation was not provided for one study, but it had sufficient power to detect a clinically important effect

where the probability value for a difference being due to chance is less than 5 percent.[63] See Evidence Table C-3 for a description of design characteristics and overall quality scores of studies relevant to this question of the review.

Primary Analysis. There were few reports of adverse events accompanying melatonin administration. The most common adverse events reported were headaches, dizziness, nausea and drowsiness. In all cases there was no significant differences found between melatonin and placebo despite tight confidence intervals.

There were a total of 33 studies with information on headaches. There was no difference between placebo and melatonin (Risk Difference: 0.00; 95 percent CI: -0.02, 0.02) and heterogeneity was minimal (I^2: 0 percent) (Figure 3-16). The results were similar for dizziness (32 studies; RD: 0.00; 95 percent CI: -0.02, 0.02; I^2: 0 percent) (Figure 3-17), nausea (33 studies; RD: 0.00; 95 percent CI: -0.02, 0.01; I^2: 0 percent) (Figure 3-18) and drowsiness (34 studies; RD: 0.00; 95 percent CI: -0.01, 0.02; I^2: 0 percent) (Figure 3-19).

Subgroup and Sensitivity Analyses. Analyses were performed on the safety outcomes for the following subgroups: gender, age, use of concurrent medications, dosage, duration, patient category, study design, quality score, and allocation concealment score. The homogeneity of the comparisons made all of these analyses irrelevant. For all outcome measures, the calculated risk difference was not significant and the point estimate was never more than a few percentage points from zero. Thus, no change was observed between melatonin and placebo in terms of headaches, dizziness, nausea or drowsiness for different doses of melatonin, type of sleep disorder (or lack thereof), duration of melatonin treatment, or for any other subgroup mentioned above.

Using the Fixed Effect Model in place of the Random Effects Model did not change any of the results due to the homogeneity of studies for all four outcomes.

A sensitivity analysis using only the studies where the specific outcome was mentioned was also performed, and still none of the results were significant. The point estimate for risk difference of headaches between melatonin and placebo included 14 studies and was just a fraction above zero and not significant (RD: 0.00; 95 percent CI: -0.04, 0.05). This estimate had moderate heterogeneity (I^2: 33.9 percent). For dizziness, only four studies were included, and again the results were just above zero and non-significant (RD: 0.03; 95 percent CI: -0.03, 0.09) with moderate heterogeneity (I^2: 36.8 percent). The nausea estimate included five studies and actually favoured melatonin (RD: -0.02; 95 percent CI: -0.05, 0.02), but was also not significant; the heterogeneity was negligible (I^2: 0 percent). Finally, the drowsiness estimate included nine studies with non-significant results that favoured placebo (RD: 0.03; 95 percent CI: -0.05, 0.11). The heterogeneity for this last estimate was substantial (I^2: 57.0 percent).

How do the harms of exogenous melatonin vary based on dose, timing of administration, and patient factors such as gender, age, and ethnicity? How do different formulations of melatonin differ with respect to safety?

There was insufficient information to answer this question in terms of timing of melatonin administration (all studies involved melatonin administration just before bed) and ethnicity (no studies reported information on ethnicity). The sub groupings for dose, gender, age, and formulation are provided in Tables 3-11, 3-12, 3-13 and 3-14 below. It is clear from these tables that there is no evidence that the adverse effects of melatonin change by gender, age, dose or

formulation. This was to be expected as the primary analysis showed that the adverse effects of melatonin were quite minimal.

Results of Qualitative Analysis

What are the various formulations of melatonin? How are the formulations different in terms of content, quality as well as safety and effectiveness? What is the clinical importance of any observed differences?

Eight studies were relevant to this question of the review. Three studies were relevant to the question relating to the effectiveness of melatonin in people with sleep disorders,[58 139 152] six studies were relevant to the question relating to the safety of melatonin,[63 78 80 90 130 143] and one study was relevant to both questions.[90] See Evidence Table C-4 for a description of study design characteristics and quality scores of studies relevant to this question of the review.

An immediate-release formulation was used in one study,[80] a fast-release formulation was used in one study,[143] a slow-release formulation was used in two studies,[57 78] and a controlled-release formulation was used in two studies.[90 130] Haimov et al. [139] compared slow-release and fast-release formulations and Suhner et al.[63] compared fast-release and controlled-release formulations. The content and quality of the formulations used in the studies were not adequately described in the reports of these studies. Thus, the corresponding authors of these studies were contacted for additional information regarding the content and quality of the formulations. To summarize the information that is available, the controlled-release formulation used by Garfinkel et al. [90] was reported to be synthetic and 100 percent pure and the slow-release formulation used by Serfaty et al. [78] was also synthetic. The pharmacokinetics of the slow-release formulation used by Almeida-Montes et al.[57] was also provided: melatonin concentrations in plasma begin to rise 30 minutes following its administration, attain maximal levels 60 minutes following its administration and reach a stable concentration 6 hours following its administration; release is sustained for 8 hours.[57] Smits et al. (2003)[143] and McArthur et al. (1998)[80] reported that the formulations used in their studies contained carboxymethylcellulose and lactose filler, respectively. Given the paucity of information available to us regarding the details of the melatonin formulations used in the various studies relevant to this question of the review, an in-depth comparison of the content and quality of the various formulations that have been used to assess its effectiveness and safety is not possible.

As mentioned in the "Results of Quantitative Analysis" section above, there was insufficient information on the melatonin formulations used in studies involving individuals with sleep disorders to allow a subgroup analysis of the effect of formulation on the effectiveness of melatonin in the treatment of sleep disorders. However, a subgroup analysis of the effect of formulation on the safety of melatonin reveals a lack of evidence showing that the adverse effects of melatonin vary by formulation.

What is the pharmacology of exogenous melatonin, including pharmacokinetics and pharmacodynamics? How is it absorbed, distributed, metabolized, excreted? What blood levels are achieved? What is its half-life? Does it penetrate the blood brain barrier?

Twenty-six studies were relevant to this question of the review. The quality of these studies was assessed using the Downs and Black Checklist[115] with the exception that the power of the

studies to detect a clinically important difference was not assessed. The overall quality score ranged from eight to 21 on a 29-point scale; one study had a score of eight,[153] 10 studies had a score between 10 and 15,[133 134 154-161] 14 studies had a score between 16 and 20,[94 127 162-173] and one study had a score of 21.[137] The quality of reporting ranged from five to nine on an 11-point scale; most studies had a score between seven and nine and six studies had a score of five or six.[133 134 153 156 159 164] Most studies had a score of zero on a three-point scale for external validity and two studies had a score of two.[137 170] The internal validity of studies ranged from three to 11 on a 13-point scale; most studies had a score between seven and nine; five studies had a score between three and six,[133 134 153 158 159] and six studies had a score of 10 or 11.[64 137 162 167 168 170] See Evidence Table C-5 for a description of design characteristics, overall quality scores, and results of studies relevant to this question of the review.

Regarding the pharmacology of exogenous melatonin, the formulation used in the studies was often not reported. Melatonin was administered orally in most studies. The timing of melatonin administration varied across studies, although in many cases, melatonin was administered in the morning. The use of co-medication by study participants was often not specified, and in some cases, participants suffered from a sleep disorder (Evidence Table C-5). Thus, the conditions of the intervention, the characteristics of the population, and the quality of reporting varied across studies relevant to this question of the review, which precluded quantitative pooling of results. Thus, we provide a qualitative synthesis of the evidence pertaining to the pharmacokinetics of exogenous melatonin. The half-life of exogenous melatonin ranged from 0.54 hours (h) to 2h and most studies reported a value between 0.54h and 0.8h. The peak concentration of melatonin achieved in the blood ranged from 14.75pg/ml to 64 730 pg/ml, which reflected a dose range of 0.003mg to 75mg. The time required to reach peak values ranged from 0.25h to 13h and most studies reported a value between 0.5h and 1.0h. The period over which the area under the melatonin versus time curve was calculated varied across studies, precluding both a quantitative and qualitative synthesis of the evidence pertaining to this outcome.

Of the studies that met eligibility criteria for any of the questions of the review involving administration of exogenous melatonin to study participants, none provided a thorough examination of the dose-response relationship of exogenous melatonin with respect to the sleep-related outcomes analyzed in this review. Thus, information on the pharmacodynamics of exogenous melatonin was not available.

Only one study[155] was identified which examined pharmacokinetic characteristics of exogenous melatonin in cerebrospinal fluid (CSF). In this study, a patient with an external CSF drainage device was examined; drainage was required due to a shunt infection. Five milligrams of melatonin was administered at 20:00h. A rapid rise in melatonin levels in the CSF was evident beginning 10 minutes after its administration and melatonin concentrations in CSF peaked within 80 minutes following its administration. The levels of melatonin in CSF declined rapidly over a period of 5 hours.[155] This study provides evidence that exogenous melatonin penetrates the blood-brain-barrier.

The mechanism by which melatonin is absorbed, distributed, metabolized, and excreted in man was not described in the studies that met inclusion criteria for this question of the review.

What is the evidence linking endogenous melatonin to sleep cycles?

A study was considered relevant to this question of the review if it involved an intervention that altered endogenous melatonin levels or the sleep cycle, such as a manipulation of light/dark exposure or the sleep schedule, and it examined either melatonin levels in blood, urine, saliva or CSF or an aspect of the sleep cycle, depending on which intervention was used. That is, if the study intervention was designed to manipulate endogenous melatonin, then it was necessary that the study examine the effect of this manipulation on an aspect of the sleep cycle, and vice-versa. These criteria allow for an understanding of the relationship between endogenous melatonin and the sleep cycle via an assessment of the effect of manipulation of one variable on the other.

Forty-four studies were relevant to this question of the review. The overall quality scores, according to the Down's and Black Checklist, ranged from eight to 23 on a 29-point scale; most studies had a score between 16 and 20, one study had a score of eight,[174] 13 studies had a score between 10 and 15[175-187] and one study had a score of 23.[188] The quality of reporting ranged from three to nine on an 11- point scale; most studies had a score between eight and nine inclusive, three studies had a score between three and five[174 176 180] and 17 studies had a score between six and seven.[175 178 181-187 189-196] The internal validity of the studies ranged from zero to three on a three-point scale; most studies had a score of zero, seven studies had a score of one,[128 191 194 197-200] one study had a score of two[188] and one study had a score of three.[189] The internal validity of studies ranged from five to 12 on a 13-point scale; most studies had a score between seven and nine; three studies had a score of five or six;[174 177 180] three studies had a score of 10 or 11[195 201 202] and one study had a score of 12.[188] For most studies, a power calculation was not reported, however, for one study, a power calculation was reported and the study had sufficient power to detect a statistically significant effect where the probability value for a difference being due to chance was less than 5 percent.[203] See Evidence Table C-6 for a description of design characteristics and overall quality scores of studies relevant to this question of the review.

One of three types of interventions was employed in the studies relevant to this question of the review: manipulation of light/dark exposure, manipulation of the sleep schedule and administration of a tryptophan-free mixture. Here, we provide the results of a qualitative analysis of evidence surrounding the relationship between endogenous melatonin and the sleep cycle according to the various interventions that have been used to manipulate one of the variables of this relationship.

Intervention: manipulation of light/dark exposure

Manipulation of light/dark exposure is designed to alter endogenous melatonin levels. The studies that employed this intervention can be categorized as those involving normal sleepers, people with a sleep disorder and people with a disorder that may or may not be accompanied by a sleep disorder. For most studies, a comparison was made between the effects of light of different intensities on endogenous melatonin and the sleep cycle, with the light of lower intensity serving as a control. The levels of light intensity varied widely across studies, such that a comparison of "bright" and "dim" light involved very different light levels across studies. Here, we use "brighter" to denote the light of higher intensity and "dimmer" to denote the light of lower intensity, for studies in which a comparison was made between the effects of light of different intensities, in order to highlight the fact that these light levels were relative and do not necessarily indicate "bright" or "dim" light in absolute terms.

Normal sleepers. The nature, magnitude, duration and timing of the light stimulus intervention varied across studies. Most studies involved direct application of light of different intensities,[128 176 183 191 194 199 204-209] while others involved application of these signals within the context of a workstation,[192] dawn simulation[179] or video display terminal.[182] Most studies compared the effect of brighter light to the effect of dimmer light,[128 176 179 182 183 191 192 194 199 204-209] while one study compared the effect of light exposure of long duration (16h) to light exposure of short duration (10h),[187] and another compared the effect of evening versus morning brighter light administration.[199] The magnitude of the light stimuli ranged from 0.1 lux to 300 lux for the dimmer light condition and 45 lux to 11000 lux for the brighter light condition, and the duration of light stimuli application ranged from three hours to 36 hours, over hours to weeks. The timing of light administration varied from early morning to late night. Most studies involved ocular light administration, while one study involved extra-ocular light administration applied to the bend of the knee.[128] Some studies involved application of light stimuli under conditions of prolonged sleep deprivation.[183 192 194 204 206 209] (Evidence Table C-6)

In the case of studies in which ocular light stimuli were administered in the evening or night, brighter light (BL) tended to suppress endogenous melatonin levels,[176 182 183 191 192 194 205 206] relative to dimmer light (DL) and one study found a delay in the phase of the melatonin rhythm.[204] The reduction in endogenous melatonin levels with BL was accompanied by no change in[194] or increased[205] sleep onset latency, a smaller and delayed accumulation of REM sleep[176] and increased REM latency[176] and NREM period length,[176] without a change in REM cycle and REM period length.[176] The suppression of endogenous melatonin levels was also accompanied by increased alertness and performance in some studies,[183 191 206] while others found no effect of BL on these variables.[182 192 194] In some studies, the suppression of endogenous melatonin levels and/or the alerting response in the presence of BL only occurred in the early night.[183 206] In the study in which bright light resulted in a delay of the melatonin rhythm, sleep onset was delayed as well.[204] (Table 19)

Three studies involved ocular BL administration during the morning or daytime.[179 207 208] Ocular BL resulted in a phase advance of the melatonin rhythm[179 207] and a suppression of endogenous melatonin levels, [179 208] relative to DL. In a study by Dijk et al., the advance in the melatonin rhythm was accompanied by a reduction in sleep duration and REM sleep, relative to DL;[207] REM latency, percent time spent in the various sleep stages and sleep quality were unaffected by BL, relative to DL.[207] In two studies, the suppression of endogenous melatonin levels with BL was accompanied by increased alertness, relative to DL.[179 208] (Table 20)

In a study by Gordijn et al. in which the effects of morning and evening ocular light exposure were compared, evening light exposure resulted in suppression of endogenous melatonin levels compared to morning light exposure, although the phase of endogenous melatonin was not affected.[199] The changes in endogenous melatonin with evening light exposure were accompanied by greater "movement time", shorter duration of the first REM episode, later time of sleep termination and no change in sleep latency and REM latency, compared to morning BL exposure.[199] In a study by Wehr et al., exposure to a longer photoperiod resulted in a reduction in the duration of the nocturnal endogenous melatonin rhythm, duration of the sleep period and the nocturnal phase of increasing sleepiness, compared to exposure to a shorter photoperiod.[187] Similarly in a study by Daurat et al., light exposure or a light/dark cycle were administered for 36 hours during sleep deprivation and no difference was found in endogenous melatonin levels or in total sleep time, REM latency, WASO and REM sleep.[209] In a study by Lushington et al. in

which light stimuli were administered behind the knee, BL did not affect endogenous melatonin, however, it resulted in increased wakefulness, relative to DL.[128] (Table 13-17)

Five of the studies included in this analysis conducted an analysis of the correlation between endogenous melatonin and the sleep cycle.[179 191 194 204 207] In the study by Kubota et al., no correlation was found between change in phase of the melatonin rhythm and change in sleep onset with BL administration,[204] while in the study by Cajochen et al., the alerting response to BL was positively correlated with the degree of suppression of endogenous melatonin levels by BL.[191] Similarly, in the study by Danilenko et al.,[179] the phase of the melatonin rhythm was correlated to sleepiness and midpoint of sleep, while in the study by Dijk et al., no correlation was found between phase of the melatonin rhythm and sleep duration.[207] Lastly, in the study by Lavoie et al., none of the vigilance variables were found to correlate to endogenous melatonin levels.[194] (Tables 3-15, 3-16, 3-17)

People with a Sleep Disorder

A number of studies in this category examined the relationship of endogenous melatonin and the sleep cycle and these differed in many aspects of study design. Many studies involved shift workers,[174 178 190 193 195 210 211] while others involved people with delayed sleep phase syndrome[188 189] or people who suffer from jet-lag.[197] Most studies involving night-shift workers employed light stimuli during the night-shift,[174 178 190 193 210 211] although one study employed the stimuli, after the night-shift.[195] While most studies involved application of light stimuli while participants were awake, one study involved administration of light stimuli during sleep, through closed eyelids.[188] All studies involved direct application of brighter or dimmer/control light stimuli, and while most studies compared brighter versus dimmer light effects on endogenous melatonin and the sleep cycle,[174 178 188-190 193 195 197 210] one study examined the effect of the frequency of light stimulation on these variables.[211] The intensity of the light stimuli ranged from 0.1 lux to 1500 lux for dimmer/control light administration and 660 lux to 12 000 lux for BL administration. The duration of application of light stimuli ranged from two to 12 hours, over hours to weeks. (Evidence Table C-6)

In the case of studies involving administration of light stimuli to night-shift workers during the night shift and comparing BL to DL/control, many studies found that BL resulted in a greater phase delay in endogenous melatonin from baseline measurements compared to dimmer light/control.[174 193 210] While one study found a suppression of endogenous melatonin levels with BL administration, compared to DL administration,[190] another study found no change in endogenous melatonin levels following BL administration, compared to DL administration.[178] Of the studies that reported alterations in endogenous melatonin with BL administration, the effects of BL on the sleep cycle were varied. While one study reported no effect of BL on sleep start time and sleep wake time,[193] another reported no effect of BL on total sleep time,[190] and yet another study reported greater sleep time and sleep continuity and no change in sleep latency with BL administration.[210] While most studies found that BL increased alertness and performance,[174 190 193 210] another did not find such an effect.[178] In a study by Ross et al., light stimuli were administered for 2h daily for one week after night shift work; the DL group readapted slightly, but faster than the BL group after the night shift. Moreover, the BL exposure resulted in a reduction in sleep latency but had no effect on sleep duration, sleep quality, night awakenings or mood, compared to DL exposure.[190] In a study by Boulos et al, participants were administered light stimuli on the first two evenings after a flight from Zurich to New York.

Although BL treatment resulted in a greater delay in endogenous melatonin secretion compared to DL, there were no differences between the two groups in sleep efficiency, sleep quality, daytime sleepiness, jet-lag severity or mood.[197] In another study involving night-shift and examining the effect of various cycles of light exposure on endogenous melatonin and the sleep cycle, 3 or 5 cycles of BL administration were not different in their effects on the phase of the melatonin rhythm nor on sleep quality, performance, or subjective feelings of tiredness.[211] (Table 22)

Two studies involving application of light stimuli to individuals with delayed sleep phase syndrome found no effect of BL on the phase of the endogenous melatonin rhythm nor on mood,[188 189] total sleep period,[189] total sleep time,[188 189] morning sleepiness,[197] or sleep quality,[188] relative to DL. (Table 22)

In the study by Boulos et al., no correlation was found between dim light melatonin onset and performance following the BL intervention.[197] (Table 22)

People with a Disorder that may or may not be Accompanied by a Sleep Disorder.

Two studies examined the effect of light on individuals with seasonal affective disorder (SAD) and found no effect of BL on either levels[203] or timing[201] of endogenous melatonin secretion, compared to DL. These results were accompanied by a lack of effect of BL on mood,[201] alertness,[201] sleepiness,[203] total sleep duration,[201] time of awakening,[201] and sleep onset,[201] compared to DL. In a similar study, BL resulted in a greater phase advance of endogenous melatonin compared to DL and this effect was accompanied by an earlier tendency for sleep termination and no change in accumulation of wakefulness.[212] In the study by Gordijn et al., no correlation was found between changes in phase of endogenous melatonin and wake-up time.[212] (Table 23)

Intervention: manipulation of the sleep schedule

Manipulation of the sleep schedule is designed to affect the sleep cycle. The majority of studies in this category examined the effect of alterations in the sleep schedule in normal sleepers,[177 180 181 184 186 198 200 202 213-217] although one study examined the effect of this type of intervention on both normal sleepers and depressed individuals (who may have an accompanying sleep disorder).[185] While many studies assessed the effect of prolonged sleep deprivation on endogenous melatonin,[181 185 198 202 213 214 216] others assessed the effect of partial sleep deprivation,[200] sleep restriction[177 180] or sleep period advance/delay[184 186 215 217] on endogenous melatonin. (Evidence Table C-6)

The results of the various studies in this category are inconsistent. For example, of the studies examining the effect of prolonged sleep deprivation on normal sleepers, endogenous melatonin was found to increase in some studies,[198 214] decrease in another study[202] or remain unchanged in other studies[181 185 213 216] during or after periods of sleep deprivation. In a study by Redwine et al., sleep deprivation of normal sleepers during the early night did not affect endogenous melatonin levels during either the early or late parts of the night.[200]

Of the studies examining the effect of sleep restriction regimens on endogenous melatonin, one study examined the effect of timing of napping in darkness on endogenous melatonin and found that morning napping resulted in a phase delay of endogenous melatonin, while afternoon napping did not affect the phase of endogenous melatonin.[177] In a similar study, the sleep restriction regimen involved either a short nap during the night or a short nap during the night accompanied by a short nap during the late afternoon. The sleep restriction conditions resulted in a phase delay of endogenous melatonin with continued elevation of melatonin levels at the end

of the nocturnal secretory phase.[180] It is important to note that changes in napping patterns would change patterns of light exposure, which itself, could have affected endogenous melatonin in these studies, depending on the timing of naps in relation to the endogenous melatonin rhythm.

Four studies examined the effect of sleep period advance/delay on endogenous melatonin.[184 186 215 217] In a study by Weibel et al., day-active study participants were subjected to an acute shift of their sleep period to daytime; endogenous melatonin was not affected by this shift.[215] Jelinkova-Vondrasova et al. reported a phase advance of one hour within six days of the endogenous melatonin rhythm following a three hour advance of the sleep period and a phase delay of one hour in six days following a subsequent three hour delay of the sleep period.[184] In a similar study, when the sleep/wake cycle was shortened by one hour per day, the melatonin rhythm did not achieve complete adjustment within the period of investigation, and when the time shift was reversed by a seven hour delay within two days, resynchronization was achieved satisfactorily only within seven days.[186] In a study by Danilenko et al, a two-hour phase advance of the sleep period resulted in a small advance in the endogenous melatonin rhythm.[217]

Intervention: administration of a tryptophan-free mixture

In these types of studies, administration of a tryptophan-free mixture was designed to reduce endogenous melatonin levels. In a study by Arnulf et al., administration of a tryptophan-free mixture mid-morning, which resulted in reduced serum tryptophan, did not alter endogenous melatonin levels, mood, sleep latency, total sleep time, total sleep duration, duration of wakefulness after sleep onset, stages one-two and three to four of NREM sleep and REM sleep, but did result in increased REM latency.[175]

Summary: Endogenous melatonin and the sleep/wake cycle

To summarize, our literature review indicated a link between endogenous melatonin and the sleep cycle. A key result was that a decrease in endogenous melatonin levels was often accompanied by increased latency to sleep and decreased duration of sleep, as well as increased vigilance and performance during waking hours. In addition, changes in the rhythm of endogenous melatonin were often accompanied by changes in the sleep rhythm.

What are the basic mechanisms by which melatonin produces sleepiness?

None of the studies identified through our search met our initial inclusion criteria for this question of the review, namely, that the study characterize and/or evaluate a mechanism by which melatonin produces sleepiness in humans. Thus, the inclusion criteria for this question of the review were revised; a study was considered relevant to this question of the review if it fulfilled the inclusion criteria of the question relating to the effect of melatonin in normal sleepers and the question relating to the effect of melatonin in people with sleep disorders, and the report provided a proposed mechanism by which melatonin produces sleepiness, based on findings of the study. Eleven studies met the revised inclusion criteria for this question of the review. See Evidence Table C-7 for a description of study design characteristics and overall quality scores of these studies.

The mechanisms by which melatonin induces sleepiness in humans have not been fully elucidated. However, a number of hypotheses exists: 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 areas of the brain. Studies of the effects of melatonin in humans have led to postulates of the mechanism of action of melatonin that either favour or refute one or a number of the current hypotheses of the mechanism by which melatonin promotes sleepiness.

A number of investigators that have been involved in studies of the effect of melatonin on people with sleep disorders have supported the notion that melatonin induces sleepiness through a re-entrainment of the endogenous circadian pacemaker and not through a direct action on somnogenic structures of the brain.[65 74 152] In one case, this conclusion was based on findings that melatonin advanced sleep onset time without increasing sleep duration,[74] while in another case it was based on findings that melatonin did not affect polysomnographic and subjective measures of sleep quality[152] and in yet another case was based on findings that melatonin did not affect sleep duration.[65] By contrast, others have proposed that the sleep-inducing effects of melatonin may not be mediated by a shift of the endogenous circadian oscillator and may be due to direct actions of the hormone, based on findings that melatonin improved the quality of sleep and increased its duration without affecting either sleep onset time or sleep latency.[70] Andrade et al. have concluded that melatonin is not a sedative/hypnotic, based on findings that evening melatonin administration advanced sleep onset without producing drowsiness or hangover effects the next day.[54] Edwards et al. drew the same conclusion based on the finding that melatonin had no significant effect on the ease of getting to sleep or the number of waking episodes in jet-lag sufferers.[218]

A number of investigators that have been involved in studies of the effect of melatonin on normal sleepers have supported the hypothesis that melatonin promotes sleepiness via a direct action on somnogenic structures of the brain.[92 123 219 220] Zhdanova et al. proposed that their findings of decreased sleep onset latency and latency to stage two sleep with evening administration of melatonin is mediated by a direct action of melatonin rather than via a biological timing mechanism.[220] In a study by Terlot et al.,[219] afternoon administration of melatonin resulted in increased feelings of sleepiness, fatigue and confusion and decreased feelings of vigor and concentration, leading the investigators to argue that since the effects of afternoon administration of melatonin were similar to those observed with comparable doses administered at noon or in the evening, the effects of melatonin are not-time dependent and, therefore, may not be mediated by a phase-shifting effect on the endogenous circadian clock.[219] In a study by Matsumoto et al., morning administration of melatonin was found to increase sleep duration in diurnal sleep, without affecting rectal temperature during this sleep. Based on these results, the investigators suggested that melatonin has a direct hypnotic effect on diurnal sleep.[92] Satomura et al. supported the latter notion based on findings that daytime administration of melatonin resulted in increased sleep duration and efficiency and, in the case of the higher dose of melatonin, a lack of a hypothermic effect.[123]

In a study by Mishima et al., morning administration of 9 mg of melatonin to normal sleepers had a hypnotic effect, while 3 mg of melatonin did not have this effect. However, both doses induced the same degree of body temperature suppression and the hypnotic effect of exogenous melatonin was sustained during a period when serum melatonin levels and body temperature had returned to physiological values. These findings led the investigators to support the hypothesis that the sleep-inducing action of melatonin is likely not mediated by suppression of body temperature.[221] In a study by Holmes et al., afternoon administration of melatonin to normal sleepers resulted in a reduction in sleep onset latency and an accompanying decrease in core body temperature, leading the investigators to suggest that the sleep-promoting property of melatonin may involve modulation of core body temperature.[222]

How is endogenous melatonin involved in circadian rhythms?

The scope of this question was limited to an analysis of how endogenous melatonin is involved in the temperature rhythm. The analysis of evidence relevant to this question was approached in a similar manner as for the question relating to the link between endogenous melatonin and the sleep cycle, in that we addressed the link between endogenous melatonin and the temperature rhythm. A study was considered relevant to this question of the review if it involved an intervention that altered endogenous melatonin levels or the temperature rhythm, such as a manipulation of light/dark exposure or body temperature, and it examined either melatonin levels in blood, urine, saliva or CSF or an aspect of the temperature rhythm, depending on which of these variables was manipulated. Thus, if the study intervention was designed to manipulate endogenous melatonin, then it was necessary that the study examine the effect of this manipulation on an aspect of the temperature rhythm, and vice-versa. These criteria allow for an understanding of the relationship between endogenous melatonin and the temperature rhythm via assessment of the effect of manipulation of one variable on the other.

Twenty-four studies were relevant to this question of the review. The overall quality score, based on the Downs and Black Checklist, ranged from 11 to 19 on a 29-point scale; most studies had a score between 16 and 19 and eight studies had a score between 11 and 15.[176 178 179 182 183 223-225] The quality of reporting ranged from five to nine on an 11-point scale; one study had a score of 5,[176] 11 studies had a score of six or seven[178 182 183 189 191 193 194 223-226] and 12 studies had a score between eight and nine.[128 179 199 204-206 208-210 212 227 228] The external validity of studies ranged from zero to three on a three-point scale; most studies had a score of zero, four studies had a score of one[128 191 194 199] and one study had a score of three.[189] The internal validity of studies ranged from five to nine on a 13-point scale; most studies had a score of eight or nine, two studies had a score of five or six[179 224] and two studies had a score of seven.[176 225] None of the studies relevant to this question of the review reported a power calculation or addressed whether the study had sufficient power to detect a clinically significant effect where the probability value for a difference being due to chance was less than 5 percent. See Evidence Table C-8 for a description of design characteristics and overall quality scores of studies relevant to this question of the review.

One of two types of interventions was employed in the studies relevant to this question of the review: manipulation of light/dark exposure or manipulation of body temperature. Here, we provide the results of a qualitative analysis of evidence surrounding the relationship between endogenous melatonin and the temperature rhythm according to the interventions that have been used to manipulate one of the variables of this relationship.

Intervention: manipulation of light/dark exposure

The studies that employed this intervention can be categorized as those involving normal sleepers, people with a sleep disorder and people with a disorder that may or may not be accompanied by a sleep disorder. For most studies, a comparison was made between the effects of light of different intensities on endogenous melatonin and the temperature rhythm, with the light of lower intensity serving as a control. The levels of light intensity varied widely across studies, such that a comparison of "bright" and "dim" light involved very different light levels across studies. Here, we use "brighter" to denote the light of higher intensity and "dimmer" to denote the light of lower intensity, for studies in which a comparison was made between the

effects of light of different intensities, in order to highlight the fact that these light levels were relative and do not necessarily indicate “bright” or “dim” light in absolute terms.

Normal Sleepers. The nature, magnitude, duration and timing of the light stimulus intervention varied across studies. Most studies involved direct application of brighter (BL) or dimmer (DL) stimuli,[128 176 183 191 194 199 204-206 208 209 223-225 228] while others involved application of these signals within the context of dawn simulation[179] or a video display terminal.[182] Most studies compared the effect of BL to DL,[128 176 179 182 183 191 194 199 204-206 208 223-225 228] while one study compared the effect of evening versus morning BL administration.[199] The magnitude of the light stimuli ranged from 0.1 lux to 200 lux for DL administration and 45 lux to 13 000 lux for BL administration and the duration of light stimuli application ranged from 2 to 36 hours, over hours to weeks. The timing of light administration varied from early morning to late night. Most studies involved ocular light administration,[176 179 182 183 191 194 199 204-206 208 209 223 225 228] while two studies involved extra-ocular light administration applied to the bend of the knee.[128 224] Some studies involved application of light stimuli under conditions of prolonged sleep deprivation.[183 194 204 206 209 224 225 228] (Evidence Table C-8)

Most studies involved application of light stimuli during the evening or night,[128 176 182 183 191 194 204-206 223-225] while some studies involved light exposure during the morning or night,[199] morning,[179] daytime[208] or during a prolonged period of sleep deprivation.[209 228] Of the studies involving application of ocular light stimuli during the evening or night, some studies found that BL delayed the onset of endogenous melatonin secretion, relative to DL[204 223] and all studies found that BL suppressed endogenous melatonin levels, relative to DL. The delay in the phase of the melatonin rhythm was accompanied by a delay in the core body temperature rhythm in one study,[204] while the change in phase of the melatonin rhythm was not accompanied by a change in the value or timing of the core body temperature minima in another study.[223] Of the studies that found a suppression of endogenous melatonin levels with BL, many studies found an accompanying increase in core body temperature,[176 182 194 205 206] while one study found no change in core body temperature.[191] In a study by Strassman et al., the suppression of endogenous melatonin levels was accompanied by an increase in minimum rectal temperature and no change in the maximum rectal temperature,[225] while in a study by Daurat et al., the suppression of endogenous melatonin levels was accompanied by a reduction and delay in the temperature minimum.[206] In studies by Horne et al. and Bunnell et al., the suppression of endogenous melatonin was not accompanied by any change in oral temperature[183] or tympanic temperature.[176] In a study by Wright et al., whereby light exposure occurred during a 45-hour period of sleep deprivation, BL resulted in suppression of endogenous melatonin levels accompanied by increased body temperature, relative to DL.[228] In a similar study by Daurat et al., whereby either BL or a light/dark cycle were imposed on subjects for 36 hours during sleep deprivation, there were no differences in endogenous melatonin levels between conditions. However, during one of the follow-up nights, the BL group showed increased rectal temperature compared to the light/dark group, although the phase of the temperature rhythm was not different.[209] In a study by Lushington et al., BL administered behind the knee during the daytime did not have an effect on endogenous melatonin or the phase of nocturnal core body temperature, relative to DL administration.[128] In a similar study, extra-ocular light exposure in the evening did not affect either the phase of the melatonin rhythm or core body temperature.[224] In a study by Gordijn et al., the application of light stimuli in the evening resulted in the suppression of endogenous melatonin levels during the early evening, without a change in the phase of the melatonin rhythm, compared to morning light exposure. This effect was

accompanied by increased body temperature without a change in the phase of the temperature rhythm.[199] In a study by Wakamura et al., ocular light stimuli were administered during the daytime and resulted in a suppression of endogenous melatonin levels, which was accompanied by a reduction in minimum core body temperature, no change in maximum core body temperature and an advance of the core body temperature rhythm.[208] (Table 24)

In a study by Danilenko et al., morning BL exposure suppressed endogenous melatonin levels, and the phase shift in the melatonin rhythm (DLMOn and DLMOff) was correlated with the phase shift in the temperature rhythm.{Danilenko, Wirz-Justice, et al. 2000 #22510} By contrast, in a study by Kubota et al., a correlation was not found between the change in phase of the melatonin rhythm and that of the temperature rhythm, following BL administration.[204] (Table 25)

People with a Sleep Disorder. A number of studies in this category involved shift workers,[178 193 210] while another study involved people with delayed sleep phase syndrome.[189] In the case of all studies involving night-shift workers, light stimuli were administered during the night-shift,[178 189 193 210] and in the case of the study involving people with delayed sleep phase syndrome light stimuli were administered in the early morning.[189] The magnitude of the light stimuli ranged from 0.1 lux to 300 lux for dim/control light administration and 400 lux to 4300 lux for BL administration. The duration of light stimuli application ranged from 4 periods of 40-minute exposures to an entire night-shift, over hours to days. All studies involved ocular light administration. (Evidence Table C-8)

Of the studies involving night-shift work,[178 193 210] BL delayed the melatonin rhythm in two studies[193 210] and had no effect on endogenous melatonin levels in another study,[178] relative to DL. Moreover, while the delay in the melatonin rhythm was accompanied by a phase delay in core body temperature in one study,[193] it was not accompanied by a change in the temperature rhythm in another study.[210] The lack of effect of BL on endogenous melatonin levels, relative to DL, in the study by Costa et al., was paralleled by a lack of effect on the temperature rhythm.[178] (Table 26)

In a study by Ando et al., patients with delayed sleep phase syndrome received either 500 lux for three hours over 12 days prior to awakening or 0.1 lux of the same timing. BL had no significant effect on the phase of either the melatonin or temperature rhythm, compared to DL.[189]

People with a Disorder that may or may not be Accompanied by a Sleep Disorder. One study involved application of either morning or evening light to people with non-seasonal depression. Morning administration of light resulted in a phase advance of both the melatonin and temperature rhythms compared to evening light administration.[212] Moreover, no correlation was found between the shifts in the phase of the melatonin and temperature rhythms.[212]

Intervention: manipulation of body temperature

In a study by Fletcher et al., participants were exposed to heat of 32V, 138W from 0230h until termination of the sleep period. Heating induced an increase in core body temperature, without an effect on endogenous melatonin levels.[227] In a similar study, participants were exposed to light of different color temperature and the light of higher color temperature was found to increase core body temperature and decrease endogenous melatonin levels.[226]

Summary: Endogenous melatonin and the temperature rhythm

To summarize, our literature review indicated evidence of a link between endogenous melatonin and the temperature rhythm. Specifically, a reduction in endogenous melatonin levels

was often accompanied by an increase in core body temperature, and a shift in the rhythm of endogenous melatonin was often accompanied by a similar shift in the rhythm of core body temperature.

How do the benefits and harms of melatonin compare to those of other approved pharmacological treatments for sleep disorders?

Only four studies compared the effects of melatonin to other pharmacological treatments for sleep disorders in terms of sleep variables; three of these involved normal sleepers[123 222 229] and one of these involved people suffering from jet-lag.[61] The overall quality score, according to the Down's and Black Checklist, ranged from 11 to 20 on a 29-point scale and the quality of reporting ranged from four to eight on an 11-point scale. The external validity of studies ranged from zero to one on a three-point scale; two studies had a score of zero[123 229] and two studies had a score of one.[222 230] The internal validity of studies ranged from seven to 11 on a 13-point scale; two studies had a score of seven,[123 229] one study had a score of eight[222] and one study had a score of 11.[61] For none of the studies was a power calculation reported. See Evidence Table C-9 for a description of design characteristics and overall quality scores of studies relevant to this question of the review.

Of the studies involving normal sleepers, two studies compared the effects of melatonin and triazolam,[123 229] while another study compared the effect of melatonin and zopiclone,[222] on sleep variables. In a study by Satomura et al., participants received either 1, 3 or 6 mg melatonin or 0.125 mg triazolam at 13:30h; there were no differences in the effect of the two agents on total sleep time, sleep efficiency, and REM latency. Melatonin decreased sleep onset latency to a greater extent than triazolam, however, the effect of these compounds on sleep onset latency was not significantly different from placebo. The authors did not report on adverse events or adverse effects of the two agents, precluding a comparison of the harms of these agents.[123] In a similar study by Ferini-Strambi et al., participants received either 100 mg melatonin or 0.125 mg triazolam at 22:30h; there were no differences in the effect of the two agents on total sleep time, sleep onset latency, wakefulness after sleep onset, sleep efficiency, number of awakenings, percent time spent in the various sleep stages, REM latency and REM periods. As in the study by Satomura et al., the authors did not report on adverse effects of the two agents, precluding a comparison of the harms of these agents.[229] In a study by Holmes et al., normal sleepers received either 5mg melatonin or 7.5mg zopiclone at 14:00h and sleep onset latency was assessed hourly from 11:00h to 20:00h using a modified multiple sleep latency test. Zopiclone reduced sleep onset latency to a greater extent than melatonin at 15:00h and from 17:00h to 19:00h. The authors did not report on adverse events or adverse effects of the two agents.[222]

In a study comparing melatonin and zolpidem, air travellers, crossing six to nine time-zones, received either 5mg melatonin or 10mg zolpidem on an eastbound return flight to Switzerland and once daily at bedtime on four consecutive days after the flight.[61] The agents did not differ in their effects on total sleep time, sleep latency, number of awakenings, wakefulness after sleep onset and overall sleep quality during the flight. Moreover, the agents did not differ in overall sleep quality, sleep onset latency, number of awakenings and wakefulness after sleep onset across the four nights following the flight. When subjects were asked to rate the effectiveness of their study medication in alleviating jet-lag, the responses did not differ between agents. In general, out of the 35 people taking melatonin, only one person reported adverse events, while six people out of 34 people taking zolpidem reported adverse events. The individual taking

melatonin who reported adverse events suffered from insomnia and palpitations. Of the individuals taking zolpidem who reported adverse events, four people reported nausea, two people reported vomiting, two people reported confusion, one person reported dizziness, two people reported headache, one person reported lack of concentration, one person reported amnesia, one person reported trembling, one person reported agitation, one person reported palpitation, one person reported difficulties in articulation and one person reported dry mouth.[61]

Overall Grade of Evidence Pertaining to Effectiveness and Safety of Melatonin

The source of funding was either not reported or unclear for the majority of studies relevant to the questions relating to the effectiveness of melatonin in people with sleep disorders and the safety of melatonin. Of the studies for which the source of funding was described, most studies received public sources of funding. For studies in which there was a discrepancy in the number of participants enrolled in the study and the number of participants for whom data was analyzed, the planning or conduct of an intention-to-treat analysis was reported in only two studies relevant to the question relating to the effectiveness of melatonin in people with sleep disorders [78 144] and two studies relevant to the question relating to the safety of melatonin.[78 135] The overall evidence surrounding the effectiveness of melatonin for treatment of sleep disorders and the safety of melatonin was graded using the framework of the Oxford Centre for Evidence-based Medicine (Table 27). The evidence surrounding the effectiveness of melatonin for the treatment of sleep disorders receives a grade of "A" and a level of evidence designation of "1b". The evidence surrounding the safety of melatonin receives a grade of "B" and a level of evidence designation of "2b".

Flow Diagram 2: Study Retrieval and Selection for Melatonin and Sleep Disorders Review

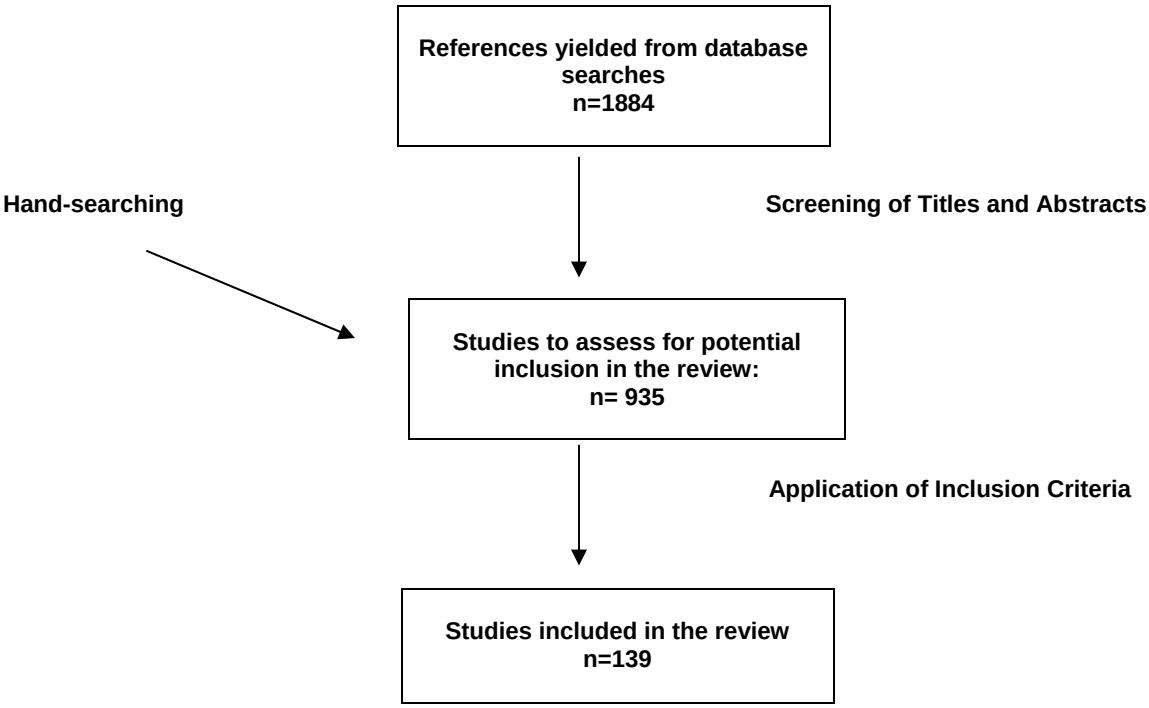


Figure 1: Meta-Graph: Sleep Onset Latency in Normal Sleepers

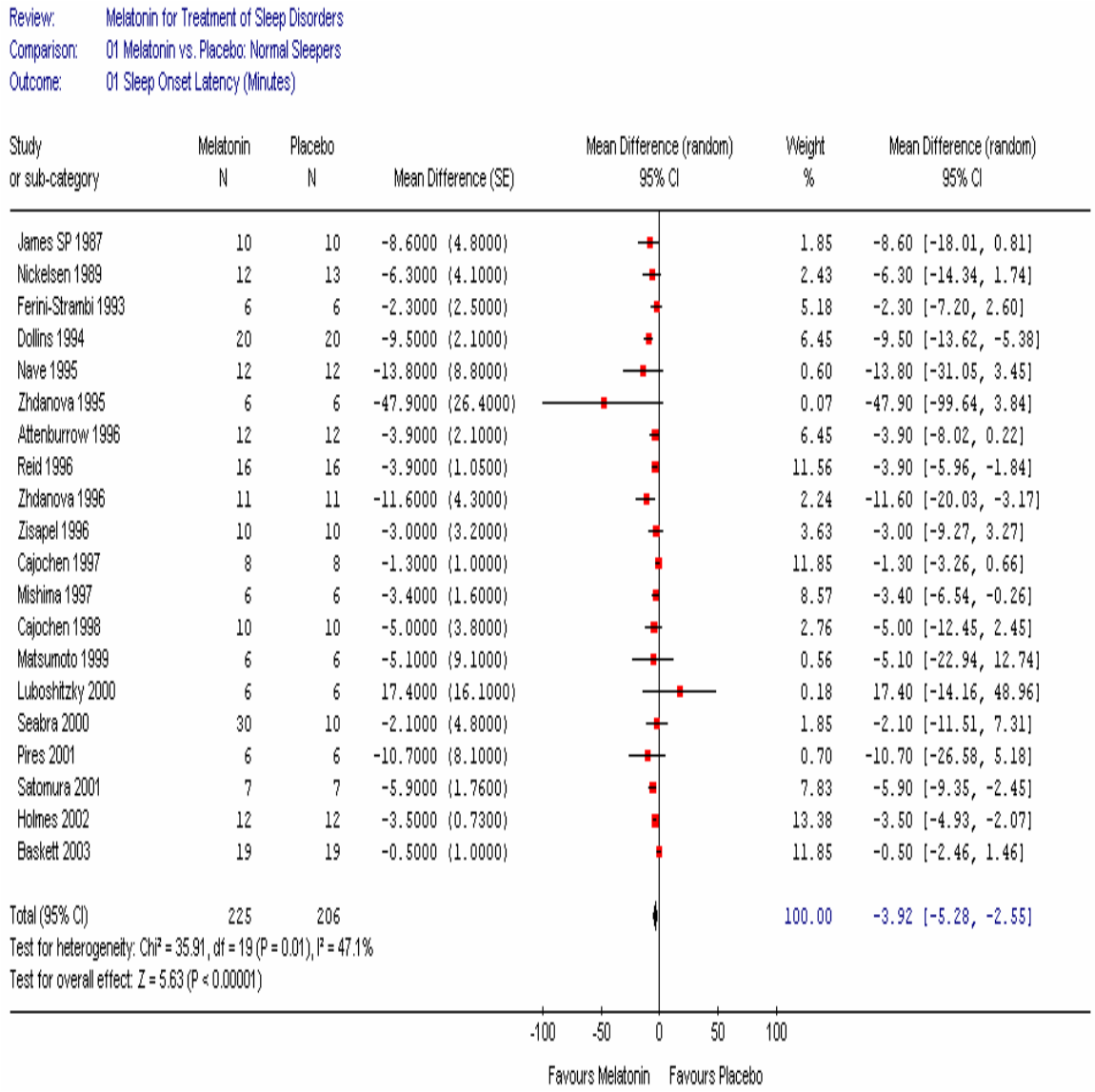
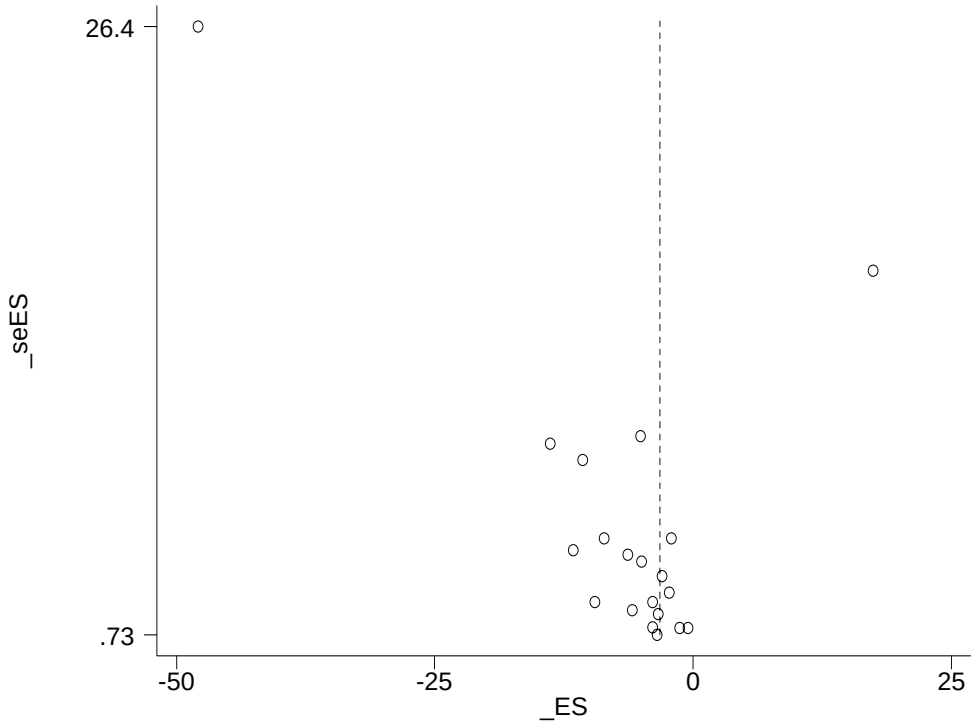


Figure 2: Funnel Plot: Sleep Onset Latency in Normal Sleepers



Abbreviations: _**ES**: effect size, _**seES**: standard error of effect size; note that the smaller studies are associated with a larger standard error.

Figure 3: Meta-Graph: Sleep Efficiency in Normal Sleepers

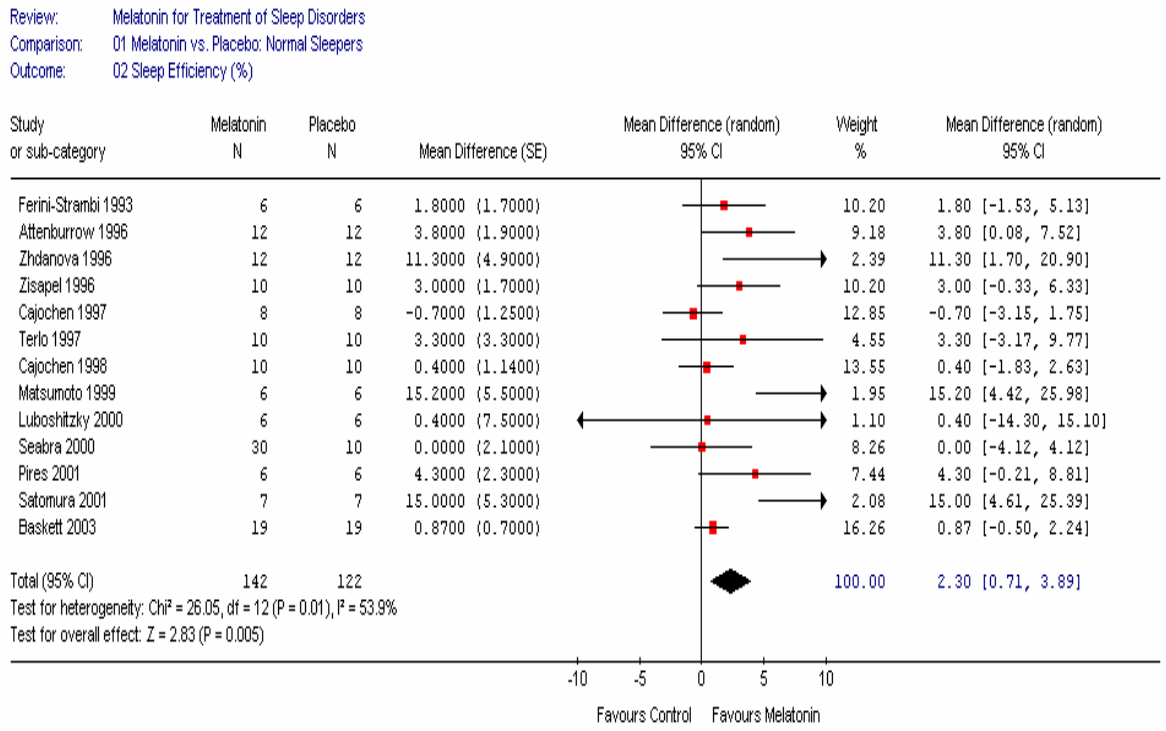
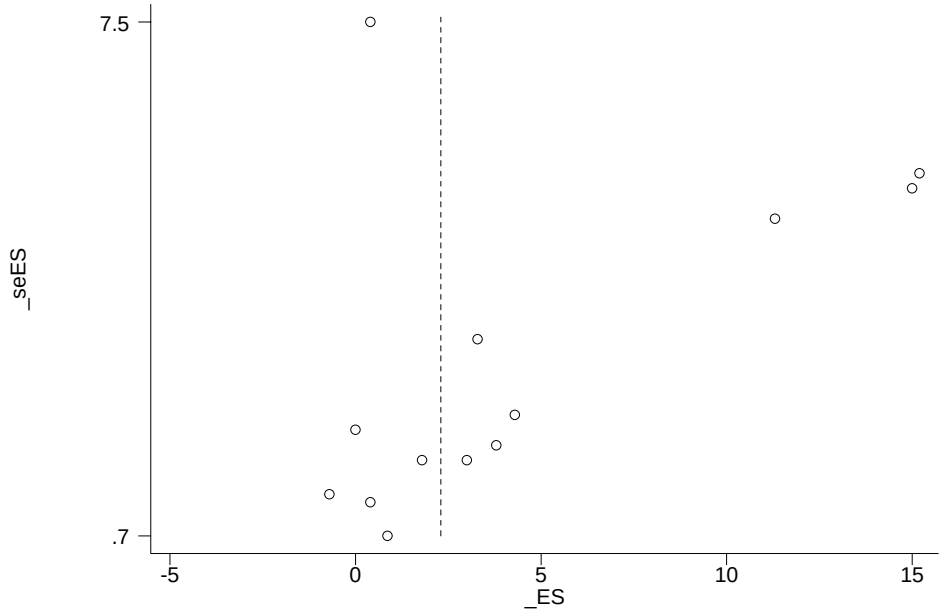


Figure 4: Funnel Plot: Sleep Efficiency in Normal Sleepers



Abbreviations: _**ES**: effect size, **_seES**: standard error of effect size; note that the smaller studies are associated with a larger standard error.

Figure 5: Meta-Graph: REM Latency in Normal Sleepers

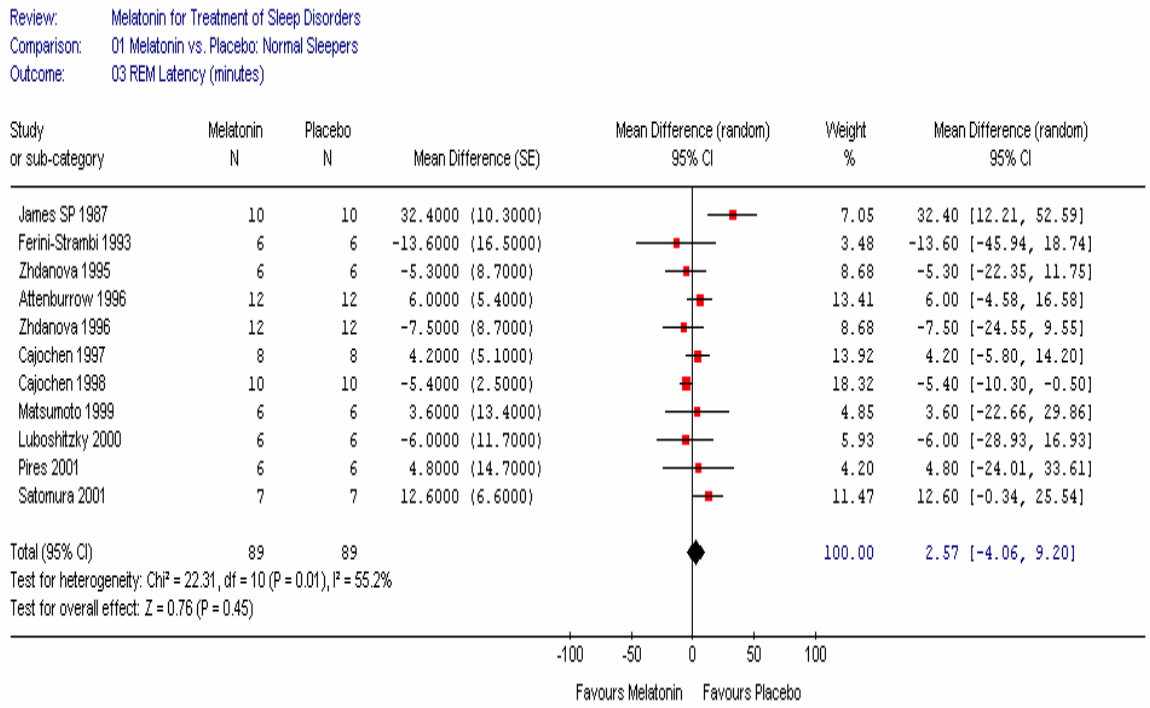
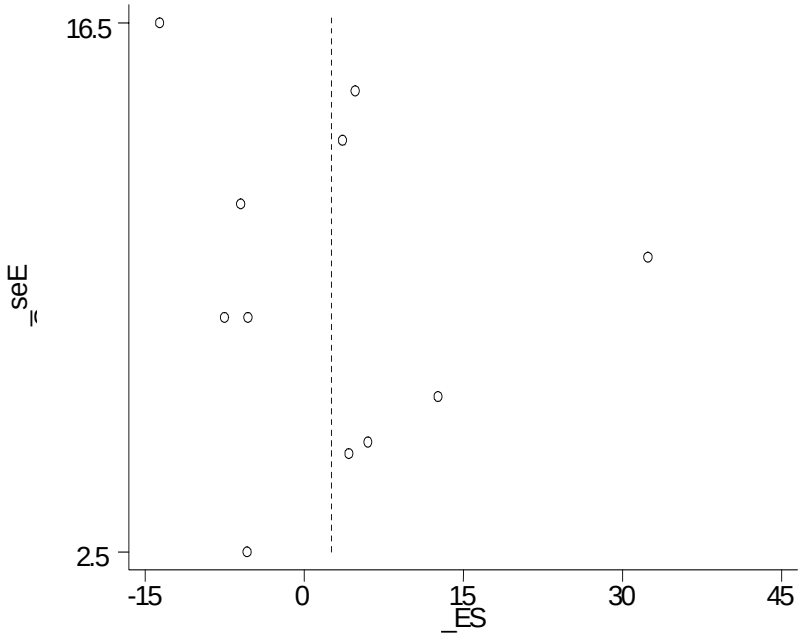


Figure 6: Funnel Plot: REM Latency in Normal Sleepers



Abbreviations: _**ES**: effect size, _**seES**: standard error of effect size; note that the smaller studies are associated with a larger standard error.

Figure 7: Meta-Graph: Sleep Onset Latency in People with a Primary Sleep Disorder

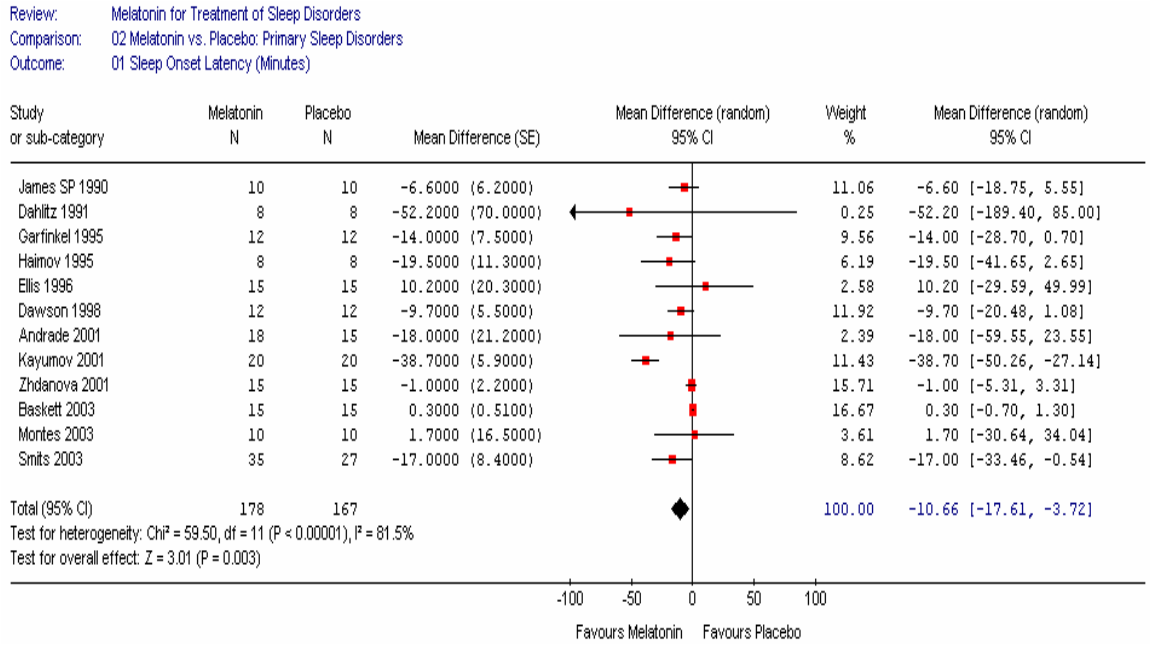
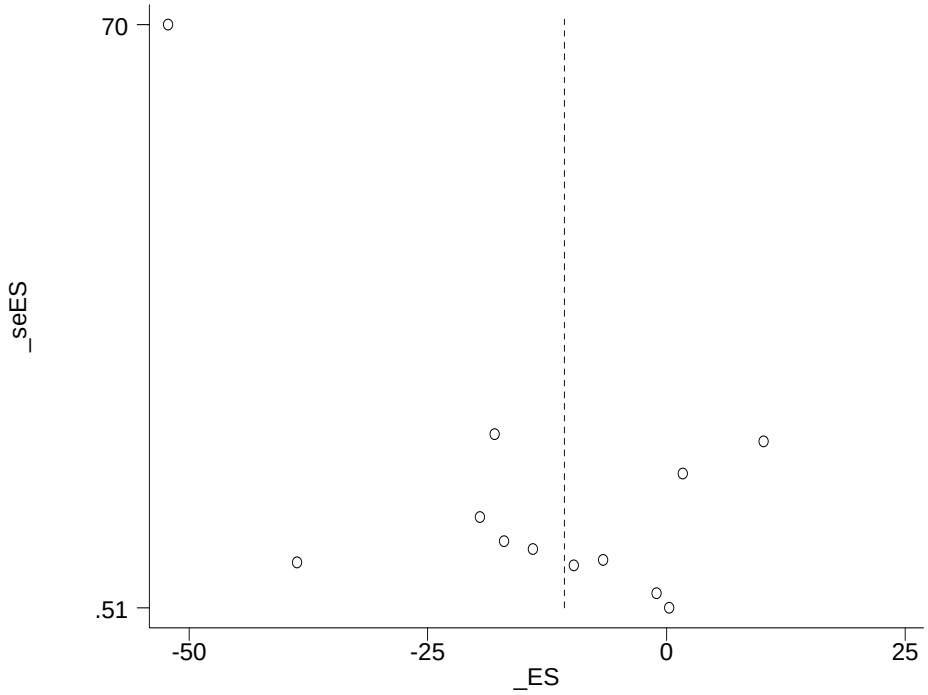


Figure 8: Funnel Plot: Sleep Onset Latency in People with a Primary Sleep Disorder



Abbreviations: _**ES**: effect size, _**seES**: standard error of effect size; note that the smaller studies are associated with a larger standard error.

Figure 9: Meta-Graph: Sleep Efficiency in People with a Primary Sleep Disorder

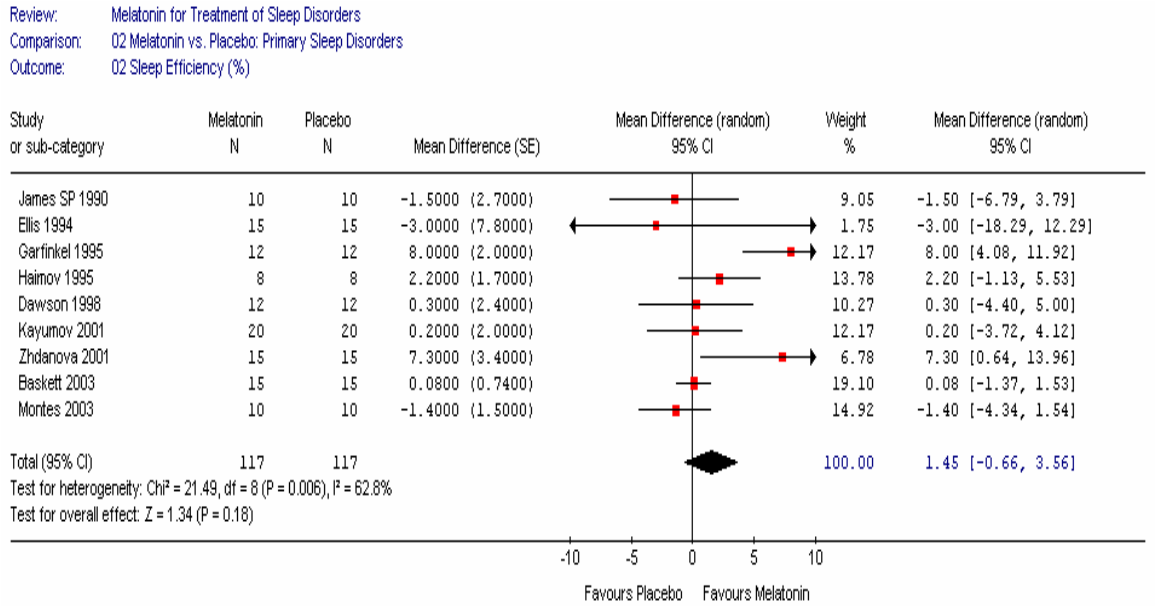
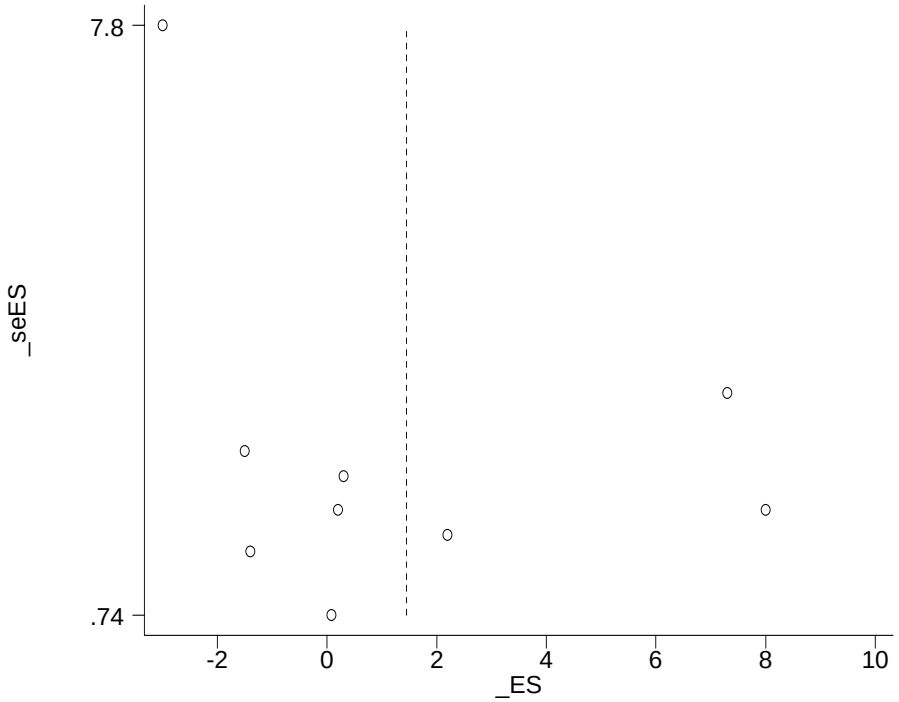


Figure 10: Funnel Plot: Sleep Efficiency in People with a Primary Sleep Disorder



Abbreviations: **_ES**: effect size, **_seES**: standard error of effect size; note that the smaller studies are associated with a larger standard error.

Figure 11: Meta-Graph: Sleep Onset Latency in People with a Secondary Sleep Disorder

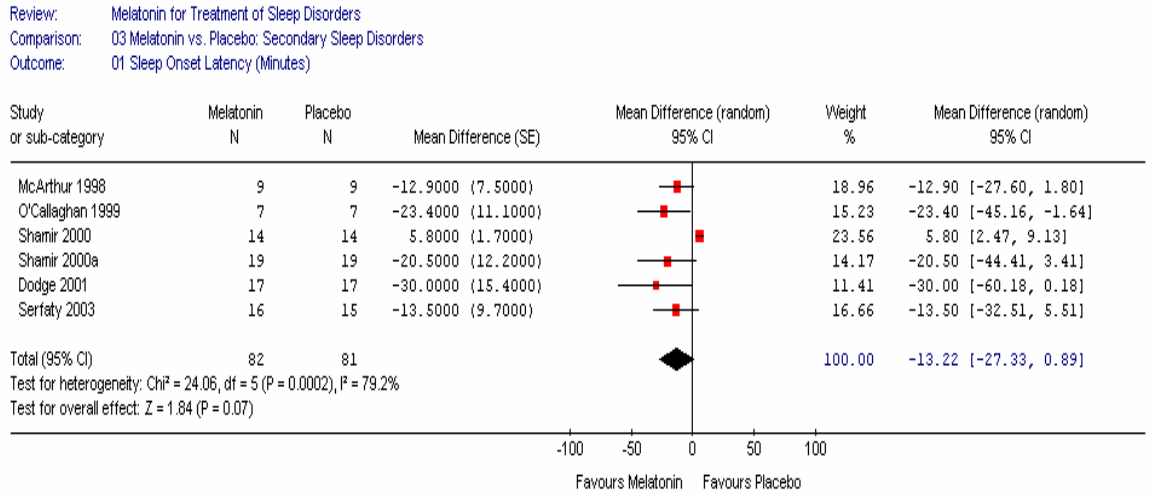


Figure 12: Meta-Graph: Sleep Efficiency in People with a Secondary Sleep Disorder

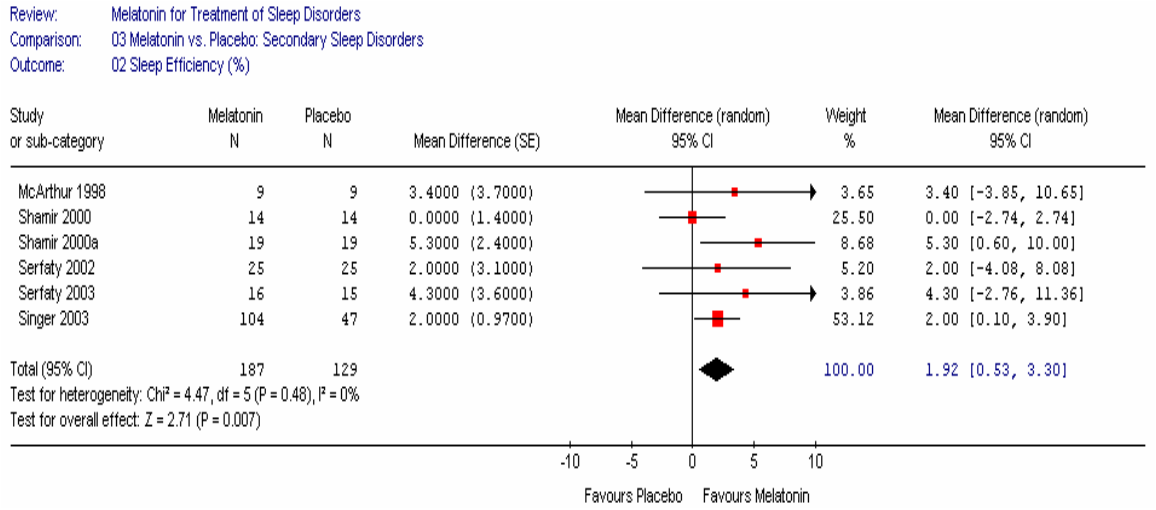


Figure 13: Meta-Graph: Sleep Onset Latency in People Suffering from Sleep Restriction

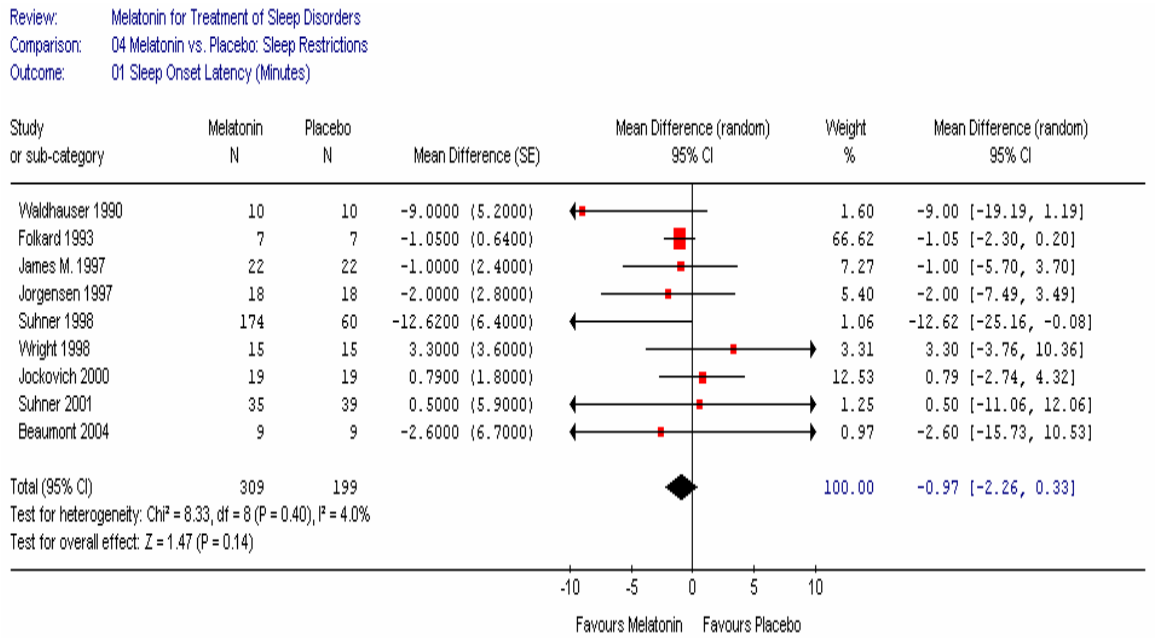
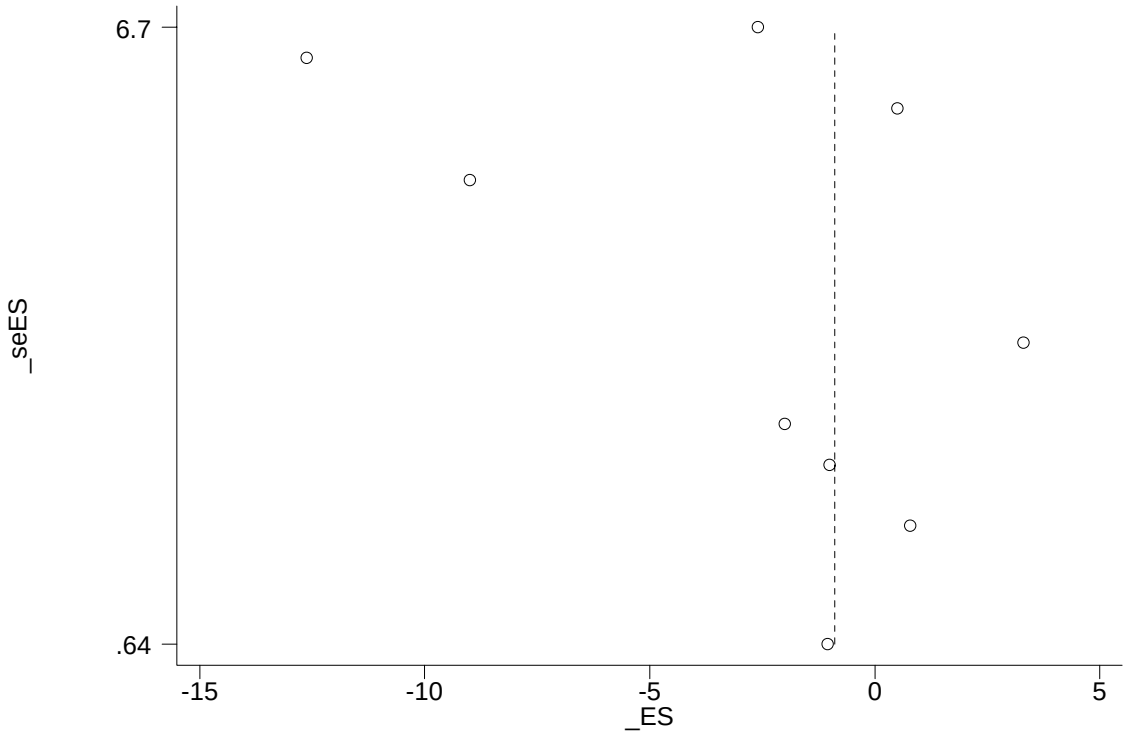


Figure 14: Funnel Plot: Sleep Onset Latency in People Suffering from Sleep Restriction



Abbreviations: **_ES**: effect size, **_seES**: standard error of effect size; note that the smaller studies are associated with a larger standard error.

Figure 15: Meta-Graph: Sleep Efficiency in People Suffering from Sleep Restriction

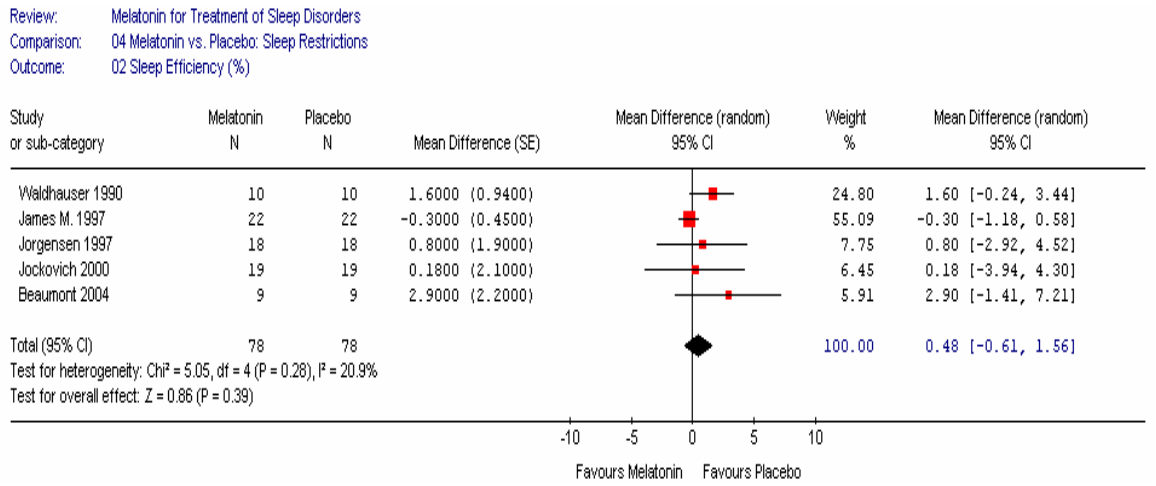


Figure 16: Meta-Graph: Headaches

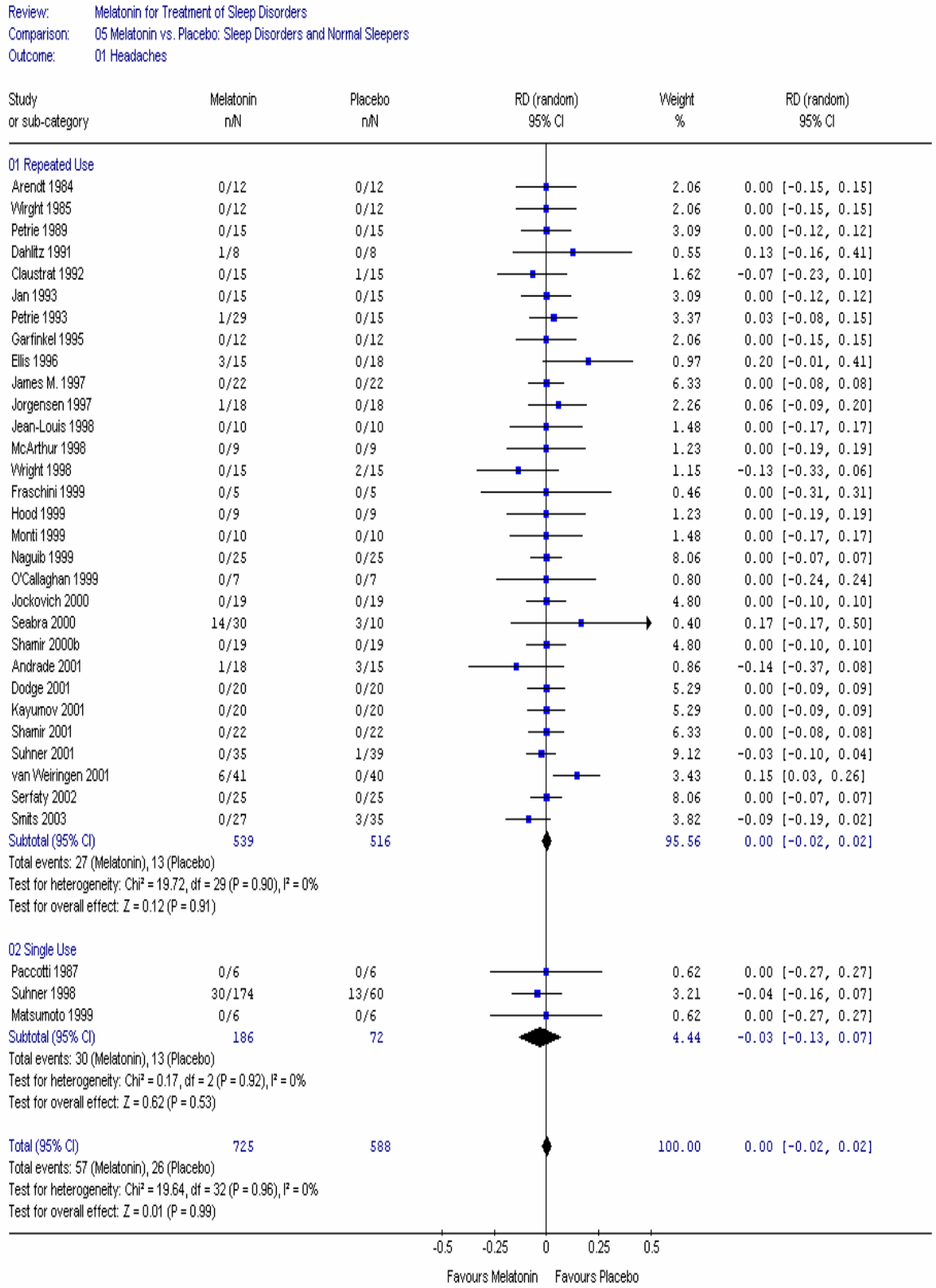


Figure 17: Meta-Graph: Dizziness

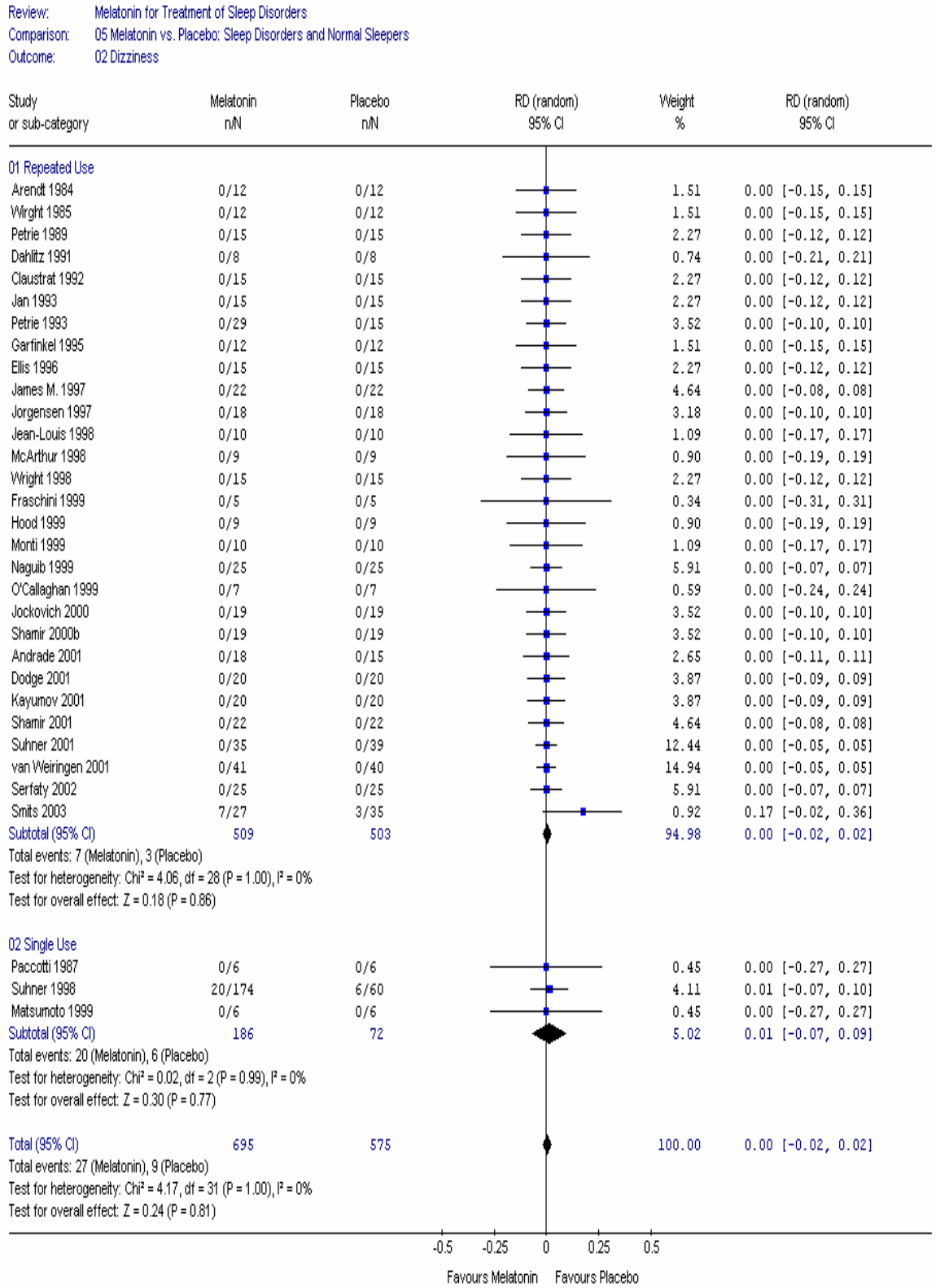


Figure 18: Meta-Graph: Nausea

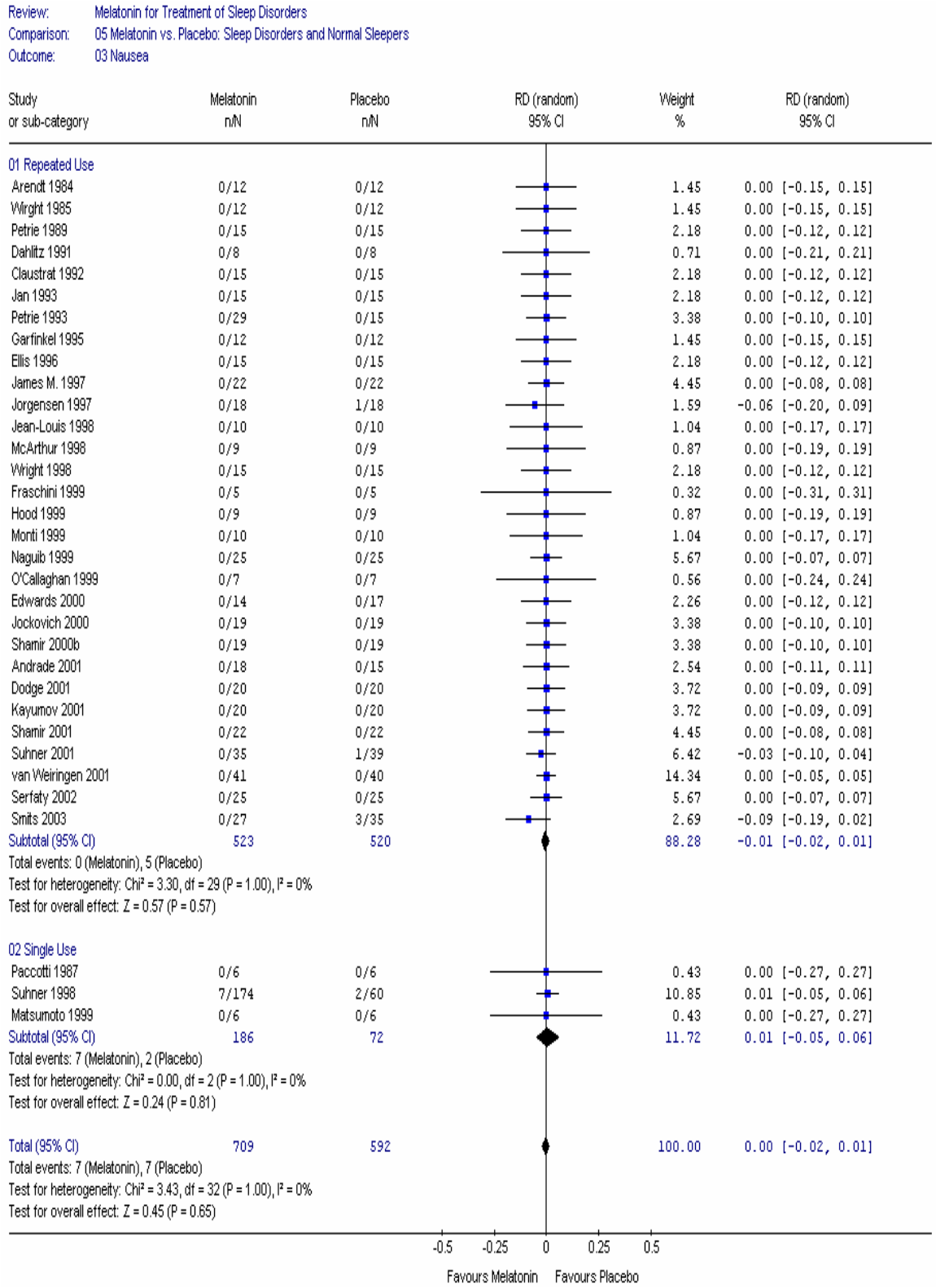


Figure 19: Meta-Graph: Drowsiness

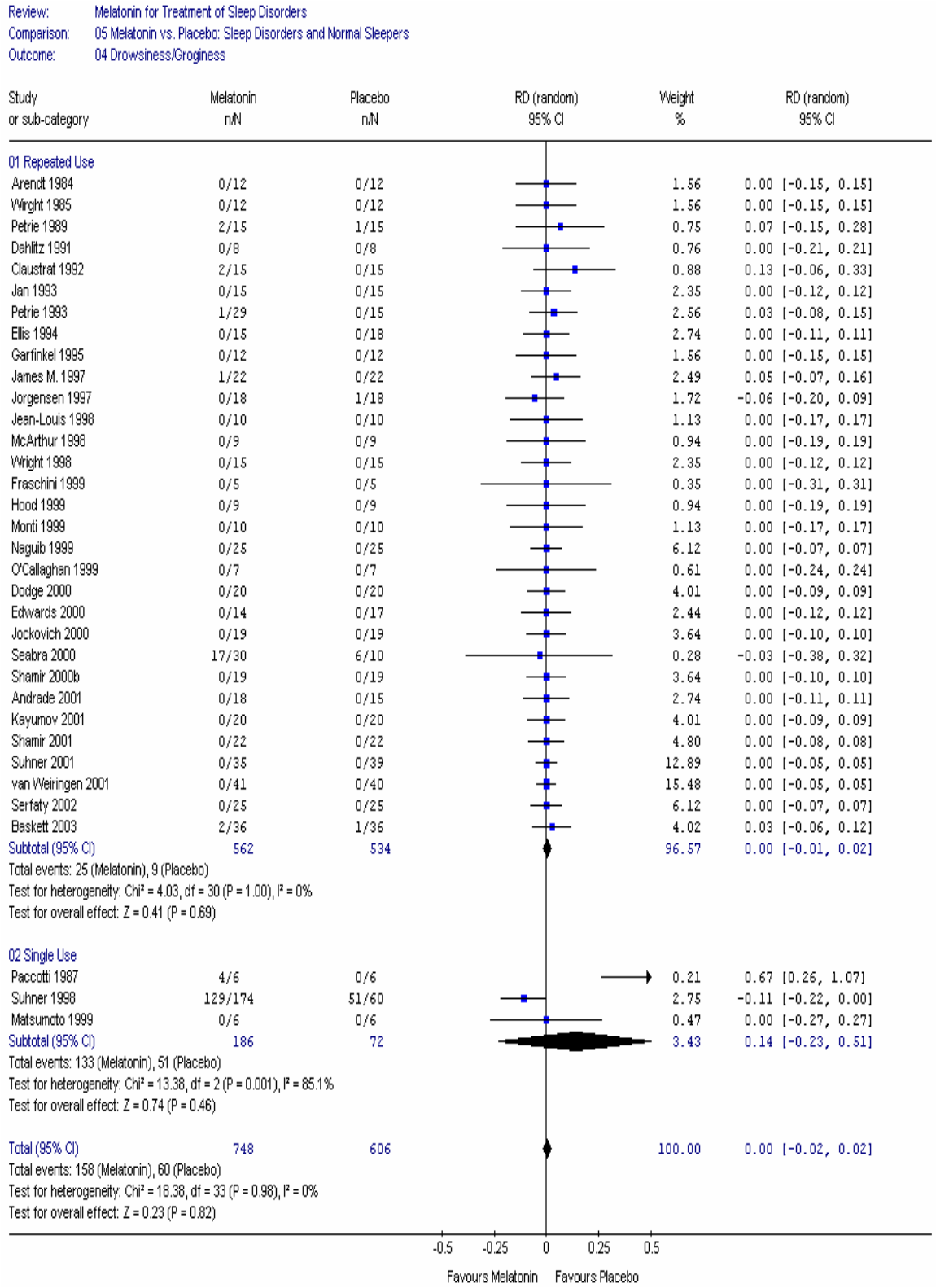


Table 5: Number of Studies relevant to Individual Questions of the Review and Type of Analysis Applied to Data Relevant to these Questions

Question	Number of Studies Relevant to Question	Type of Analysis Applied to Data Relevant to Question
Formulations of melatonin	8: (RCTs)	Qualitative and Quantitative
Pharmacology of melatonin	26: (RCTs, CCTs and Case Series)	Qualitative
Endogenous melatonin and the sleep cycle	44: (RCTs and CCTs)	Qualitative
Mechanism of action of melatonin	11: (RCTs and CCTs)	Qualitative
Effect of melatonin on normal sleepers	21: (RCTs and CCTs)	Quantitative
Endogenous melatonin and circadian rhythms	24: (RCTs and CCTs)	Qualitative
Effectiveness of melatonin among types of sleep disorders	30: (RCTs)	Quantitative
Effectiveness of melatonin among types of populations	29: (RCTs)	Quantitative
Effect of melatonin on people with sleep disorders	30: (RCTs)	Quantitative
Appropriate dosage of melatonin for treatment of sleep disorders	29: (RCTs)	Quantitative
Appropriate timing of melatonin administration for treatment of sleep disorders	0	Quantitative
Adverse effects of melatonin	34: (RCTs and CCTs)	Quantitative
Adverse effects of melatonin as a function of dose, timing, and patient factors	33: (RCTs and CCTs)	Quantitative
Melatonin and other pharmacological treatments for sleep disorders	4: (RCTs and CCTs)	Qualitative

Abbreviations: **RCT**: randomized controlled clinical trial; **CCT**: controlled clinical trial

Table 6: Subgroup and Sensitivity Analysis: Sleep Onset Latency in Normal Sleepers

Subgroup	Categorization	Number of studies	Point Estimate (min)	95 percent Confidence Interval (min)	Heterogeneity	Deeks' Chi-Square p-value
Gender	Male	14	-4.4	-6.3, -2.5	Moderate (I^2:46.5 percent)	0.24
	Mixed	6	-3.2	-5.4, -1.0	Substantial (I^2: 51.1 percent)	
Use of Concurrent Medication	Yes	1	-0.5	-2.5, 1.5	NA	NA
	No	10	-4.0	-5.3, -2.6	Minimal (I^2: 11.0 percent)	
Dosage of Melatonin Administration	< 1 mg	5	-7.6	-11.7, -3.5	Moderate (I^2: 37.9 percent)	NA
	1-3 mg	10	-6.1	-9.1, -3.2	Substantial (I^2: 54.0 percent)	
	4-5 mg	6	-2.6	-4.2, -1.1	Substantial (I^2: 57.5 percent)	
	6-10 mg	7	-6.1	-8.9, -3.3	Moderate (I^2: 30.6 percent)	
	> 10 mg	2	-3.4	-7.6, 0.8	Negligible (I^2: 0 percent)	
Timing of Melatonin Administration	< 1800h	11	-4.6	-6.0, -3.2	Moderate (I^2: 29.4 percent)	0.002
	> 1800h	10	-3.2	-5.5, -1.0	Moderate (I^2: 41.9 percent)	
Duration of Melatonin Administration	< 1 week	14	-4.2	-5.6, -2.8	Moderate (I^2: 43.7 percent)	0.03
	1-2 weeks	1	-6.3	-14.3, 1.7	NA	
	3-4 weeks	5	-2.5	-6.9, 2.0	Moderate (I^2: 27.9 percent)	
Method of Measurement of Sleep Outcomes	Polysomno-graphy	14	-3.7	-5.0, -2.4	Moderate (I^2: 25.0 percent)	0.001
	Actigraphy	4	-2.1	-4.6, 0.4	Moderate (I^2: 34.5 percent)	
	Questionnaire	2	-8.8	-12.5, -5.2	Negligible (I^2: 0 percent)	
Explicit Statement in Report that Subjects did not Suffer from a Sleep Disorder	Yes	8	-3.9	-6.5, -1.3	Substantial (I^2: 55.1 percent)	0.35
	No	12	-4.1	-5.8, -2.4	Moderate (I^2: 43.5 percent)	
Time of Sleep	Daytime	9	-4.6	-6.0, -3.2	Moderate (I^2: 30.9 percent)	NA
	Night time	13	-3.0	-4.9, -1.0	Moderate (I^2: 32.5 percent)	
Use of Multiple Sleep Onset Latency Test	Yes	3	-4.2	-5.7, -2.6	Negligible (I^2: 0 percent)	0.16
	No	17	-4.0	-5.7, -2.2	Substantial (I^2: 51.1 percent)	
Study Design	Parallel	2	-4.5	-10.6, 1.6	Negligible (I^2: 0 percent)	0.67
	Crossover	18	-3.9	-5.4, -2.5	Substantial (I^2: 51.8 percent)	

Table 6: Subgroup and Sensitivity Analysis: Sleep Onset Latency in Normal Sleepers (continued)						
Subgroup	**Categorization**	**Number of studies**	**Point Estimate (min)**	**95 percent Confidence Interval (min)**	**Heterogeneity**	**Deeks' Chi-Square p-value**
Quality Score	10-15 (low)	4	-3.8	-4.9, -2.7	Negligible (I^2: 0 percent)	0.01
	16-20 (moderate)	15	-5.0	-7.4, -2.7	Moderate (I^2: 44.3 percent)	
	21-25 (high)	1	-0.5	-2.5, 1.5	NA	

Abbreviations: **NA**: not applicable, **min**: minutes

Table 7: Subgroup and Sensitivity Analyses: Sleep Efficiency in Normal Sleepers

Subgroup	Categorization	Number of studies	Point Estimate (percent)	95 percent Confidence Interval (percent)	Heterogeneity	Deeks' Chi-Square p-value
Gender	Male	11	2.8	0.6, 4.9	Substantial (I^2: 58.1 percent)	0.73
	Mixed	2	1.8	-0.9, 4.5	Substantial (I^2: 52.2 percent)	
Use of Concurrent Medication	Yes	6	2.2	0.1, 4.3	Moderate (I^2: 24.4 percent)	NA
	No	1	0.9	-0.5, 2.2	NA	
Dosage of Melatonin Administration	< 1 mg	4	3.4	0.6, 6.1	Negligible (I^2: 0 percent)	NA
	1-3 mg	6	5.1	2.9, 7.3	Minimal (I^2: 12.7 percent)	
	4-5 mg	2	0.7	-0.4, 1.9	Negligible (I^2: 0 percent)	
	6-10 mg	5	4.8	-1.1, 10.7	Substantial (I^2: 76.6 percent)	
	> 10 mg	1	1.8	-1.5, 5.1	NA	
Timing of Melatonin Administration	< 1800h	6	1.0	-0.6, 2.5	Moderate (I^2: 43.2 percent)	0.01
	> 1800h	7	4.4	1.5, 7.4	Moderate (I^2: 43.4 percent)	
Duration of Melatonin Administration	< 1 week	9	3.3	0.9, 5.7	Substantial (I^2: 65.5 percent)	0.46
	1-2 weeks	0	NA	NA	NA	
	3-4 weeks	4	1.1	-0.2, 2.3	Negligible (I^2: 0 percent)	
Method of Measurement of Sleep Outcomes	Polysomno-graphy	10	3.0	0.6, 5.3	Substantial (I^2: 62.9 percent)	0.78
	Actigraphy	3	1.3	0.0, 2.5	Negligible (I^2: 0 percent)	
	Questionnaire	0	NA	NA	NA	
Explicit Statement in Report that Subjects do not Suffer from a Sleep Disorder	Yes	6	1.5	-0.2, 3.1	Moderate (I^2: 33.8 percent)	0.41
	No	7	3.7	0.5, 6.9	Substantial (I^2: 66.4 percent)	
Time of Sleep	Daytime	5	8.0	1.0, 15.0	Substantial (I^2: 70.6 percent)	NA
	Night time	10	1.2	-0.0, 2.4	Moderate (I^2: 20.2 percent)	
Study Design	Parallel	1	0.0	-4.1, 4.1	NA	0.50
	Crossover	12	2.6	0.9, 4.3	Substantial (I^2: 57.0 percent)	
Quality Score	10-15 (low)	2	7.5	-5.4, 20.3	Substantial (I^2: 82.2 percent)	0.44
	16-20 (mod.)	10	2.4	0.4, 4.5	Substantial (I^2: 52.1 percent)	
	21-25 (high)	1	0.9	-0.5, 2.2	NA	

Abbreviations: **NA**: not applicable

Table 8: Subgroup and Sensitivity Analyses: REM Latency in Normal Sleepers

Subgroup	Categorization	Number of studies	Point Estimate (min)	95 percent Confidence Interval (min)	Heterogeneity	Deeks' Chi-Square p-value
Gender	Male	9	-1.2	-6.2, 3.9	Minimal (I^2: 17.8 percent)	0.006
	Mixed	2	17.7	-8.0, 43.5	Substantial (I^2: 80.6 percent)	
Use of Concurrent Medication	Yes	0	NA	NA	NA	NA
	No	6	-4.0	-8.1, 0.1	Negligible (I^2: 0 percent)	
Dosage of Melatonin Administration	< 1 mg	4	-7.1	-18.9, 4.7	Moderate (I^2: 34.2 percent)	NA
	1-3 mg	6	12.7	6.8, 18.6	Negligible (I^2: 0 percent)	
	4-5 mg	3	15.2	-7.2, 37.5	Substantial (I^2: 92.0 percent)	
	6-10 mg	3	3.8	-7.9, 15.5	Negligible (I^2: 0 percent)	
	> 10 mg	1	-13.6	-45.9, 18.7	NA	
Timing of Melatonin Administration	< 1800h	4	4.3	-7.0, 15.5	Minimal (I^2: 13.9 percent)	0.21
	> 1800h	7	2.6	-5.6, 10.7	Substantial (I^2: 65.3 percent)	
Duration of Melatonin administration	< 1 week	8	0.4	-5.3, 6.2	Moderate (I^2: 39.2 percent)	0.04
	1-2 weeks	0	NA	NA	NA	
	3-4 weeks	3	11.2	-13.5, 35.9	Substantial (I^2: 69.2 percent)	
Explicit Statement in Report that Subjects do not Suffer from a Sleep Disorder	Yes	6	2.5	-7.5, 12.5	Substantial (I^2: 68.7 percent)	0.09
	No	5	4.8	-2.2, 11.9	Negligible (I^2: 0 percent)	
Time of Sleep	Daytime	2	12.4	-0.0, 24.9	Negligible (I^2: 0 percent)	NA
	Night time	10	0.9	-5.9, 7.6	Substantial (I^2: 50.0 percent)	
Use of Multiple Sleep Onset Latency Test	Yes	1	12.6	-0.3, 25.5	NA	0.04
	No	10	1.2	-5.6, 7.9	Substantial (I^2: 50.3 percent)	
Quality Score	10-15 (low)	2	3.9	-20.3, 28.1	Substantial (I^2: 54.0 percent)	0.11
	16-20 (mod.)	9	1.8	-5.2, 8.8	Substantial (I^2: 54.5 percent)	
	21-25 (high)	0	NA	NA	NA	

Abbreviations: **REM**: rapid eye movement, **NA**: not applicable, **min**: minutes

Table 9: Subgroup and Sensitivity Analyses: Sleep Onset Latency in People with a Primary Sleep Disorder

Subgroup	Categorization	Number of studies	Point Estimate (min)	95 percent Confidence Interval (min)	Heterogeneity	Deeks' Chi-Square p-value
Age	Children	1	-17.0	-33.5, -0.5	NA	0.002
	Adult	7	-11.2	-27.7, 5.4	Substantial (I^2: 84.0 percent)	
	Elderly	4	-7.8	-17.4, 1.7	Substantial (I^2: 69.6 percent)	
Ethnicity	Caucasian	2	-17.5	-33.9, -1.2	Negligible (I^2: 0 percent)	NA
Use of Concurrent Medication	Yes	1	-14.0	-28.7, 0.7	NA	NA
	No	1	1.7	-30.6, 34.0	NA	
Dosage of Melatonin Administration	< 1 mg	2	-0.9	-5.4, 3.6	Negligible (I^2: 0 percent)	NA
	1-3 mg	5	-6.0	-12.9, 0.8	Moderate (I^2: 28.0 percent)	
	4-5 mg	6	-13.3	-30.3, 3.7	Substantial (I^2: 90.0 percent)	
Duration of Melatonin Administration	< 1 week	1	-9.7	-20.5, 1.1	NA	0.07
	1-2 weeks	5	-7.9	-17.5, 1.6	Negligible (I^2: 0 percent)	
	3-4 weeks	6	-12.4	-21.9, -2.8	Substantial (I^2: 90.3 percent)	
Method of Measurement of Sleep Outcomes	Polysomno-graphy	5	-14.2	-27.9, -0.5	Substantial (I^2: 89.5 percent)	0.001
	Actigraphy	3	-8.1	-21.3, 5.0	Substantial (I^2: 70.0 percent)	
	Questionnaire	4	-2.3	-23.5, 18.9	Negligible (I^2: 0 percent)	
Primary Diagnosis	Insomnia	10	-4.3	-8.4, -0.1	Moderate (I^2: 44.9 percent)	< 0.00001
	Delayed Sleep-Phase Syndrome	2	-38.8	-50.3, -27.3	Negligible (I^2: 0 percent)	
Study Design	Parallel	2	-17.1	-32.4, -1.8	Negligible (I^2: 0 percent)	0.03
	Crossover	10	-9.9	-17.2, -2.5	Substantial (I^2: 83.8 percent)	
Quality Score	Moderate (2-3)	4	-5.4	-11.8, 0.9	Moderate (I^2: 37.2 percent)	0.13
	High (4-5)	8	-13.1	-28.9, 2.8	Substantial (I^2: 86.7 percent)	
Allocation Concealment	Unclear	10	-9.6	-17.2, -2.0	Substantial (I^2: 82.7 percent)	0.007
	Adequate	2	-15.3	-26.3, -4.4	Negligible (I^2: 0 percent)	

Abbreviations: **NA**: not applicable, **min**: minutes

Table 10: Subgroup and Sensitivity Analyses: Sleep Efficiency in People with a Primary Sleep Disorder

Subgroup	Categorization	Number of studies	Point Estimate (percent)	95 percent Confidence Interval (percent)	Heterogeneity	Deeks' Chi-Square p-value
Age	Adult	6	-0.0	-1.6, 1.5	Minimal (I^2: 16.1 percent)	0.004
	Elderly	3	3.6	-0.8, 8.0	Substantial (I^2: 73.0 percent)	
Use of Concurrent Medication	Yes	1	8.0	4.1, 11.9	NA	NA
	No	1	-1.4	-4.3, 1.5	NA	
Dosage of Melatonin Administration	< 1 mg	2	3.4	-4.6, 11.3	Substantial (I^2: 78.8 percent)	NA
	1-3 mg	5	2.4	-1.7, 6.5	Substantial (I^2: 77.9 percent)	
	4-5 mg	4	-0.0	-1.4, 1.3	Negligible (I^2: 0 percent)	
Duration of Melatonin Administration	< 1 week	1	0.3	-4.4, 5.0	NA	0.91
	1-2 weeks	5	0.8	-2.1, 3.8	Moderate (I^2: 45.6 percent)	
	3-4 weeks	3	2.6	-2.1, 7.2	Substantial (I^2: 85.7 percent)	
Method of Measurement of Sleep Outcomes	Polysomno-graphy	5	0.2	-2.1, 2.6	Moderate (I^2: 31.1 percent)	0.48
	Actigraphy	3	3.1	-1.2, 7.5	Substantial (I^2: 85.9 percent)	
	Questionnaire	1	-3.0	-18.3, 12.3	NA	
Primary Diagnosis	Insomnia	8	1.7	-0.8, 4.1	Substantial (I^2: 67.3 percent)	0.75
	Sleep-Phase Syndrome	1	0.2	-3.7, 4.1	NA	
Quality Score	Moderate (2-3)	4	1.7	-1.2, 4.6	Moderate (I^2: 34.0 percent)	0.39
	High (4-5)	5	1.3	-1.9, 4.5	Substantial (I^2: 75.3 percent)	
Allocation Concealment	Unclear	8	0.3	-0.9, 1.5	Minimal (I^2: 6.3 percent)	0.0002
	Adequate	1	8.0	4.1, 11.9	NA	

Abbreviations: NA: not applicable

Table 11: Subgroup and Sensitivity Analyses: Sleep Onset Latency in People with a Secondary Sleep Disorder

Subgroup	Categorization	Number of studies	Point Estimate (min)	95 percent Confidence Interval (min)	Heterogeneity	Deeks' Chi-Square p-value
Age	Children	3	-18.1	-29.4, -6.8	Negligible (I^2: 0 percent)	0.0001
	Adult	3	-6.6	-24.6, 11.4	Substantial (I^2: 79.2 percent)	
Gender	Female	1	-12.9	-27.6, 1.8	NA	NA
Dosage of Melatonin Administration	1-3 mg	2	-4.6	-29.8, 20.6	Substantial (I^2: 78.1 percent)	NA
	4-5 mg	1	-23.4	-45.2, -1.6	NA	
	6-10 mg	1	-13.5	-32.5, 5.5	NA	
Duration of Melatonin Administration	1-2 weeks	2	-25.7	-43.3, -8.0	Negligible (I^2: 0 percent)	< 0.00001
	3-4 weeks	2	-4.6	-29.8, 20.6	Substantial (I^2: 78.1 percent)	
	> 4 weeks	2	-13.1	-24.8, -1.5	Negligible (I^2: 0 percent)	
Method of Measurement of Sleep Outcomes	Polysomno-graphy	1	5.8	2.5, 9.1	NA	< 0.00001
	Actigraphy	3	-14.5	-25.0, -4.1	Negligible (I^2: 0 percent)	
	Questionnaire	2	-25.7	-43.3, -8.0	Negligible (I^2: 0 percent)	
Co-Morbidity	Schizophrenia	2	-4.6	-29.8, 20.6	Substantial (I^2: 78.1 percent)	NA
Study Design	Parallel	1	-13.5	-32.5, 5.5	NA	0.08
	Crossover	5	-13.5	-29.7, 2.8	Substantial (I^2: 81.0 percent)	
Allocation Concealment	Unclear	5	-17.4	-26.4, -8.4	Negligible (I^2: 0 percent)	< 0.00001
	Adequate	1	5.8	2.5, 9.1	NA	

Abbreviations: NA: not applicable, **min**: minutes

Table 12: Sensitivity and Subgroup Analyses: Sleep Efficiency in People with a Secondary Sleep Disorder

Subgroup	Categorization	Number of studies	Point Estimate (percent)	95 percent Confidence Interval (percent)	Heterogeneity	Deeks' Chi-Square p-value
Age	Children	1	3.4	-3.9, 10.7	NA	0.89
	Adult	3	2.6	-1.3, 6.4	Substantial (I^2: 52.9 percent)	
	Elderly	2	2.0	0.2, 3.8	Negligible (I^2: 0 percent)	
Use Concurrent Medication	Yes	3	2.3	-1.4, 6.0	Moderate (I^2: 48.9 percent)	NA
Dosage of Melatonin Administration	1-3 mg	3	1.9	-0.5, 4.3	Moderate (I^2: 47.4 percent)	NA
	6-10 mg	3	2.2	0.1, 4.3	Negligible (I^2: 0 percent)	
Duration of Melatonin Administration	1-2 weeks	1	2.0	-4.1, 8.1	NA	0.99
	3-4 weeks	4	2.5	-0.5, 5.4	Moderate (I^2: 32.6 percent)	
	> 4 weeks	1	2.0	0.1, 3.9	NA	
Method of Measurement of Sleep Outcomes	Polysomo-graphy	1	0.0	-2.7, 2.7	NA	0.28
	Actigraphy	5	2.6	1.0, 4.2	Negligible (I^2: 0 percent)	
Co-Morbidity	Schizophrenia	2	2.3	-2.9, 7.4	Substantial (I^2: 72.5 percent)	NA
Study Design	Parallel	2	2.2	0.3, 4.0	Negligible (I^2: 0 percent)	0.93
	Crossover	4	2.0	-0.7, 4.7	Moderate (I^2: 23.8 percent)	
Allocation Concealment	Unclear	4	2.6	1.0, 4.3	Negligible (I^2: 0 percent)	0.33
	Adequate	2	0.3	-2.2, 2.8	Negligible (I^2: 0 percent)	

Abbreviations: NA: not applicable

Table 13: Subgroup and Sensitivity Analyses: Sleep Onset Latency in People Suffering from Sleep Restriction

Subgroup	Categorization	Number of studies	Point Estimate (min)	95 percent Confidence Interval (min)	Heterogeneity	Deeks' Chi-Square p-value
Use of Concurrent Medication	No	2	-3.4	-10.4, 3.7	Substantial (I^2: 56.7 percent)	NA
Dosage of Melatonin Administration	< 1 mg	1	-11.8	-23.6, -0.0	NA	NA
	1-3 mg	2	-4.5	-17.3, 8.3	Substantial (I^2: 75.3 percent)	
	4-5 mg	5	-1.0	-4.0, 2.1	Minimal (I^2: 18.2 percent)	
	10-20 mg	1	-2.0	-7.5, 3.5	NA	
Method of Measurement of Sleep Outcomes	Polysomno-graphy	2	-6.6	-14.7, 1,5	Negligible (I^2: 0 percent)	0.24
	Actigraphy	1	0.8	-2.7, 4.3	NA	
	Questionnaire	6	-1.1	-2.2, 0.1	Negligible (I^2: 0 percent)	
Type of Sleep Restriction	Jet Lag	3	-4.7	-12.6, 3.1	Minimal (I^2: 16.9 percent)	0.17
	Shift Work	5	-0.8	-1.9, 0.3	Negligible (I^2: 0 percent)	
	Deprivation	1	-9.0	-19.2, 1.2	NA	
Study Design	Parallel	4	-6.1	-11.9, -0.2	Negligible (I^2: 0 percent)	0.08
	Crossover	5	-0.8	-1.9, 0.3	Negligible (I^2: 0 percent)	
Quality Score	High (4-5)	5	-1.2	-4.6, 2.3	Minimal (I^2: 18.6 percent)	1.00
	Moderate (2-3)	4	-0.9	-2.7, 0.8	Minimal (I^2: 12.2 percent)	
Allocation Concealment	Unclear	6	-1.4	-3.8, 1.1	Moderate (I^2: 26.2 percent)	0.73
	Adequate	3	-0.5	-3.7, 2.7	Negligible (I^2: 0 percent)	

Abbreviations: NA: not applicable, **min**: minutes

Table 14: Subgroup and Sensitivity Analyses: Sleep Efficiency in People Suffering from Sleep Restriction

Subgroup	Categorization	Number of studies	Point Estimate (percent)	95 percent Confidence Interval (percent)	Heterogeneity	Deeks' Chi-Square p-value
Method of Measurement of Sleep Outcomes	Polysomno-graphy	2	1.8	0.1, 3.5	Negligible (I^2: 0 percent)	0.11
	Actigraphy	1	0.2	-3.9, 4.3	NA	
	Questionnaire	2	-0.2	-1.1, 0.6	Negligible (I^2: 0 percent)	
Type of Sleep Restriction	Jet Lag	1	2.9	-1.4, 7.2	NA	0.10
	Shift Work	3	-0.2	-1.1, 0.6	Negligible (I^2: 0 percent)	
	Deprivation	1	1.6	-0.2, 3.4	NA	
Study Design	Parallel	2	1.8	0.1, 3.5	Negligible (I^2: 0 percent)	0.11
	Crossover	3	-0.2	-1.1, 0.6	Negligible (I^2: 0 percent)	
Quality Score	High (4-5)	2	-0.2	-1.1, 0.6	Negligible (I^2: 0 percent)	0.14
	Moderate (2-3)	3	1.6	0.0, 3.1	Negligible (I^2: 0 percent)	
Allocation Concealment	Unclear	2	-0.2	-1.1, 0.6	Negligible (I^2: 0 percent)	0.14
	Adequate	3	1.6	0.0, 3.1	Negligible (I^2: 0 percent)	

Abbreviations: NA: not applicable

Table 15: Subgroup Analysis: Headaches

Subgroup	Categorization	Number of studies	Risk Difference	95 percent Confidence Interval	Heterogeneity	Deeks' Chi-Square p-value
Gender	Male	3	0.04	-0.13, 0.19	Negligible (I^2: 0 percent)	NA
	Female	2	0.00	-0.07, 0.07	Negligible (I^2: 0 percent)	
Age	Children	6	-0.02	-0.08, 0.03	Negligible (I^2: 0 percent)	0.74
	Adult	22	0.00	-0.02, 0.03	Negligible (I^2: 0 percent)	
	Elderly	5	0.00	-0.06, 0.06	Negligible (I^2: 0 percent)	
Dosage	1-3 mg	8	0.00	-0.05, 0.04	Negligible (I^2: 0 percent)	NA
	4-5 mg	14	0.00	-0.03, 0.04	Minimal (I^2: 18.9 percent)	
	6-10 mg	9	0.00	-0.04, 0.04	Negligible (I^2: 0 percent)	
	> 10 mg	2	0.00	-0.20, 0.20	Negligible (I^2: 0 percent)	
Formulation	Fast Release	3	-0.06	-0.14, 0.02	Negligible (I^2: 0 percent)	NA
	Slow Release	4	0.00	-0.05, 0.05	Negligible (I^2: 0 percent)	

Abbreviations: **NA**: not applicable

Table 16: Subgroup Analysis: Dizziness

Subgroup	Categorization	Number of studies	Risk Difference	95 percent Confidence Interval	Heterogeneity	Deeks' Chi-Square p-value
Gender	Male	2	0.00	-0.19, 0.19	Negligible (I^2: 0 percent)	NA
	Female	2	0.00	-0.07, 0.07	Negligible (I^2: 0 percent)	
Age	Children	6	0.02	-0.04, 0.08	Negligible (I^2: 0 percent)	1.00
	Adult	21	0.00	-0.02, 0.02	Negligible (I^2: 0 percent)	
	Elderly	5	0.00	-0.06, 0.06	Negligible (I^2: 0 percent)	
Dosage	1-3 mg	8	0.00	-0.04, 0.05	Negligible (I^2: 0 percent)	NA
	4-5 mg	14	0.00	-0.02, 0.03	Negligible (I^2: 0 percent)	
	6-10 mg	7	0.00	-0.04, 0.04	Negligible (I^2: 0 percent)	
	> 10 mg	2	0.00	-0.20, 0.20	Negligible (I^2: 0 percent)	
Formulation	Fast Release	3	0.05	-0.04, 0.15	Minimal (I^2: 14.6 percent)	NA
	Slow Release	4	0.00	-0.05, 0.05	Negligible (I^2: 0 percent)	

Abbreviations: **NA**: not applicable

Table 17: Subgroup Analysis: Nausea

Subgroup	Categorization	Number of studies	Risk Difference	95 percent Confidence Interval	Heterogeneity	Deeks' Chi-Square p-value
Gender	Male	2	0.00	-0.19, 0.19	Negligible (I^2: 0 percent)	NA
	Female	2	0.00	-0.07, 0.07	Negligible (I^2: 0 percent)	
Age	Children	6	-0.02	-0.08, 0.03	Negligible (I^2: 0 percent)	0.81
	Adult	21	0.00	-0.02, 0.02	Negligible (I^2: 0 percent)	
	Elderly	5	0.00	-0.06, 0.06	Negligible (I^2: 0 percent)	
Dosage	1-3 mg	8	0.00	-0.03, 0.03	Negligible (I^2: 0 percent)	NA
	4-5 mg	14	-0.01	-0.04, 0.02	Negligible (I^2: 0 percent)	
	6-10 mg	9	0.00	-0.04, 0.03	Negligible (I^2: 0 percent)	
	> 10 mg	2	0.00	-0.20, 0.20	Negligible (I^2: 0 percent)	
Formulation	Fast Release	3	-0.02	-0.08, 0.03	Negligible (I^2: 0 percent)	NA
	Slow Release	4	0.00	-0.04, 0.05	Negligible (I^2: 0 percent)	

Abbreviations: **NA**: not applicable

Table 18: Subgroup Analysis: Drowsiness

Subgroup	Categorization	Number of studies	Risk Difference	95 percent Confidence Interval	Heterogeneity	Deeks' Chi-Square p-value
Gender	Male	3	0.19	-0.21, 0.60	Substantial (I^2: 76.6 percent)	NA
	Female	2	0.00	-0.07, 0.07	Negligible (I^2: 0 percent)	
Age	Children	5	0.00	-0.06, 0.06	Negligible (I^2: 0 percent)	1.00
	Adult	24	0.00	-0.02, 0.02	Negligible (I^2: 0 percent)	
	Elderly	6	0.01	-0.04, 0.05	Negligible (I^2: 0 percent)	
Dosage	1-3 mg	8	-0.01	-0.06, 0.04	Negligible (I^2: 0 percent)	NA
	4-5 mg	13	0.00	-0.03, 0.03	Negligible (I^2: 0 percent)	
	6-10 mg	9	0.01	-0.04, 0.05	Negligible (I^2: 0 percent)	
	> 10 mg	2	0.32	-0.37, 1.01	Substantial (I^2: 86.4 percent)	
Formulation	Fast Release	2	-0.07	-0.19, 0.06	Negligible (I^2: 0 percent)	NA
	Slow Release	4	-0.01	-0.06, 0.04	Negligible (I^2: 0 percent)	

Abbreviations: **NA**: not applicable

Table 19: Effect of Manipulation of Light/Dark Exposure on Endogenous Melatonin and the Sleep Cycle in Normal Sleepers: Manipulation during Evening or Night

Study	Endogenous Melatonin	Sleep Cycle	Assessment of Correlation
Bunnell, 1992	↓ endogenous MLT levels	↑ REM latency and NREM period length, ≠ REM cycle and period length	Not conducted
Burgress, 2001	↓ endogenous MLT levels	↑ SOL	Not conducted
Cajochen, 2000	↓ endogenous MLT levels	↑ alertness and performance	Positive correlation was found between changes
Daurat, 1996	↓ endogenous MLT levels	↑ alertness and performance	Not conducted
Dollins, 1993	↓ endogenous MLT levels	≠ alertness and performance	Not conducted
Higuchi, 2003	↓ endogenous MLT levels	≠ alertness and performance	Not conducted
Horne, 1991	↓ endogenous MLT levels	↑ alertness and performance	Not conducted
Kubota, 2002	Delayed MLT rhythm	Delayed sleep onset	No correlation was found between changes
Lavoie, 2003	↓ endogenous MLT levels	≠ SOL, ≠ alertness and performance	None of the vigilance variables were found to correlate to endogenous MLT levels.

Abbreviations: **MLT**: melatonin, **SOL**: sleep onset latency, **REM**: rapid eye movement, **NREM**: non-REM, ↑: increased ↓: decreased, ≠: no change in

Table 20: Effect of Manipulation of Light/Dark Exposure on Endogenous Melatonin and the Sleep Cycle in Normal Sleepers: Manipulation During Morning or Daytime

Study	Endogenous Melatonin	Sleep Cycle	Assessment of Correlation
Danilenko, 2000	Advance of MLT rhythm, ↓ endogenous MLT levels	↑ alertness,	Phase of MLT rhythm was correlated to sleepiness and mid-point of sleep
Dijk, 1989	Advance of MLT rhythm	↓ sleep duration and REM sleep, ≠ REM latency, percent time spent in various sleep stages and sleep quality	No correlation between phase of MLT rhythm, and sleep duration
Wakamura, 2000	↓ endogenous MLT levels	↑ alertness	Not conducted

Abbreviations: **MLT**: melatonin, **REM**: rapid eye movement, ↑: increased, ↓: decreased, ≠: no change in

Table 21: Effect of Manipulation of Light/Dark Exposure on Endogenous Melatonin and the Sleep Cycle in Normal Sleepers: Manipulation Involves Unique Conditions

Study	Endogenous Melatonin	Sleep Cycle	Assessment of Correlation
Daurat, 1997	≠ endogenous MLT levels	≠ TST, REM latency, WASO and REM sleep	Not conducted
Gordijn, 1999	↓ endogenous MLT, ≠ phase of MLT rhythm	↑ movement time, ↓ duration of first REM episode, delayed sleep termination, ≠ sleep latency and REM latency	Not conducted
Lushington, 2002	≠ endogenous MLT levels or phase of MLT rhythm	↑ wakefulness	Not conducted
Wehr, 1991	↓ duration of nocturnal endogenous MLT	↓ sleep period	Not conducted

Abbreviations: **MLT**: melatonin, **TST**: total sleep time, **REM**: rapid eye movement, **WASO**: wakefulness after sleep onset, ↑: increased ↓: decreased, ≠: no change in

Table 22: Effect of Manipulation of Light/Dark Exposure on Endogenous Melatonin and the Sleep Cycle in People with Sleep Disorders

Study	Endogenous Melatonin	Sleep Cycle	Assessment of Correlation
Ando, 1999	≠ phase of MLT rhythm	≠ total sleep period, total sleep time and sleep quality	Not conducted
Bougrine, 1995	≠ phase of MLT rhythm	≠ sleep quality, performance and subjective feelings of tiredness	Not conducted
Boulos, 2002	Delay in MLT rhythm	≠ sleep efficiency, sleep quality, daytime sleepiness, jet-lag severity or mood	No correlation was found between phase of MLT rhythm and performance
Budnick, 1995	↓ endogenous MLT	≠ total sleep time, ↑ alertness and performance	Not conducted
Cole, 2002	≠ phase of MLT rhythm	≠ mood, total sleep time, sleep quality, morning sleepiness	Not conducted
Costa, 1997	≠ endogenous MLT levels	≠ alertness and performance	Not conducted
Horowitz, 2001	Delay in MLT rhythm	≠ sleep start time and wake time, ↑ alertness and performance	Not conducted
Kelly, 1997	Delay in MLT rhythm	↑ sleep time and continuity, ≠ sleep latency, ↑ alertness and performance	Not conducted
Ross, 1995	Not explicitly stated	↓ sleep latency, ≠ sleep duration, sleep quality, night awakenings and mood	Not conducted
Yoon, 2000	Delay in MLT rhythm	↑ alertness and performance	Not conducted

Abbreviations: **MLT**: melatonin, ↑: increased ↓: decreased, ≠: no change in

Table 23: Effect of Manipulation of Light/Dark Exposure on Endogenous Melatonin and the Sleep Cycle in People with a Disorder that may or may not be Accompanied by a Sleep Disorder

Study	Endogenous Melatonin	Sleep/Wake Cycle	Assessment of Correlation
Gordijn, 1998	Advance of MLT rhythm	Earlier tendency for sleep termination	No correlation was found between phase of MLT rhythm and wake-up time
Koorengevel, 2001	≠ phase of MLT rhythm	≠ mood, alertness, total sleep duration, time of awakening and sleep onset	Not conducted
Partonen, 1996	≠ endogenous MLT levels	≠ sleepiness	Not conducted

Abbreviations: **MLT**: melatonin, ↑: increased, ↓: decreased, ≠: no change in

Table 24: Effect of Manipulation of Light/Dark Exposure on Endogenous Melatonin and the Sleep Cycle in Normal Sleepers: Manipulation During Evening or Night

Study	Endogenous Melatonin	Temperature Rhythm	Assessment of Correlation
Bunnell, 1992	↓ endogenous MLT levels	↑ core body temperature, ≠ tympanic temperature	Not conducted
Burgress, 2001	↓ endogenous MLT levels	↑ core body temperature	Not conducted
Cagnacci, 1993	Delayed MLT rhythm, ↓ endogenous MLT levels	≠ value or timing of core body temperature minima	Not conducted
Cajochen, 2000	↓ endogenous MLT levels	≠ core body temperature	Not conducted
Daurat, 1996	↓ endogenous MLT levels	↑ core body temperature, reduced and delayed temperature minima	Not conducted
Eastman, 2000	≠ MLT rhythm	≠ core body temperature	Not conducted
Higuchi, 2003	↓ endogenous MLT levels	↑ core body temperature	Not conducted
Horne, 1991	↓ endogenous MLT levels	≠ oral temperature	Not conducted
Kubota, 2002	Delayed MLT rhythm, ↓ endogenous MLT levels	Delay in core body temperature minima	No correlation was found between the change in phase of MLT rhythm and temperature rhythm
Lavoie, 2003	↓ endogenous MLT levels	↑ core body temperature	Not conducted
Lushington, 2002	≠ endogenous MLT levels or rhythm	≠ nocturnal core body temperature rhythm	Not conducted
Strassman, 1991	↓ endogenous MLT levels	↑ minimal rectal temperature, ≠ maximal rectal temperature	Not conducted

Abbreviations: **MLT**: melatonin, ↑: increased ↓: decreased, ≠: no change in

Table 25: Effect of Manipulation of Light/Dark Exposure on Endogenous Melatonin and the Sleep Cycle in Normal Sleepers: Manipulation Involved Unique Conditions

Study	Endogenous Melatonin	Temperature rhythm	Assessment of Correlation
Danilenko, 2000	↓ endogenous MLT levels, shift in MLT rhythm	Shift in temperature rhythm	Shifts in MLT rhythm and temperature rhythm were correlated
Daurat, 1997	≠ endogenous MLT	↑ rectal temperature, ≠ phase of temperature rhythm	Not conducted
Eastman, 2000	≠ phase of MLT rhythm	≠ core body temperature	Not conducted
Gordijn, 1999	↓ endogenous MLT levels, ≠ phase of MLT rhythm	↑ body temperature, ≠ phase of temperature rhythm	Not conducted
Lushington, 2002	≠ endogenous MLT levels	≠ phase of core body temperature rhythm	Not conducted
Wakamura, 2000	↓ endogenous MLT levels	↓ minimum core body temperature, ≠ maximum core body temperature, advance of the core body temperature rhythm	Not conducted
Wright, 1997	↓ endogenous MLT levels	↑ body temperature	Not conducted

Abbreviations: **MLT**: melatonin, ↑: increased, ↓: decreased, ≠: no change in

Table 26: Effect of Manipulation of Light/Dark Exposure on Endogenous Melatonin and the Sleep Cycle in People with a Sleep Disorder

Study	Endogenous Melatonin	Temperature rhythm	Assessment of Correlation
Ando, 1999	≠ MLT rhythm	≠ temperature rhythm	Not conducted
Costa, 1997	≠ endogenous MLT levels	≠ temperature rhythm	Not conducted
Horowitz, 2001	Delay MLT rhythm	Delay of core body temperature rhythm	Not conducted
Kelly, 1997	Delay MLT rhythm	≠ temperature rhythm	Not conducted

Abbreviations: **MLT**: melatonin, ↑: increased, ↓: decreased, ≠: no change in

Table 27: Oxford Centre for Evidence-based Medicine Levels of Evidence

Grade of Recommendation	Level of Evidence	Therapeutic Use
A	1a	SR (with homogeneity) of RCTs
	1b	Individual RCT (with Narrow Confidence Interval)
	1c	All or none
B	2a	SR (with homogeneity) of cohort studies
	2b	Individual cohort study (including low quality RCT; e.g., ,80 percent follow-up)
	2c	"Outcomes Research"
	3a	SR (with homogeneity) of case-control studies
	3b	Individual case control study
C	4	Case series (and poor quality cohort and case-control studies)
D	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Abbreviations: SR: systematic review, **RCT**: randomized controlled trial

Adapted from http://minerva.minervation.com/cebm/documents/levels_cebm_23nov99.rtf

Chapter 4. Discussion

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 confidence interval (CI): -5.3 min., -2.6 min.). The magnitude of this effect appears to be **clinically insignificant**. The moderate heterogeneity across studies may be partially explained by differences in the timing and duration of melatonin administration, the method of measurement of sleep outcomes and the overall quality of studies. 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**. The substantial heterogeneity across studies analyzed for this outcome may be partially explained by differences in the timing of melatonin administration. 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 1mg 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. The substantial heterogeneity in results across studies may be partially explained by differences in the gender of the population and the duration of melatonin administration.
- 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 17 years) (WMD: -17.0 min., 95 percent CI: -33.5 min, -0.5 min.) than in adults (18-65 years) (WMD: -11.2; 95 percent CI: -27.7 min, 5.4 min.) or

elderly patients (greater than 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. The substantial heterogeneity across studies may be partially explained by differences in the age of the population, their primary diagnosis, study design, the method of measurement of sleep outcomes and whether allocation of participants to interventions was concealed. 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. The substantial heterogeneity in the results across studies may be partially explained by the age of the population and whether allocation of participants to interventions was concealed.
- 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. The substantial heterogeneity across studies may be partially explained by the age of the population, the duration of melatonin administration, the method of measurement of sleep outcomes and whether allocation of participants to interventions was concealed.
- 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.

See Table 28 for a summary of the evidence surrounding the effect of melatonin on sleep in various populations.

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 Mechanisms 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 are different 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 14.75pg/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 hypothesis 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 of Key Observations of this Review

Effectiveness of Melatonin in Normal Sleepers

One cannot draw strong conclusions regarding the effect of melatonin on the sleep cycle of normal sleepers due to the heterogeneity in results of studies relevant to this topic, evidence of possible publication bias in this selection of studies, and the relatively low quality of these studies. The results of this review suggest that the heterogeneity across studies may partially be due to details of the intervention, such as the timing and duration of melatonin administration, as well as the method of measurement of sleep outcomes, the gender of the population and the overall quality of studies. Indeed, the timing of melatonin administration has been shown to predict its effect on circadian rhythms, such that melatonin delays circadian rhythms following morning administration and advances circadian rhythms following afternoon or early evening administration.[231] In addition to timing of melatonin administration, the results of studies may be affected by the particular method used to assess sleep outcomes. The studies employed either polysomnography, actigraphy or questionnaires/sleep diaries. Indeed, many studies have found a discrepancy in the results obtained by actigraphy and/or sleep diaries compared to polysomnography. There is evidence that actigraphy overestimates sleep parameters such as sleep onset latency and sleep efficiency,[232 233] however, there is other evidence that actigraphy and sleep diaries underestimate sleep efficiency and total sleep time.[234] Kushida et al. (2001)[235] have not found a difference in sleep efficiency and total sleep time by the three methods. A "first night effect" has been described with the use of polysomnography to measure sleep outcomes in children[236] and adults,[237] whereby laboratory conditions tend to result in more awakenings and less REM sleep during the first night of recording compared to subsequent nights. Such an effect would tend to underestimate the effect of melatonin on sleep, but could be bypassed by longer study duration.

Our literature review indicated that melatonin decreased sleep onset latency and increased sleep efficiency in normal sleepers and that the effect on sleep efficiency, but not on sleep onset latency, was more pronounced in normal sleepers that were given melatonin and tested during the day versus those that were given melatonin and tested during the night. These results may reflect differences in the conditions of studies involving daytime sleep versus night time sleep. For example, many of the studies involving daytime sleep used the Multiple Sleep Onset Latency Test (MSLT) to assess sleep onset latency, and sleep opportunities were relatively short compared to those for night-time sleepers. Thus, the increased sleep efficiency in normal sleepers tested during the daytime compared to the night-time could simply reflect shorter sleep opportunities. However, the possibility exists that melatonin is more effective in maintaining daytime sleep compared to night-time sleep in normal sleepers. The finding that melatonin significantly increased REM latency only when administered at doses between 1 and 3mg, and not at lower or higher doses, may indicate that melatonin modulates sleep architecture in normal sleepers in a dose-dependent manner. However, given that melatonin did not have any overall effect on sleep efficiency in this population, further research into the pharmacodynamics of melatonin in terms of its effect on REM latency in normal sleepers is required to confirm the possible dose-dependency of this effect.

Effectiveness of Melatonin in the 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. That is, the reduction in sleep onset latency would decrease exposure to evening light, which normally delays the pacemaker,[12] such that individuals would only receive phase-advancing morning light,[12] advancing the rhythm of endogenous melatonin and alleviating the sleep disorder. The finding that the effect of melatonin on sleep onset latency in people with primary sleep disorders was greater for children than adults or the elderly was based on only one study involving children,[59] and the effect of melatonin on sleep efficiency in people with secondary sleep disorders did not vary with age. Thus, one cannot draw a firm conclusion on the effect of age on the effectiveness of melatonin in people with primary sleep disorders, and further research in this area is required. Our literature survey indicates that there is no evidence to suggest that the effect of melatonin on sleep onset latency in people with primary sleep disorders and on sleep efficiency in people with secondary sleep disorders is dependent on dose or duration of melatonin administration. Similarly, we found no evidence to suggest that the effect of melatonin on sleep onset latency and sleep efficiency in normal sleepers is dose dependent. These findings appear to contrast with the finding that the effect of melatonin on REM latency in normal sleepers is dose-dependent. It appears that research into the pharmacodynamics of melatonin with respect to the dose-dependence of the effect of melatonin on various sleep parameters is required. 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.

It is noteworthy that the observations of this review regarding the effects of melatonin on people with primary sleep disorders are based on studies with relatively short trial durations of four weeks or less. Therefore, the effects of melatonin on sleep onset latency and sleep efficiency reported here may reflect only the short-term effects of melatonin on this population. It is necessary that trials of longer duration be conducted in order to determine the long-term effects of melatonin on this population.

Interestingly, the authors did not come across studies involving the use of melatonin in people with sleep apnoea, a type of sleep disorder. The search strategies employed in this review would have captured such studies, which suggests that research in this area is lacking. Nonetheless, it is important to consider that the effects of melatonin reported herein may not be applicable to people with sleep apnoea, and research into the area of melatonin and sleep apnoea is necessary in order to understand the effects of exogenous melatonin on this population.

The authors noted the working definitions of sleep onset latency in the studies included in the review. For studies employing sleep diary, questionnaire or actigraphy in the measurement of

SOL, and for which a definition of SOL was provided in the report, this outcome was defined in a similar manner across studies. By contrast, for studies employing polysomnography in the measurement of SOL, and for which a definition of SOL was provided in the report, this outcome was defined slightly differently across studies. In the current review, a subgroup analysis was conducted based on the method of measurement of sleep outcomes. This analysis allowed us to examine whether the differences in the working definitions of SOL among studies employing sleep diary/questionnaire, compared to studies employing polysomnography, for measurement of sleep outcomes, could potentially yield differences in the observed effect of melatonin on SOL. However, the subtle differences in the working definitions of SOL in studies employing polysomnography precluded us from performing a subgroup analysis based on working definition within this group of studies, since individual subgroups of this analysis would be based on only one study in most cases and would not provide meaningful results. Future research in the area of melatonin and sleep disorders requires that working definitions of primary outcomes be clearly defined such that appropriate comparisons across studies can be made.

Effectiveness of Melatonin in People with Secondary Sleep Disorders

The summary estimate of the effect of melatonin on sleep onset latency in people with secondary sleep disorders is markedly changed by the results of a study by Shamir et al.[132] When the results of this study are incorporated into the analysis, the results suggest that melatonin does not have an effect on sleep onset latency in people with secondary sleep disorders, whereas if the results of this study are omitted, they suggest that melatonin does have an effect. Moreover, although the summary estimate indicated that melatonin increased sleep efficiency in people with secondary sleep disorders, the study by Shamir et al. did not find such an increase. 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. It is also noteworthy that this study was of sufficient duration to bypass the "first night effect", which would tend to underestimate the effect of melatonin on sleep efficiency. Thus, although the results of this study are markedly different from other studies of this category, its results appear to be valid. It is possible that this discrepancy is due to publication or reporting bias, but with only six studies in this category, this bias is impossible to verify. 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.

Similar to the observations related to the effects of melatonin on people with primary sleep disorders, the observations of this review regarding the effects of melatonin on people with secondary sleep disorders are based on studies with relatively short trial durations of four weeks or less. Therefore, the effects of melatonin on sleep onset latency and sleep efficiency reported here may reflect only the short-term effects of melatonin on this population. It is necessary that trials of longer duration be conducted in order to determine the long-term effects of melatonin on this population.

It is noteworthy that the increase in sleep efficiency with melatonin in people with secondary sleep disorders was accompanied by an increase in total sleep time, but no evidence of a change in wakefulness after sleep onset (WASO). This apparent inconsistency may be explained by the difference in the number of studies that reported on the various outcomes; while six studies reported on sleep efficiency and nine studies reported on total sleep time, only three studies

reported on WASO. Thus, the outcomes for which there were more data indicated evidence of an effect of melatonin, while the outcome for which there was little data showed a lack of evidence of an effect of melatonin. The latter finding may simply indicate that the there was insufficient power to detect evidence of an effect of melatonin on WASO.

Effectiveness of Melatonin in People Suffering from Sleep Restriction Disorders

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.[100 102] These reviews assessed the effectiveness of melatonin in alleviating jet lag by examining the effect of this hormone on global assessments of jet lag, which encompass assessments of both the daytime fatigue and sleep disturbance aspects of jet lag. 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. The current review differs from the previous reviews in that the objective was to determine the effectiveness of melatonin in alleviating the sleep disturbance aspect of jet lag, and not the daytime sleepiness aspect of this 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. The lack of substantial heterogeneity or evidence of possible publication bias across studies of this category and the moderate to high quality of the studies lend support to the results of the current review.

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.

Formulations and Pharmacology of Melatonin

In general, the quality of reporting of the content and quality of the various formulations of melatonin that have been used in assessing its effectiveness and safety was poor, and it remains unclear which formulation of melatonin is optimal for the potential treatment of sleep disorders. The details of the formulations used in studies of the pharmacology of melatonin were often not reported, which precluded a quantitative analysis of the half-life of melatonin. Nonetheless, it appears that melatonin has a short half-life, which would tend to suggest that a sustained-release formulation of melatonin would be more effective than a fast-release formulation of melatonin in treating sleep disorders. However, it was unclear from our review of the literature whether the effectiveness of melatonin varies by formulation, and future research in this area is required. The finding that exogenous melatonin penetrates the blood-brain-barrier in one study suggests that exogenous melatonin exerts its effects via a similar mechanism as endogenous melatonin.

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 the effectiveness of melatonin in the treatment of 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.

Link Between Endogenous Melatonin and the Sleep Cycle

Our literature review indicated evidence of a link between endogenous melatonin and the sleep cycle. A key result was that a decrease in endogenous melatonin levels was often accompanied by increased latency to sleep and decreased duration of sleep, as well as increased vigilance and performance during waking hours. In addition, changes in the rhythm of endogenous melatonin were often accompanied by changes in the sleep rhythm. This relationship between endogenous melatonin and the sleep cycle is consistent with a role for exogenous melatonin in the alteration of the sleep cycle in humans. However, the nature of this relationship remains to be defined; it is unclear under what conditions a change in endogenous melatonin will be accompanied by a change in the sleep cycle and how these conditions would affect the magnitude and direction of these changes. A better understanding of this relationship would add to our knowledge of the conditions under which the effects of exogenous melatonin can be optimized. We also found evidence that manipulation of the sleep schedule can produce alterations in endogenous melatonin; however, the direction of these changes varied across studies. It is likely that the variation across studies is due to the particular conditions of sleep-schedule alterations as well the timing of assessment of the melatonin rhythm. It is important to note the possibility that the primary function of the inhibition of the superior cervical ganglion

by light may be inhibition of pupil dilation rather than inhibition of endogenous melatonin secretion by the pineal gland, such that the effect of light on endogenous melatonin may be a secondary effect of light in humans.

Link Between Endogenous Melatonin and the Temperature Rhythm

Similar to the analysis of the link between endogenous melatonin and the sleep cycle, our literature review indicated evidence of a link between endogenous melatonin and the temperature rhythm. Specifically, a reduction in endogenous melatonin levels was often accompanied by an increase in core body temperature, and a shift in the rhythm of endogenous melatonin was often accompanied by a similar shift in the rhythm of core body temperature. The observation of a phase-link in the melatonin and temperature rhythms is consistent with current knowledge that the same biological clock, the SCN, controls both of these rhythms.[238] It has been suggested that exogenous melatonin induces sleepiness via a reduction in core body temperature, and the relationship between changes in endogenous melatonin and the temperature rhythm is consistent with this proposed mechanism. Only two studies examined the effect of manipulation of body temperature on endogenous melatonin, and the results were opposite. Additional research in this area is required to elucidate the effect of temperature on endogenous melatonin.

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 effect of melatonin on people with primary and secondary sleep disorders, beyond four weeks, remains to be determined. The short-term 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. There are very few studies that 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
- There is evidence of a link between endogenous melatonin and the temperature rhythm.

Table 28: Summary of the Evidence Surrounding the Effect of Melatonin on Sleep in Various Populations

	Normal Sleepers	Primary Sleep Disorder	Secondary Sleep Disorder	Sleep Restriction
Sleep Onset Latency	Decreased WMD: -3.9 min; 95 percent CI: -5.3 min., -2.6 min. N=20	Decreased WMD: -10.7 min.; 95 percent CI: -17.6 min., -3.7 min. N=12	No Effect N=6	No Effect N=9
Sleep Efficiency	Increased WMD: 2.3 percent; 95 percent CI: 0.7 percent, 3.9 percent N=13	No Effect N=9	Increased WMD: 1.9 percent; 95 percent CI: 0.5 percent, 3.3 percent N=6	No Effect N=5

Abbreviations: WMD: weighted mean difference, **CI**: confidence interval

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List of Excluded Studies

Seven hundred and ninety-six studies were excluded from the review. Of these, 328 were reviews, book chapters or commentaries, and have not been included in this chapter. Other reasons for exclusion included inappropriate topic (n=36), study design (n=272), intervention (n=21), population (n=7) and outcomes (n=101). Three studies were not included because of inadequate reporting of outcomes. The reports of 25 studies were unobtainable at the time of this writing and two were realized upon completion of the final report.

Excluded-Topic

We sought to synthesize evidence related to four topic areas, including the physiology and pharmacology of melatonin; the populations that would benefit most from melatonin treatment; the effectiveness of melatonin treatment; and the safety of melatonin treatment. The following studies were excluded because the topic of the study was not appropriate to any of the questions of the review.

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Excluded-Design

In general, only controlled clinical trials were included for each 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. The following studies did not have the design that was appropriate to the question(s) of the review to which they were potentially relevant.

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Excluded-Population

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Addendum

The authors acknowledge the existence of the following two studies, which they became aware of only upon completion of the final report.

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Definitions of Terminology

The definitions of key words, as they are used in this report, are provided below.

endogenous melatonin = melatonin levels in either blood/serum/plasma, urine, saliva or cerebrospinal fluid and/or phase of melatonin rhythm in either blood/serum/plasma, urine, saliva or cerebrospinal fluid

effectiveness = the degree to which an intervention does what it is intended to do, under ordinary conditions

exogenous melatonin =melatonin that is administered to individuals from a source outside of the body

half-life of melatonin ($t_{1/2}$) = time required for circulating levels of melatonin to be reduced to half of its peak value

percentage time in REM sleep (% time spent in REM sleep)= amount of time spent in REM sleep expressed as a percentage of total sleep time

REM latency = amount of time required to begin REM sleep after sleep onset

sleep disorder = primary sleep disorder, secondary sleep disorder, sleep restriction

- primary sleep disorder = sleep disorder is not accompanied by another clinical problem that could potentially be its cause
- secondary sleep disorder = sleep disorder is accompanied by another clinical problem that may be its cause
- sleep restriction = sleep disorder is due to altered sleep schedules or transmeridian air travel, such as in shift-work disorder and jet-lag, respectively.

sleep efficiency = amount of time spent asleep expressed as a percentage of the time spent in bed

sleep onset latency (SOL) = amount of time required before the onset of stage one sleep after retiring to bed

sleep quality = overall quality of sleep

total sleep time (TST)= total time spent asleep while in bed

wakefulness after sleep onset (WASO) = amount of time spent awake in bed following first attainment of stage one sleep

Appendix A: Exact Search Strings

Search Strategies

Evidence Table A-1: MEDLINE: melatonin and sleep disorders
Evidence Table A-2: EMBASE: melatonin and sleep disorders
Evidence Table A-3: CINAHL: melatonin and sleep disorders
Evidence Table A-4: CENTRAL: melatonin and sleep disorders
Evidence Table A-5: Science Citation Index: melatonin and sleep disorders
Evidence Table A-6: Global Health [CAB Health]: melatonin and sleep disorders
Evidence Table A-7: PubMed: melatonin and sleep disorders

Evidence Table A-1: MEDLINE: melatonin and sleep disorders

MEDLINE	1966 to June, Week 3, 2003
Set # and Keyword Search	
1. exp MELATONIN/	
2. melatonin.mp.	
3. melatonine.mp.	
4. 73-31-4.rn.	
5. 5-Methoxy-N-acetyltryptamine.mp.	
6. N-Acetyl-5-methoxytryptamine.mp.	
7. luzindole.mp.	
8. or/1-7	
9. exp Sleep Disorders/	
10. sleep disorder$.mp.	
11. dyssomnia$.mp.	
12. insomnia$.mp.	
13. narcoleps$.mp.	
14. hypersomnia$.mp.	
15. central alveolar hypoventilat$.mp.	
16. periodic limb movement$.mp.	
17. restless leg.mp.	
18. nocturnal eating.mp.	
19. nocturnal drinking.mp.	
20. time-zone change$.mp.	
21. jet lag.mp.	
22. parasomnia$.mp.	
23. confusional arousal$.mp.	
24. rhythmic movement disorder$.mp.	
25. nocturnal leg cramp$.mp.	
26. nightmare$.mp.	
27. nocturnal paroxysmal dystonia$.mp.	
28. sudden unexplained nocturnal death syndrome.mp.	
29. SUNDS.mp.	
30. snoring.mp.	
31. snore$.mp.	
32. congenital central hypoventilation.mp.	
33. sudden infant death syndrome$.mp.	
34. exp Sudden Infant Death/	
35. SIDS.mp.	
36. subwakefulness.mp.	
37. fragmentary myoclonus.mp.	
38. hypnagogic hallucination$.mp.	
39. (sleep$ or circadian$).mp.	
40. exp Sleep/	
41. exp arousal/	
42. or/9-41	
43. 8 and 42	
44. RANDOMIZED CONTROLLED TRIAL.pt.	
45. CONTROLLED CLINICAL TRIAL.pt.	
46. RANDOMIZED CONTROLLED TRIALS/	
47. RANDOM ALLOCATION/	
48. DOUBLE BLIND METHOD/	
49. SINGLE-BLIND METHOD/	
50. or/44-49	
51. ANIMAL/ not HUMAN/	
52. 50 not 51	
53. CLINICAL TRIAL.pt.	
54. exp CLINICAL TRIALS/	
55. (clin$ adj25 trial$).ti,ab.	
56. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	

Evidence Table A-1: MEDLINE: melatonin and sleep disorders (continued)	
Medline	**1966 to June, Week 3, 2003**
Set # and Keyword Search	
57. PLACEBOS/ 58. placebo$.ti,ab. 59. random$.ti,ab. 60. RESEARCH DESIGN/ 61. or/53-60 62. 61 not 51 63. 62 not 52 64. COMPARATIVE STUDY/ 65. exp EVALUATION STUDIES/ 66. FOLLOW UP STUDIES/ 67. PROSPECTIVE STUDIES/ 68. (control$ or prospectiv$ or volunteer$ or cohort$ or case series).ti,ab,sh. 69. or/64-68 70. 69 not 51 71. 70 not (52 or 63) 72. 52 or 63 or 70 73. meta-analysis.pt. 74. (meta-anal$ or metaanal$).mp. 75. (((quantitativ$ adj3 review$1) or quantitativ$) adj3 overview$).mp. 76. (((systematic adj3 review$1) or systematic) adj3 overview$1).mp. 77. (((methodologic adj3 review$1) or methodologic) adj3 overview$).mp. 78. (integrat$ adj5 research).mp. 79. (quantitativ$ adj3 synthes$).mp. 80. or/73-79 81. review.pt. or (review$ or overview$).mp. 82. (medline or medlars or pubmed or index medicus or embase or cochrane).mp. 83. (scisearch or web of science or psycinfo or psychinfo or cinahl or cinhal).mp. 84. (excerpta medica or psychlit or psyclit or current contents or science citation index or sciences citation index).mp. 85. (hand search$ or manual search$).mp. 86. ((((electronic adj3 database$) or bibliographic) adj3 database$) or periodical index$).mp. 87. (pooling or pooled or mantel haenszel).mp. 88. (peto or der simonian or dersimonian or fixed effect$).mp. 89. ((combine$ or combining) adj5 (data or trial or trials or studies or study or result or results)).mp. 90. or/82-89 91. 81 and 90 92. 80 or 91 93. (hta$ or health technology assessment$ or biomedical technology assessment$).mp. 94. technology assessment, biomedical/ or biomedical technology asssessment/ 95. 93 or 94 96. 92 or 95 97. limit 43 to review 98. 43 and 96 99. 97 or 98 100. 43 and 72 101. 99 not 100 102. limit 100 to human 103. limit 101 to human	

Evidence Table A-2: EMBASE: melatonin and sleep disorders

EMBASE	1988 to Week 26, 2003
Set # and Keyword Search	
1. exp MELATONIN/	
2. melatonin.mp.	
3. melatonine.mp.	
4. 73-31-4.rn.	
5. 5-Methoxy-N-acetyltryptamine.mp.	
6. N-Acetyl-5-methoxytryptamine.mp.	
7. luzindole.mp.	
8. or/1-7	
9. exp Sleep Disorders/	
10. sleep disorder$.mp.	
11. dyssomnia$.mp.	
12. insomnia$.mp.	
13. narcoleps$.mp.	
14. hypersomnia$.mp.	
15. central alveolar hypoventilat$.mp.	
16. periodic limb movement$.mp.	
17. restless leg.mp.	
18. nocturnal eating.mp.	
19. nocturnal drinking.mp.	
20. time-zone change$.mp.	
21. jet lag.mp.	
22. parasomnia$.mp.	
23. confusional arousal$.mp.	
24. rhythmic movement disorder$.mp.	
25. nocturnal leg cramp$.mp.	
26. nightmare$.mp.	
27. nocturnal paroxysmal dystonia$.mp.	
28. sudden unexplained nocturnal death syndrome.mp.	
29. SUNDS.mp.	
30. snoring.mp.	
31. snore$.mp.	
32. congenital central hypoventilation.mp.	
33. sudden infant death syndrome$.mp.	
34. exp Sudden Infant Death/	
35. SIDS.mp.	
36. subwakefulness.mp.	
37. fragmentary myoclonus.mp.	
38. hypnagogic hallucination$.mp.	
39. (sleep$ or circadian$).mp.	
40. exp Sleep/	
41. exp arousal/	
42. exp wakefulness/	
43. or/9-42	
44. exp Melatonin Receptor/	
45. exp MELATONIN DERIVATIVE/	
46. or/8,44-45	
47. 46 and 43	
48. Randomized Controlled Trial/	
49. exp Randomization/	
50. Double Blind Procedure/	
51. Single Blind Procedure/	
52. or/48-51	
53. Clinical Trial/	
54. (clin$ adj25 trial$).mp.	
55. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).mp.	
56. exp Placebo/	
57. (placebo$ or random$).mp.	

Evidence Table A-2: EMBASE: melatonin and sleep disorders (continued)	
EMBASE	**1988 to Week 26, 2003**
Set # and Keyword Search	
58. exp Methodology/ 59. exp Comparative Study/ 60. exp Evaluation/ 61. exp Follow Up/ 62. exp Prospective Study/ 63. (control$ or prospectiv$ or volunteer$).mp. 64. or/53-63 65. 52 or 64 66. (cohort$ or case series).mp. 67. exp cohort analysis/ 68. exp Case Study/ 69. or/66-68 70. or/65,69 71. meta-analysis.pt. 72. (meta-anal$ or metaanal$).mp. 73. (((quantitativ$ adj3 review$1) or quantitativ$) adj3 overview$).mp. 74. (((systematic adj3 review$1) or systematic) adj3 overview$1).mp. 75. (((methodologic adj3 review$1) or methodologic) adj3 overview$).mp. 76. (integrat$ adj5 research).mp. 77. (quantitativ$ adj3 synthes$).mp. 78. or/71-77 79. review.pt. or (review$ or overview$).mp. 80. (medline or medlars or pubmed or index medicus or embase or cochrane).mp. 81. (scisearch or web of science or psycinfo or psychinfo or cinahl or cinhal).mp. 82. (excerpta medica or psychlit or psyclit or current contents or science citation index or sciences citation index).mp. 83. (hand search$ or manual search$).mp. 84. ((((electronic adj3 database$) or bibliographic) adj3 database$) or periodical index$).mp. 85. (pooling or pooled or mantel haenszel).mp. 86. (peto or der simonian or dersimonian or fixed effect$).mp. 87. ((combine$ or combining) adj5 (data or trial or trials or studies or study or result or results)).mp. 88. or/80-87 89. 79 and 88 90. 78 or 89 91. (hta$ or health technology assessment$ or biomedical technology assessment$).mp. 92. technology assessment, biomedical/ or biomedical technology asssessment/ 93. 91 or 92 94. 90 or 93 95. Review/ 96. 94 or 95 97. 47 and 70 98. 47 and 96 99. limit 97 to human 100. limit 98 to human 101. Nonhuman/ 102. 99 not 101 103. 100 not 101	

Evidence Table A-3: CINAHL: melatonin and sleep disorders

CINAHL	1982 to June Week 4, 2003
Set # and Keyword Search	
1. exp MELATONIN/	
2. melatonin.mp.	
3. melatonine.mp.	
4. 73-31-4.rn.	
5. 5-Methoxy-N-acetyltryptamine.mp.	
6. N-Acetyl-5-methoxytryptamine.mp.	
7. luzindole.mp.	
8. or/1-7	
9. exp Sleep Disorders/	
10. sleep disorder$.mp.	
11. dyssomnia$.mp.	
12. insomnia$.mp.	
13. narcoleps$.mp.	
14. hypersomnia$.mp.	
15. central alveolar hypoventilat$.mp.	
16. periodic limb movement$.mp.	
17. restless leg.mp.	
18. nocturnal eating.mp.	
19. nocturnal drinking.mp.	
20. time-zone change$.mp.	
21. jet lag.mp.	
22. parasomnia$.mp.	
23. confusional arousal$.mp.	
24. rhythmic movement disorder$.mp.	
25. nocturnal leg cramp$.mp.	
26. nightmare$.mp.	
27. nocturnal paroxysmal dystonia$.mp.	
28. sudden unexplained nocturnal death syndrome.mp.	
29. SUNDS.mp.	
30. snoring.mp.	
31. snore$.mp.	
32. congenital central hypoventilation.mp.	
33. sudden infant death syndrome$.mp.	
34. exp Sudden Infant Death/	
35. SIDS.mp.	
36. subwakefulness.mp.	
37. fragmentary myoclonus.mp.	
38. hypnagogic hallucination$.mp.	
39. (sleep$ or circadian$).mp.	
40. exp Sleep/	
41. exp arousal/	
42. exp wakefulness/	
43. or/9-42	
44. 8 and 43	
45. random assignment/	
46. random sample/	
47. crossover design/	
48. exp clinical trials/	
49. exp comparative studies/	
50. "control (research)".mp.	
51. control group/	
52. factorial design/	
53. quasi-experimental studies/	
54. nonrandomized trials/	
55. placebos/	
56. meta analysis/	
57. clinical nursing research.mp. or clinical research/	

Evidence Table A-3: CINAHL: melatonin and sleep disorders (continued)	
CINAHL	**1982 to June Week 4, 2003**
Set # and Keyword Search	
58. community trials/ or experimental studies/ or one-shot case study/ 59. community trials/ or experimental studies/ or one-shot case study/ or pretest-posttest design/ or solomon four-group design/ or static group comparison/ or study design/ 60. (clinical trial or systematic review).pt. 61. random$.mp. 62. ((singl$ or doubl$ or tripl$ or trebl$) adj10 (blind$ or mask$)).mp. 63. (cross?over or placebo$ or control$ or factorial or sham$).mp. 64. ((clin$ or intervention$ or compar$ or experiment$ or preventive or therapeutic) adj10 trial$).mp. 65. (meta?analy$ or systematic review$).mp. 66. or/45-65 67. convenience sample/ 68. exp research, allied health/ or research, medical/ or research, nursing/ 69. research question/ 70. nursing practice, research-based/ 71. research methodology/ 72. exp evaluation research/ 73. [evaluation/mt] 74. concurrent prospective studies/ or prospective studies/ 75. (nursing interventions or research).pt. 76. or/67-75 77. 66 or 76 78. 44 and 77 79. meta-analysis.pt. 80. (meta-anal$ or metaanal$).mp. 81. (((quantitativ$ adj3 review$1) or quantitativ$) adj3 overview$).mp. 82. (((systematic adj3 review$1) or systematic) adj3 overview$1).mp. 83. (((methodologic adj3 review$1) or methodologic) adj3 overview$).mp. 84. (integrat$ adj5 research).mp. 85. (quantitativ$ adj3 synthes$).mp. 86. or/79-85 87. review.pt. or (review$ or overview$).mp. 88. (medline or medlars or pubmed or index medicus or embase or cochrane).mp. 89. (scisearch or web of science or psycinfo or psychinfo or cinahl or cinhal).mp. 90. (excerpta medica or psychlit or psyclit or current contents or science citation index or sciences citation index).mp. 91. (hand search$ or manual search$).mp. 92. ((((electronic adj3 database$) or bibliographic) adj3 database$) or periodical index$).mp. 93. (pooling or pooled or mantel haenszel).mp. 94. (peto or der simonian or dersimonian or fixed effect$).mp. 95. ((combine$ or combining) adj5 (data or trial or trials or studies or study or result or results)).mp. 96. or/88-95 97. 87 and 96 98. 86 or 97 99. (hta$ or health technology assessment$ or biomedical technology assessment$).mp. 100. technology assessment, biomedical/ or biomedical technology asssessment/ 101. 99 or 100 102. 98 or 101 103. limit 44 to (review or systematic review) 104. or/102-103 105. 44 and 104 106. cohort.mp.	

Evidence Table A-3: CINAHL: melatonin and sleep disorders (continued)	
CINAHL	**1982 to June Week 4, 2003**
Set # and Keyword Search	
107. case series.mp. 108. exp case studies/ 109. case study.pt. 110. or/106-108 111. 44 and 110 112. 105 not 78 113. 78 or 111	

Evidence Table A-4: CENTRAL: melatonin and sleep disorders

CENTRAL - Issue 2 2003	**3rd Quarter, 2003**
Set # and Keyword Search	
1. MELATONIN single term (MeSH) 316	
2. melatonin 454	
3. melatonine 2	
4. 73-31-4 0	
5. 5-methoxy-n-acetyltryptamine 0	
6. n-acetyl-5-methoxytryptamine 6	
7. luzindole 0	
8. (1 or 2 or 3 or 4 or 5 or 6 or 7) 456	
9. SLEEP DISORDERS explode all trees (MeSH) 1643	
10. dyssomnia* 3	
11. insomnia* 1625	
12. narcoleps* 73	
13. hypersomnia* 66	
14. (central next alveolar next hypoventilat*) 0	
15. (periodic next limb next movement*) 30	
16. (restless next leg) 9	
17. (nocturnal next eating) 1	
18. (nocturnal next drinking) 0	
19. (time-zone next change*) 0	
20. (jet next lag) 33	
21. parasomnia* 12	
22. (confusional next arousal*) 0	
23. (rhythmic next movement next disorder*) 0	
24. (nocturnal next leg next cramp*) 20	
25. nightmare* 90	
26. (nocturnal next paroxysmal next dystonia*) 1	
27. (sudden next unexplained next nocturnal next death next syndrome) 0	
28. sunds 0	
29. snoring 156	
30. snore* 76	
31. (congential next central next hypoventilation) 0	
32. (sudden next infant next death next syndrome*) 41	
33. sids 27	
34. subwakefulness 0	
35. (fragmentary next myoclonus) 0	
36. (hypnagogic next hallucination*) 2	
37. sleep* or circadian* 8680	
38. SLEEP explode all trees (MeSH) 2300	
39. AROUSAL explode all trees (MeSH) 3330	
40. (9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39) 12449	
41. (8 and 40) 290	

Evidence Table A-5: Science Citation Index: melatonin and sleep disorders

Science Citation Index		Search performed July 4, 2003
Set #	**Results**	**Search History**
28	265	21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
27	44	8 AND 17 *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
26	177	8 AND 16 *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
25	27	#8 AND #15 *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
24	151	8 AND 14 *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
23	9	8 AND 13 *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
22	18	8 AND 12 *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
21	12	8 AND 11 *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
20	48	#18 OR #19 *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
19	13	#8 AND #10 *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
18	36	#8 AND #9 *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
17	>100,000	TS=random* *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
16	67,296	TS=placebo* *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
15	69,106	TS=clinical trial* *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
14	69,590	TS=(single-blind*) OR TS=(double-blind*) *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
13	68,166	TS=cohort* OR TS=case series *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
12	>100,000	TS=follow up OR TS=prospective *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
11	32,268	TS=randomized controlled trial* OR TS=controlled clinical trial* OR TS=random allocation OR TS=randomly allocated OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
10	74,601	TS=quantitative synthes* OR TS=hta* OR TS=(health technology assessment*) OR TS=(biomedical technology assessment*) OR TS=meta analys* OR TS=meta-analys* OR TS=metaanalys* OR TS=(quantitativ* review*) OR TS=(quantitativ* overview*) OR TS=overview* *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
9	>100,000	TS=review* *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
8	1,468	#6 AND #7 *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*

Evidence Table A-5: Science Citation Index: melatonin and sleep disorders (continued)		
Science Citation Index		**Search performed July 4, 2003**
Set #	**Results**	**Search History**
7	67,627	TS=sleep disorder* OR TS=dyssomnia* OR TS=insomnia* OR TS=narcoleps* OR TS=hypersomnia* OR TS=central alveolar hypoventilat* OR TS=periodic limb movement* OR TS=restless leg OR TS=nocturnal eating OR TS=nocturnal drinking OR TS=time zone* OR TS=jet lag* OR TS=parasomnia* OR TS=confusional arousal* OR TS=rhythmic movement disorder* OR TS=nocturnal leg cramp* OR TS=nightmare* OR TS=nocturnal paroxysmal dystonia* OR TS=sudden unexplained nocturnal death syndrome* OR TS=SUNDS OR TS=snore* OR TS=snoring OR TS=congenital central hypoventilation OR TS=(sudden infant death syndrome) OR TS=SIDS OR TS=subwakefulness OR TS=fragmentary myoclonus OR TS=hypnagogic hallucination* OR TS=sleep* OR TS=circadian OR TS=arousal OR TS=arouse *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
6	11,454	#1 OR #2 OR #3 OR #4 OR #5 *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
5	92	TS=luzindole *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
4	80	TS=N-Acetyl-5-methoxytryptamine *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
3	15	TS=5-Methoxy-N-acetyltryptamine *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
2	1	TS=73-31-4 *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*
1	11,450	TS=melatonin OR TS=melatonine *DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2003*

Evidence Table A-6: Global Health [CAB Health]: melatonin and sleep disorders

Global Health [CAB Health]		**Search performed July 8, 2003**
Set # and Keyword Search		
Set	**Items**	**Description**
S1	203	MELATONIN OR MELATONINE OR 5?METHOXY?N?ACETYLTRYPTAMINE OR N?ACETYL?5?METHOXYTRYPTAMINE OR LUZINDOLE
S2	2735	SLEEP? OR DYSSOMNIA? OR INSOMNIA? OR NARCOLEPS? OR HYPERSOMNIA?
S3	287	PARASOMNIA? OR NIGHTMARE? OR SUNDS OR SNORING OR SNORE? OR SIDS
S4	1502	SUBWAKEFUL? OR AROUS? OR CIRCADIAN
S5	0	CENTRAL(W)ALVEOLAR(W)HYPOVENTILAT?
S6	0	PERIODIC(W)LIMB(W)MOVEMENT?
S7	6	RESTLESS(W)LEG?
S8	13	NOCTURNAL(W)EAT?
S9	5	NOCTURNAL(W)DRINK?
S10	9	TIME?ZONE? OR TIME(W)ZONE?
S11	17	JET?LAG? OR JET(W)LAG?
S12	0	CONFUSIONAL(W)AROUS?
S13	0	RHYTHMIC(W)MOVEMENT(W)DISORDER?
S14	4	NOCTURNAL(W)LEG(W)CRAMP?
S15	0	NOCTURNAL(W)PAROXYSMAL(W)DYSTONIA?
S16	1	SUDDEN(W)UNEXPLAINED(W)NOCTURNAL(W)DEATH(W)SYNDROME?
S17	0	CONGENITAL(W)CENTRAL(W)HYPOVENTILAT?
S18	435	SUDDEN(W)INFANT(W)DEATH?
S19	0	FRAGMENTARY(W)MYOCLUNUS
S20	0	HYPNAGOGIC(W)HALLUCINATION?
S21	3	CATAPLEX? OR NIGHT(W)TERROR?
S22	4530	S2 OR S3 OR S4 OR S7 OR S8 OR S9 OR S10 OR S11 OR S14 OR S16 OR S18 OR S 21
S23	36	S1 AND S22

Evidence Table A-7: PubMed: melatonin and sleep disorders

PubMed		Search performed July 9, 2002	
Set # and Keyword Search			
Search	**Most Recent Queries**	**Time**	**Result**
20	Search 17 NOT 16 Field: All Fields, Limits: 180 Days, Human	14:53:23	7
18	Search 17 NOT 16	14:52:57	525
19	Search 13 AND 14 Field: All Fields, Limits: 180 Days, Human	14:52:41	21
16	Search 13 AND 14	14:52:23	1146
17	Search 13 AND 15	14:51:59	729
15	Search (meta analys*) OR (metaanalys*) OR (review*) OR (overview*) OR (quantitative synthes*) OR (HTA) OR (health technology assessment) OR (biomedical technology assessment) OR (systematic[sb])	14:51:29	1287351
14	Search (randomized controlled trial [PTYP] OR drug therapy [SH] OR therapeutic use [SH:NOEXP] OR random* [WORD]) OR (random allocation) OR (randomly allocated) OR (single blind*) OR (double blind*) OR (clinical trial*) OR (placebo*) OR (research design*) OR (comparative stud*) OR (evaluation stud*) OR (follow up stud*) OR (prospective stud*) OR (cohort*) OR (case series)	14:51:11	2845077
13	Search #11 AND #12	14:50:53	4218
12	Search ((sleep [MESH]) OR (Sleep Disorders [MESH]) OR (Arousal [MESH]) OR (sleep*) OR (sleep disorder*) OR (dyssomnia*) OR (insomnia*) OR (narcoleps*) OR (hypersomnia*) OR (central alveolar hypoventilat*) OR (periodic limb movement*) OR (nocturnal eating) OR (nocturnal drinking) OR (time-zone*) OR (time zone*) OR (jet lag*) OR (parasomnia*) OR (confusional arousal*) OR (rhythmic movement disorder*) OR (nocturnal leg cramp*) OR (nightmare*) OR (nocturnal paroxysmal dystonia*) OR (sudden unexplained nocturnal death syndrome*) OR (SUNDS) OR (snoring) OR (snore*) OR (congential central hypoventilat*) OR (sudden infant death syndrome*) OR (SIDS) OR (subwakefulness) OR (fragmentary mycoclonus) OR (hypnagogic hallucination*) OR (arous*) OR (circadian))	14:50:17	163039
11	Search (Melatonin [MESH]) OR (Melatonin*) OR (73-31-4) OR (5-Methoxy-N-acetyltryptamine) OR (N-Acetyl-5-methoxytryptamine) OR (luzindole) OR (N-acetyl-methoxytryptamine))	14:49:37	10374

BIO ABS **Search performed July 4, 2003**
Keyword Search

((randomized controlled trial*) or (controlled clinical trial*) or (random allocation) or (randomly allocated) or (single blind*) or (double blind*) or (clinical trial*) or (placebo*) or (research design*) or (comparative stud*) or (evaluation stud*) or (follow up stud*) or (prospective stud*) or (cohort*) or (case series) or (meta analys*) or (metaanalys*) or (review*) or (overview*) or (quantitative synthes*) or (HTA) or (health technology assessment) or (biomedical technology assessment) or (random*)) and (((Melatonin*) or (73-31-4) or (5-Methoxy-N-acetyltryptamine) or (N-Acetyl-5-methoxytryptamine) or (luzindole) or (N-acetyl-methoxytryptamine) or (N-(2-(5-Methoxy-1H-indol-3-yl)ethyl)acetamide) or (3-(2-acetamidoethyl)-5-methoxyindole) or (N-(2-(5-Methyxyindol-3-yl)ethyl)acetamide)) and ((sleep*) or (sleep disorder*) or (dyssomnia*) or (insomnia*) or (narcoleps*) or (hypersomnia*) or (central alveolar hypoventilat*) or (periodic limb movement*) or (nocturnal eating) or (nocturnal drinking) or (time-zone*) or (time zone*) or (jet lag*) or (parasomnia*) or (confusional arousal*) or (rhythmic movement disorder*) or (nocturnal leg cramp*) or (nightmare*) or (nocturnal paroxysmal dystonia*) or (sudden unexplained nocturnal death syndrome*) or (SUNDS) or (snoring) or (snore*) or (congential central hypoventilat*) or (sudden infant death syndrome*) or (SIDS) or (subwakefulness) or (fragmentary mycoclonus) or (hypnagogic hallucination*) or (arous*) or (circadian)))

International Pharmaceutical Abstracts **1970 to August, 2003**

This database was searched using the same strategy as for MEDLINE.

PreMEDLINE **Search performed June 30and July 4, 2003**

This database was searched using the same strategy as for MEDLINE.

NLM Gateway **Search performed August 13, 2003**

Searched for books and conference proceedings using ‘melatonin*’ and ‘sleep’

OCLC Papers First and Proceedings First **Search performed July 11, 2003**

Searched for conference proceedings using ‘melatonin*’ and ‘sleep’

TOXLINE **Search performed July 4, 2003**
Keyword Search

(((((melatonin*) OR (73-31-4) OR (5-Methoxy-N-acetyltryptamine) OR (luzindole) OR (N-Acetyle-5-methyxoytryptamine)) AND (circadian*) AND ((randomized controlled trial*) or (controlled clinical trial*) or (random allocation) or (randomly allocated) or (single blind*) or (double blind*) or (clinical trial*) or (placebo*) or (research design*) or (comparative stud*) or (random*) or (evaluation stud*) or (follow up stud*) or (prospective stud*) or (cohort*) or (case series) or (meta analys*) or (metaanalys*) or (review*) or (overview*) or (quantitative synthes*) or (HTA) or (health technology assessment) or (biomedical technology assessment)))) NOT ((((melatonin*) OR (73-31-4) OR (5-Methoxy-N-acetyltryptamine) OR (luzindole) OR (N-Acetyle-5-methyxoytryptamine)) AND ((sleep*) OR (sleep disorder*) OR (dyssomnia*) OR (insomnia*) OR (narcoleps*) OR (hypersomnia*) OR (central alveolar hypoventilat*) OR (periodic limb movement*) OR (nocturnal eating) OR (nocturnal drinking) OR (time-zone*) OR (time zone*) OR (jet lag*) OR (parasomnia*) OR (confusional arousal*) OR (rhythmic movement disorder*) OR (nocturnal leg cramp*) OR (nightmare*) OR (nocturnal paroxysmal dystonia*) OR (sudden unexplained nocturnal death syndrome*) OR (SUNDS) OR (snoring) OR (snore*) OR (congential central hypoventilat*) OR (sudden infant death syndrome*) OR

(SIDS) OR (subwakefulness) OR (fragmentary mycoclonus) OR (hypnagogic hallucination*) OR (arous*)) AND ((randomized controlled trial*) or (controlled clinical trial*) or (random allocation) or (randomly allocated) or (single blind*) or (double blind*) or (clinical trial*) or (placebo*) or (research design*) or (comparative stud*) or (random*) or (evaluation stud*) or (follow up stud*) or (prospective stud*) or (cohort*) or (case series) or (meta analys*) or (metaanalys*) or (review*) or (overview*) or (quantitative synthes*) or (HTA) or (health technology assessment) or (biomedical technology assessment)))))

Hand-searched Associated Professional Sleep Society abstracts 1999-2003

Appendix B: Quality Assessment and Data Extraction Forms

Form B-1: Quality Assessment Form: Jadad Scale and Allocation Concealment for Quality Assessment of RCTs
Form B-2: Quality Assessment Form: Downs and Black Checklist for Quality Assessment of non-RCTs
Form B-3: Data Extraction Form

Form B-1: Jadad Scale and Allocation Concealment for Quality Assessment of RCTs

Study # _____ Initials of Assessor: _____

Part 1 (from Jadad – Controlled Clin Trials 1996; 17:1-12)

Score

1. Was the study described as randomized (this includes the use of words such as randomly, random and randomization)?
   Yes = 1 No = 0 _____

2. Was the study described as double-blind?
   Yes = 1 No = 0 _____

3. Was there a description of withdrawals and drop-outs?
   Yes = 1 No = 0 _____

Additional points: Add 1 point if:

Method to generate the sequence of randomization was described and was appropriate (e.g. table of random numbers, computer generated, coin tossing, etc.) _____

Method of double-blinding described and appropriate (identical placebo, active placebo, dummy) _____

Point deduction: Subtract 1 point if:

Method of randomization described and it was **in**appropriate (allocated alternately, according to date of birth, hospital number, etc.) -_____

Method of double-blinding described but it was **in**appropriate (comparison of tablet vs injection with no double dummy) -_____

OVERALL SCORE (Maximum 5) _____

Part 2 (from Schulz – JAMA 1995; 273:408-12)

Concealment of treatment allocation:

- ☐ Adequate
- ☐ Inadequate
- ☐ Unclear

Adequate:	e.g. central randomization; numbered/coded containers; drugs prepared by pharmacy; serially numbered, opaque, sealed envelopes
Inadequate:	e.g. alternation, use of case record numbers, dates of birth or day of week; open lists
Unclear:	Allocation concealment approach not reported or fits neither above category

Form B-2: Downs and Black Checklist for Quality Assessment of non- RCTs

Quality Assessor: _____ Reference Number: _____

Date: day___ mo___ yr___ First author: _____

(from Downs and Black, J Epidemiol Community Health 1998;52:377-384)

Reporting

1. **Is the hypothesis/aim/objective of the study clearly described?** This question refers to a clear statement of the objective, i.e. to measure the effectiveness of x in population y with respect to z, even if x, y and z are not clearly described (see questions 2, 3 and 4)

Yes	1	
No	0	

2. **Are the main outcomes to be measured clearly described in the Introduction or Methods section?** If the main outcomes are first mentioned in the Results section, the question should be answered no. In case-control studies the case definition should be considered the outcome.

Yes	1	
No	0	

3. **Are the characteristics of the patients included in the study clearly described in the Introduction or Methods section?** In cohort studies and trials, inclusion and or exclusion criteria should be given. In case-control studies, a case definition and the source for controls should be given.

Yes	1	
No	0	

4. **Are the interventions of interest clearly described in the Introduction or Methods section?** Treatments and placebo (where relevant) that are to be compared should be clearly described.

Yes	1	
No	0	

5. **Are the distributions of principal confounders in each group of subjects to be compared clearly described?** A list of principal confounders is provided.

Yes	2	
Partially	1	
No	0	

6. **Are the main findings of the study clearly described?** Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. This question does not cover statistical tests, which are considered below.

Yes	1	
No	0	

7. **Does the study provide estimates of the random variability in the data for the main outcomes?** In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.

Yes	1	
No	0	

8. **Have all important adverse events that may be a consequence of the intervention been reported?** This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).

Yes	1	
No	0	

9. **Have the characteristics of patients lost to follow-up been described?** This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no where a study does no report the number of patients lost to follow-up.

Yes	1	
No	0	

10. **Have 95 percent CIs and/or actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?** (both CI and p value, either CI or p value, neither)

Yes	1	
No	0	

External validity

11. **Were the subjects asked to participate in the study representative of the entire population from which they were recruited?** The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.

Yes	1	
No	0	
Unable to determine	0	

12. **Were those subjects who were prepared to participate representative of the entire population from which they were recruited?** The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.

Yes	1	
No	0	
Unable to determine	0	

13. **Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?** For the study to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.

Yes	1	
No	0	
Unable to determine	0	

Internal validity – bias

14. **Was an attempt made to blind study subjects to the intervention they have received?** For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.

Yes	1	
No	0	
Unable to determine	0	

15. Was an attempt made to blind those measuring the main outcomes of the intervention?

Yes	1	
No	0	
Unable to determine	0	

16. If any of the results of the study were based on "data dredging", was this made clear? Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.

Yes	1	
No	0	
Unable to determine	0	

17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? Where follow-up was the same for all study patients that answer should be yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.

Yes	1	
No	0	
Unable to determine	0	

18. Were the statistical tests used to assess the main outcomes appropriate? The statistical techniques used must be appropriate to the data. For example non-parametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.

Yes	1	
No	0	
Unable to determine	0	

19. Was compliance with the interventions reliable? Where there was non compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.

Yes	1	
No	0	
Unable to determine	0	

20. Were the main outcome measures used accurate (valid and reliable)? For studies where the outcome measured are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.

Yes	1	
No	0	
Unable to determine	0	

Internal validity – confounding (selection bias)

21. **Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?** For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case-control studies where there is no information concerning the source of patients included in the study.

Yes	1	
No	0	
Unable to determine	0	

22. **Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?** For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.

Yes	1	
No	0	
Unable to determine	0	

23. **Were the subjects randomized to intervention groups?** Studies which state that subjects were randomized should be answered yes except where method of randomization would not ensure random allocation. For example alternate allocation would score no because it is predictable.

Yes	1	
No	0	
Unable to determine	0	

24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? All non-randomized studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.

Yes	1	
No	0	
Unable to determine	0	

25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders different between the treatment groups but was not taken into account in the analyses. In non-randomized studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.

Yes	1	
No	0	
Unable to determine	0	

26. Were losses to patients to follow-up take into account? (yes, no, unable to determine) If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.

Yes	1	
No	0	
Unable to determine	0	

Power

27. Was a power calculation reported for the primary outcome?

Yes	1	
No	0	
Unable to determine	0	

28. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance in less than 5 percent?

Yes	1	
No	0	
Unable to determine	0	

Form B-3: Data Extraction Form

GENERAL INFORMATION

<table>
<tr><td colspan="7">To be extracted from all studies.</td></tr>
<tr><td>RECORD ID</td><td>QUESTIONS OF REVIEW TO WHICH STUDY IS RELEVANT</td><td>REVIEWER/ DATE</td><td>VERIFIER/ DATE</td><td>FIRST AUTHOR</td><td>YEAR OF PUBLICATION</td><td>LANGUAGE OF PUBLICATION</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">COUNTRY WHERE STUDY TOOK PLACE</td><td colspan="2">FUNDING</td><td rowspan="2">OBJECTIVE (S)</td><td rowspan="2">DESIGN AS REPORTED BY AUTHOR</td><td rowspan="2">PROTOCOL</td><td rowspan="2">DESIGN AS JUDGED BY REVIEWER</td></tr>
<tr><td>PRIVATE</td><td>PUBLIC</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>

GENERAL INFORMATION (continued)

To be extracted from all studies						
POPULATION	**INCLUSION CRITERIA**	**EXCLUSION CRITERIA**	**NUMBER OF PEOPLE ELIGIBLE FOR THE STUDY**	**NUMBER OF PEOPLE ENROLLED IN THE STUDY**	**NUMBER AND TYPE OF COMPARISON GROUPS**	**NUMBER OF PEOPLE ALLOCATED TO EACH COMPARISON GROUP**
NUMBER OF PARTICIPANTS WHO WITHDREW FROM THE STUDY AND GROUP FROM WHICH THEY WITHDREW	**INTERVENTION(S)**	**PRIMARY OUTCOME(S)**	**SECONDARY OUTCOME(S)**	**DO PARTI-CIPANTS SUFFER FROM A METABOLIC DISORDER? IF SO, WHAT TYPE?**	**ARE PARTICIPANTS ON ANY MEDICATION? IF SO, WHAT TYPE?**	

GENERAL INFORMATION (continued)

To be extracted from all studies						
BASELINE CHARACTERISTICS OF PARTICIPANTS AS A WHOLE AND ACCORDING TO TREATMENT GROUP						
GENDER	**AGE**	**ETHNICITY**	**OTHER**			
TREATMENT PERIOD	**FOLLOW-UP PERIOD**	**WAS AN INTENTION TO TREAT ANALYSIS PLANNED OR CONDUCTED?**	**OTHER**	**COMMENTS**	**CONCLUSION**	

GENERAL INFORMATION (continued)

To be extracted from studies relevant to the following questions of the review: 2, 5, 9, 12						
FORMULATION OF MELATONIN ADMINISTERED TO PARTICIPANTS	**CONTENT AND QUALITY OF FORMULATION OF MELATONIN ADMINISTERED TO PARTIPANTS**	**DOSAGE, REGIMEN AND ROUTE OF MELATONIN ADMINISTRATION**				
To be extracted from studies relevant to the following questions of the review: 2, 5, 9						
TYPE OF SLEEP DISORDER FROM WHICH PARTICIPANTS SUFFER						
PRIMARY SLEEP DISORDER	**SECONDARY SLEEP DISORDER**	**SLEEP RESTRICTION**				

OUTCOME MEASURES

To be extracted from studies relevant to the following questions of the review: 2, 3, 6						
[MLT] IN SERUM	**[MLT] IN URINE**	**[MLT] IN SALIVA**				
To be extracted from studies relevant to the following questions of the review: 3, 5, 9						
SLEEPINESS/ FATIGUE/ ALERTNESS/ MOOD IN THE EVENING	**SLEEPINESS/ FATIGUE/ ALERTNESS/ MOOD IN THE DAYTIME**	**SLEEP ONSET LATENCY (SOL)**	**TOTAL SLEEP TIME (TST)**	**SLEEP QUALITY**	**WAKEFULNESS AFTER SLEEP ONSET (WASO)**	
SLEEP EFFICIENCY	**SLEEP ARCHITECTURE**	**REM LATENCY**	**NUMBER OF REM EPISODES**	**REM DURATION**	**DIM LIGHT MELATONIN ONSET (DLMO)**	**OTHER**

Appendix C: Evidence Tables

Evidence Table C-1: Formulations of Melatonin: Study Characteristics

Abbreviations: RCT: randomized controlled trial, **MLT:** melatonin, **FR:** fast-release, **SR:** slow-release, **SD:** standard deviation, **mg**: milligrams, **h**: hours, **NS:** not specified

Author	Year	Population		Sample Size	N	Study Design	Intervention
Almeida-Montes, LG	2003	Age (Years)		Treatment Group		RCT	Formulation
		Mean (SD):	50 (NS)	Enrolled :	10	Double-blind	Sustained-release MLT
Quality Score	16	Range:	30-72	Analyzed:	10	Cross-over	Route of Administration
		Gender		Control Group			Oral
		Female:	4	Enrolled :	10		Dosage and Timing
		Male:	6	Analyzed :	10		0.3 mg or 1 mg of MLT 1h before bedtime
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: Insomnia					One dose/day for 14 days

Author	Year	Population		Sample Size	N	Study Design	Intervention
Garfinkel, D	1995	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	24	Mean (SD):	76 (NS)	Enrolled :	12	Double-blind	Controlled-release MLT
		Range:	68-93	Analyzed:	12	Cross-over	Route of Administration
		Gender		Control Group			Oral
		Female:	5	Enrolled :	12		Dosage and Timing
		Male:	7	Analyzed :	12		2 mg of MLT 2h before desired bedtime
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: Long-term insomnia					One dose/night for 3 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Haimov, I	1995	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	18	Mean (SD):	73.1 (3.9)	Enrolled :	8	Double-blind	Sustained-release or Fast-release MLT
		Range:	NS	Analyzed:	8	Cross-over	Route of Administration
		Gender		Control Group			Oral
		Female:	4	Enrolled :	8		Dosage and Timing
		Male:	4	Analyzed :	8		2 mg FR, 2 mg SR or 1 mg SR MLT 2h before desired bedtime
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: Insomnia					One dose/day of 2 mg FR and 2 mg SR for 1 week, and one dose/day of 1 mg SR for 2 months

Author	Year	Population		Sample Size	N	Study Design	Intervention
McArthur, A	1998	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	21	Mean (SD):	10.1 (1.5)	Enrolled :	9	Double-blind	Immediate-release MLT
		Range	4-17	Analyzed:	9	Cross-over	Route of Administration
		Gender		Control Group			Oral or by gastrostomy tube
		Female:	9	Enrolled :	9		Dosage and Timing
		Male:	0	Analyzed :	9		Dosage based on individual body weight, range 2.5-7.5 mg
		Ethnicity: NS					of MLT given 1h before bedtime
		Sleep Disorder:					Frequency and Duration
		Sleep dysfunction accompanying Rett Syndrome					One dose/day for 4 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Serfaty, M	2002	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	22	Mean (SD):	84.2 (7.6)	Enrolled :	44	Double-blind	Slow release MLT
		Range:	NS	Analyzed:	25	Cross-over	Route of Administration
		Gender		Control Group			Oral
		Female:	9	Enrolled :	44		Dosage and Timing
		Male:	16	Analyzed :	25		6 mg of MLT at usual bedtime
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder:					One dose/day for 2 weeks
		Sleep disturbances accompanying dementia					

Author	Year	Population		Sample Size	N	Study Design	Intervention
Shamir, E	2001	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	24	Mean (SD):	64.2 (14.3)	Enrolled :	10	Double-blind	Controlled-release MLT
		Range:	28-82	Analyzed:	8	Cross-over	Route of Administration
		Gender		Control Group			Not specified
		Female:	11	Enrolled :	12		Dosage and Timing
		Male:	11	Analyzed :	12		2.5 mg MLT, timing: NS
		Ethnicity: NS					Frequency and Duration

Author	Year	Population		Sample Size	N	Study Design	Intervention
Smits, MG	2003	Age (Years)		3 treatments		RCT	Formulation
Quality Score	25	Mean (SD):		FR =0.5mg, 5mg		Double-blind	Fast-release or Controlled-release MLT
		Treatment group	9.2 (2.1)	CR= 2mg		Parallel	Route of Administration
		Control group	10.1 (1.7)	Treatment Groups			Oral
		Range:	NS	Enrolled :	NS		Dosage and Timing
		Gender		Analyzed:	NS		5 mg of MLT at 19:00 h
		Treatment group					Frequency and Duration
		Female:	20				One dose/day for 4 weeks
		Male:	6	Control Group			
		Control group		Enrolled :	NS		
		Female:	6	Analyzed :	NS		
		Male:	29				
		Ethnicity: NS					
		Sleep Disorder: Idiopathic chronic sleep-onset insomnia					

Author	Year	Population		Sample Size	N	Study Design	Intervention
Suhner, A	1998	Age (Years)		3 treatment groups		RCT	Formulation
Quality Score	20	Mean (SD):	36 (NS)	0.5 mg FR MLT		Double-blind	Fast-release or Controlled-release MLT
		Range:	20-65	5.0 mg FR MLT		Parallel	Route of Administration
		Gender		2 mg CR MLT			NS
		Female:	148	Treatment Groups			Dosage and Timing
		Male:	172	Enrolled :	NS		0.5 mg FR, 5.0 mg FR, 2 mg CR MLT at bedtime after
		Ethnicity: NS		Analyzed:	NS		23:10 h +/-1.52 h
		Sleep Disorder: Jet lag		Control Group			Frequency and Duration
				Enrolled :	NS		One dose/day for 4 days after eastward flight
				Analyzed :	NS		

Evidence Table C-1: References

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Evidence Table C-2 Pharmacokinetics of Melatonin: Study Characteristics

Abbreviations: RCT: randomized controlled trial, **CCT**: controlled clinical trial, **MLT**: melatonin, **FR**: fast-release, **SR:** slow-release,
SD: standard deviation, SE: standard error, mg: milligrams, h: hours, NS: not specified
Control Group received placebo unless otherwise indicated.

Author	Year	Population		Study Design	N	Intervention
Aldhous, M	1985	Age (Years)		CCT		Formulation
Quality Score	14	mean:	NS	Blindedness: NS		Slow-release MLT
		range:	21-39	Parallel		Route of Administration
		Gender		Treatment Group		Oral
		female:	6	*2mg MLT:*		Dosage and Timing
		male:	6	Enrolled:	5	2mg MLT gelatine-coated capsules or 2mg slow-
		Co-Medication: NS		Analyzed:	5	release tablets or 2mg MLT in corn oil at 1000h
		Sleep Disorder: None		*2mg MLT slow-release:*		Frequency and Duration
				Enrolled:	5	1 capsule or dose/day for 2 days
				Analyzed:	5	
				Control Group		
				2mg MLT in corn oil:		
				Enrolled:	4	
				Analyzed :	4	

Outcomes:
Half-Life +/-SEM
2mg MLT capsules, fasting : 0.54h +/- 0.03h; 2 mg MLT in corn oil, fed: 0.67 +/- 0.03h
Time to Reach Peak +/- SEM
2 mg MLT capsules, fed: 0.46h +/-07h; 2 mg MLT in corn oil, fasting: 0.95 +/- 0.42h
AUC +/- SEM
AUC (time period not specified): 2mg MLT capsules, fed: 8036 +/- 2455 pg/mL, 2mg MLT capsules, fasting: 3712 +/- 703 pg-h/ml; 2 mg MLT in corn oil, fed: 5826 +/- 2644 pg-h/mL; 2 mg MLT in corn oil, fasting: 3953 +/- 1533 pg-h/mL

Author	Year	Population		Study Design	N	Intervention
Benes, L	1997	Age (Years)		RCT		Formulation
Quality Score	16	mean (SD):	23(2)	Blindedness: NS		Not specified
		range:	21-27	Cross-over		Route of Administration
		Gender		Treatment Group		Oral (O), Transdermal (TD), Transmucosal (TM)
		female:	0	Enrolled:	12	Dosage and Timing
		male:	12	Analyzed:	12	0.76mg (oral), 8 mg (TD), or 0.5 mg (TM) at 0800h
		Co-Medication: None		Control Group		Frequency and Duration
		Sleep Disorder: None		Enrolled:	12	Single dose for 3 days one week apart
				Analyzed :	12	

Outcomes:
Time to Reach Peak
O: 1.3h (range 0.5 - 7h), TD: 13.0h (range 10.5 - 14h), TM: 7.9h (range 5-10.5h)
Peak [MLT] (Cmax)
O: 82.4 pg/mL (range 30 - 417 pg/mL), TD: 172.6 pg/mL (range 44 - 856 pg/mL), TM: 193.8 pg/mL (range 153 - 294 pg/mL)
AUC
AUC (0 - 24h): O: 894.3 pg-h/mL (range 247 - 4007), TD: 2226 pg-h/mL (range 626 - 8700), TM: 1820 pg-h/mL (range 1248 - 2830)

Author	Year	Population		Study Design	N	Intervention
Cagnacci, A	1995	Age (Years)		RCT		Formulation
Quality Score	16	mean:	NS	Double-blind		Not specified
		range:	25-35	Cross-over		Route of Administration
		Gender		Treatment Group		Oral
		female:	12	Enrolled:	6	Dosage and Timing
		male:	0	Analyzed:	6	1mg MLT at 0800h, 0.75mg at 1000h, 0.75 mg
		Co-Medication: NS		Control Group		at 1200h
		Sleep Disorder: None		Enrolled:	6	Frequency and Duration
				Analyzed :	6	Single dose

Outcomes:
Time to Reach Peak
1.5 - 2h
Peak [MLT] (Cmax) +/-SE
1984.14 +/- 425.07 pg/mL

Author	Year	Population		Study Design	N	Intervention
Cagnacci, A	1996	Age (Years)		RCT		Formulation
Quality Score	13	mean:	NS	Double-blind		Not specified
		range:	25-35	Cross-over		Route of Administration
		Gender		Treatment Group		Not specified
		female:	7	Enrolled:	7	Dosage and Timing
		male:	0	Analyzed:	7	1 mg MLT at 0800h, 0.75mg at 1000h, 0.75mg
		Co-Medication: NS		Control Group		at 1200h, total dose = 2.5mg
		Sleep Disorder: None		Enrolled:	7	Frequency and Duration
				Analyzed :	7	2.5mg/day for 2 days

Outcomes:
FP= Follicular Phase LP= Luteal Phase
AUC +/-SE
AUC (0-24h): FP: 637.82 +/- 258.11 pg-h/ml; LP: 668.69 +/- 309.22 pg-h/ml

Author	Year	Population		Study Design	N	Intervention
Cavallo, A	1996	Age (Years)		Case series		Formulation
Quality Score	17	mean:	NS	Blindedness: NS		Not specified
		range:	6-31yrs	Treatment Group		Route of Administration
		Gender		Enrolled:	30	Intravenous
		female:	18	Analyzed:	30	Dosage and Timing
		male:	12			0.5mug/kg MLT over 10 minutes
		Co-Medication: NS				Frequency and Duration
		Sleep Disorder: None				Single dose

Outcomes:
Half-Life +/- SD
Total Population: 0.76h +/-0.13h. By subject groups: Prepubertal (9; 5M, 4F): 0.67 +/- 0.12 h; Pubertal (8; 4M, 4F): 0.78 +/- 0.11; Adult females (7): 0.81 +/- 0.12; Adult males (9): 0.82 +/- 0.15; Adults, all (16): 0.79 +/- 0.10
AUC +/-SD
AUC (time frame not clear): Total population: 327.5 +/- 145.9 pg-h/mL.
By subject groups: Prepubertal (9; 5M, 4F): 250.9 +/- 91.8 pg-h/ml; Pubertal (8; 4M, 4F): 300.1 +/- 131.0 pg-h/ml; Adult females (7): 384.4 +/- 159.9 pg-h/ml; Adult males (9): 390.2 +/- 173.1 pg-h/ml; Adults, all (16): 376.9 +/- 154.3 pg-h/ml

Author	Year	Population		Study Design	N	Intervention
Dawson, D	1996	Age (Years)		RCT		Formulation
Quality Score	17	mean:	NS	Double-blind		Not specified
		range:	18-38	Cross-over		Route of Administration
		Gender		4 MLT dose groups		Oral
		female:	21	0.1, 0.5, 1, or 5 mg;		Dosage and Timing
		male:	11	Enrolled in each group:	8	0.1, 0.5, 1.0, or 5 mg MLT at 1600hr
		Co-Medication: None		Analyzed:	NS	Frequency and Duration
		Sleep Disorder: None		Control group		Single dose
				Enrolled in each group:	8	
				Analyzed:	NS	

Outcomes:
Half-Life +/-SD
Time to Reach Peak +/-SD
0.1 mg: 1.25 +/-0.48h, 0.5 mg: 0.88 +/-0.33h, 1.0 mg: 0.78 +/-0.47h, 5.0 mg: 0.97 +/-0.75h
Peak [MLT] (Cmax) +/-SD
0.1 mg: 124.5+/-97.8 pg/mL, 0.5 mg: 709.4 +/- 702.0pg/mL, 1.0 mg:
1356.3 +/- 1397.6 pg/mL, 5.0 mg: 5570.5 +/-3842.8 pg/mL

Author	Year	Population		Study Design	N	Intervention
Deacon, S	1995	Age (Years)		RCT		Formulation
Quality Score	20	mean (SD):	27.2(3.7)	Double-blind		Not specified
		range:	23-34	Cross-over		Route of Administration
		Gender		Treatment Group		Oral
		female:	3	Enrolled:	6	Dosage and Timing
		male:	3	Analyzed:	6	0.05mg, 0.5mg or 5.0 mg MLT at 1700h
		Co-Medication: None		Control Group		Frequency and Duration
		Sleep Disorder: None		Enrolled:	6	Single dose of either 0.05mg, 0.5mg, or 5mg for
				Analyzed :	6	1 day, 1 day per session, 4 sessions

Outcomes:
Half-Life +/-SEM
0.05 mg: 64.8 +/- 16.2, 0.5 mg: 42.6 +/- 12.6, 5.0 mg: 2 +/- 19.2 (units not specified)
Time to Reach Peak
0.05 mg: 0.5h, 0.5 mg: 1 h, 5.0 mg: 0.5h
Peak [MLT] (Cmax) +/-SEM
0.05 mg: 118 +/- 37 pg/mL (range 13 - 274 pg/mL), 0.5 mg: 1327 +/- 491 pg/mL (range 454 - 3700 pg/mL), 5.0 mg: 18495 +/- 3326 pg/mL (range 7830 - 31450)

Author	Year	Population		Study Design	N	Intervention
Debus, O	2002	Age (Years)		Case series		Formulation
Quality Score	14	mean:	3.4	Blindedness: NS		Not specified
		range:	one to five	Treatment Group		Route of Administration
		Gender		Enrolled:	5	Oral
		female:	2	Analyzed:	5	Dosage and Timing
		male:	3	*Only Patient 3*		5mg MLT at 2000h
		Co-Medication: 1 female took		*took melatonin*		Frequency and Duration
		chloral hydrate sleep medication				Single dose
		Sleep Disorder: None				

Outcomes:
Time to Reach Peak +/-NS
Patient 3: 1.2h
Peak [MLT] (Cmax) +/-NS
Patient 3: 18,650 pg/ml (in vCSF)

Author	Year	Population		Study Design	N	Intervention
Di, Wei-Di	1997	Age (Years)		Case series		Formulation
Quality Score	8	mean:	NS	Blindedness: NS		Not specified
		range:	21-32	Treatment Group		Route of Administration
		Gender		Enrolled:	4	Intravenous (IV) and Oral
		female:	0	Analyzed:	4	Dosage and Timing
		male:	4			20ug MLT (IV) and 500ug MLT (oral) on 2 separate occasions, timing: NS
		Co-Medication: NS				Frequency and Duration
		Sleep Disorder: None				Single dose

Outcomes:
Half-Life +/-SD
0.78h +/- 0.05h
Peak [MLT] (Cmax)(range)
480 - 9200 pg/mL

Author	Year	Population		Study Design	N	Intervention
Dollins, A	1993	Age (Years)		RCT		Formulation
Quality Score	18	mean (SD):	25(1.47)	Double-blind		Not specified
		range:	19-39	Cross-over		Route of Administration
		Gender		Treatment Groups		Oral
		female:	0	*Group 1 enrolled:*	20	Dosage and Timing
		male:	20	Ingested 10 mg MLT		10, 20, 40, or 80 mg MLT capsules at 1145 h
		Co-Medication: NS		*Group 2 enrolled:*	20	Frequency and Duration
		Sleep Disorder: None		Ingested 20 mg MLT		Single dose
				Group 3 enrolled:	20	
				Ingested 40 mg MLT		
				Group 4 enrolled:	20	
				Ingested 80 mg MLT		
				Control Group		
				Group 5 enrolled:	20	
				Ingested placebo.		
				Total analysed: NS		

Outcomes:
AUC +/-SEM
AUC (1000h to 1630h): 10 mg: 12,228 +/-5736.1 pg/mL, 20 mg: 27,186 +/-14,268.5 pg/mL, 40 mg: 52,557 +/- 26,401.6pg/mL,
80 mg: 106,223 pg/mL +/- 63.038.3

Author	Year	Population		Study Design	N	Intervention
Dollins, A	1994	Age (Years)		RCT		Formulation
Quality Score	18	mean (SD):	23.05(4.22)	Double-blind		Not specified
		range:	18-24	Cross-over		Route of Administration
		Gender		Treatment Groups		Oral
		female:	0	*0.1, 0.3, 1.0, 10mg*		Dosage and Timing
		male:	20	Enrolled:	20	0.1, 0.3, 1.0 or 10mg MLT at 1145h
		Co-Medication: NS		Analyzed:	12	Frequency and Duration
		Sleep Disorder: None		Control Group		Single dose/group over 5 days
				Enrolled:	20	
				Analyzed :	12	
				All 20 subjects participated in each treatment group		

Outcomes:

AUC +/- SEM

AUC (0000h to 1730h): 0.1 mg: 213.2+/-25.02 pg/ml, 0.3 mg: 459.9 +/-62.7pg/ml, 1.0 mg: 1599.0 +/-141.7pg/ml, 10 mg: 21000.4 +/-3752.3pg/ml

Author	Year	Population		Study Design	N	Intervention
Helrich, E	2002	Age (Years)		RCT		Formulation
Quality Score	13	mean:	25	Blindedness: NS		Not specified
		range:	NS	Cross-over		Route of Administration
		Gender		Treatment Groups		Intranasal
		female:	0	*200ug MLT*		Dosage and Timing
		male:	8	Enrolled:	8	0.200mg or 0.4mg MLT, timing: NS
		Co-Medication: NS		Analyzed:	7	Frequency and Duration
		Sleep Disorder: None		*400 ug MLT*		Single dose
				Enrolled:	8	
				Analyzed :	8	
				Control Group		
				Enrolled:	8	
				Analyzed :	8	

Outcomes:

Half-Life +/-SD

0.2mg MLT: 0.73h +/- 0.12h, 0.4mg MLT: 1h +/- 0.33h

AUC +/- SD

AUC (0 - 8h): 200ug MLT: 2.99 +/- 1.16, 400 ug MLT: 598 +/- 2.23 (units not specified)

Author	Year	Population		Study Design	N	Intervention
Hoffman, H	1998	Age (Years)		RCT		Formulation
Quality Score	14	mean:	NS	Blindedness: NS		Fast- and controlled-release MLT
		range:	25-35	Cross-over		Route of Administration
		Gender		Treatment Groups		Oral
		female:	0	*Fast-release (A)*		Dosage and Timing
		male:	15	Enrolled:	15	A (5mg) or B(10mg) or C (10mg) MLT
		Co-Medication: NS		Analyzed:	15	between 0800h and 0830h
		Sleep Disorder: None		*Controlled-release (B)*		Frequency and Duration
				Enrolled:	15	Single dose
				Analyzed:	15	
				Controlled-release (C)		
				Enrolled:	15	
				Analyzed:	15	

Outcomes:
Half-Life
A: 0.64h, B: 0.80h, C: 0.84h
Time to Reach Peak
Run 1: A: 0.5h, B: 0.75h, C: 0.5h; Run 2: A: NA, B: 3.5h, C: 3.5h
Peak [MLT] (Cmax)
Run 1: A: 4817.49 pg/mL, B: 3816.36 pg/mL, C: 2260.08 pg/mL
Run 2: A: NA, B: 3028.93 pg/mL, C: 4067.22 pg/mL
AUC
AUC (over 10 hour period): A: 4271.63 pg-h/mL, B: 8382.99 pg-h/mL, C: 9844.03 pg-h/mL
AUC: (0 - infinity): A: 4276.27 pg-h/mL, B: 8454.99 pg-h/mL, C: 9911.39 pg-h/mL

Author	Year	Population		Study Design	N	Intervention
Kane, M	1994	Age (Years)		Case series		Formulation
Quality Score	17	mean:	NS	Blindedness: NS		Not specified
		range:	13-83	Treatment Group		Route of Administration
		Gender		Enrolled:	5	Oral
		female:	2	Analyzed:	5	Dosage and Timing
		male:	3			50mg MLT, timing: NS
		Co-Medication: NS				Frequency and Duration
		Sleep Disorder: None				Every 4 hours for the subsequent 24 hours

Outcomes:
Time to Reach Peak
1-2 h
Peak [MLT] (Cmax) +/-SE
41600 +/-17700 pg/mL

Author	Year	Population		Study Design	N	Intervention
Kovacs, J	2000	Age (Years)		Case Series		Formulation
Quality Score	15	mean (SD):	29.7(7.9)	Blindedness: NS		Not specified
		range:	NS	Treatment Group		Route of Administration
		Gender		Enrolled:	17	Not specified
		female:	5	Analyzed:	NS	Dosage and Timing
		male:	12			3 mg MLT at 1000h
		Co-Medication: None				Frequency and Duration
		Sleep Disorder: None				Single dose

Outcomes:
Time to Reach Peak
1h
Peak [MLT] (Cmax) +/-SD
4701 +/- 6415 pg/mL (range 940 - 27240 pg/mL)
AUC +/- SD
AUC (0-16h): 9514 +/- 9152 pg-h/mL (range 2451 - 40302 pg-h/mL)

Author	Year	Population		Study Design	N	Intervention
Lee, B	1997	Age (Years)		CCT		Formulation
Quality Score	10	mean:	NS	Blindedness: NS		Not specified
		range:	NS	Parallel		Route of Administration
		Gender		Treatment Group		Oral
		female:	NS	*MLT Batch 1*		Dosage and Timing
		male:	NS	Enrolled:	4	0.2 mg MLT at 1000h to 1100h
		Co-Medication: NS		Analyzed:	NS	Frequency and Duration
		Sleep Disorder: None		Control Group		Single dose
				MLT Batch 2		
				Enrolled:	6	
				Analyzed :	NS	

Outcomes:
Time to Reach Peak
Batch 1: 0.5h, Batch 2: 1.0h
Peak [MLT] (Cmax) +/-SD
Batch 1: 117 +/- 21 pg/mL, Batch 2: 108 +/- 33 pg/ml
AUC +/-SD
AUC (time frame not specified): Batch 1: 515.5 +/- 206.2 pg-h/mL Batch 2: 555.6 +/- 334.9 pg-h/mL

Author	Year	Population		Study Design	N	Intervention
Lewy, A.J	1998	Age (Years)		CCT		Formulation
Quality Score	14	mean:	NS	Blindedness: NS		Not specified
		range:	22-77	Cross-over		Route of Administration
		Gender		Treatment Group		Oral
		female:	5	Enrolled:	6	Dosage and Timing
		male:	1	Analyzed:	6	0.5mg MLT, the average administration time for the morning dose was 0845h (range 0700-1100h) and for the evening dose was 1730h (range 1700-1800h)
		Co-Medication: NS		Control Group		
		Sleep Disorder: None		Enrolled:	6	
				Analyzed :	6	
						Frequency and Duration
						Single dose

Outcomes:
Half-Life +/- SEM
after morning dose: 0.84h +/-0.1h, after evening dose: 1.06h +/-0.15h

Author	Year	Population		Study Design	N	Intervention
MacFarlane, J.G	1991	Age (Years)		CCT		Formulation
Quality Score	20	mean:	NS	Double-blind		Not specified
		range:	25-85	Cross-over		Route of Administration
		Gender		Treatment Group		Oral
		female:	8	Enrolled:	6	Dosage and Timing
		male:	5	Analyzed:	6	75 mg MLT at 2200h
		Co-Medication: Free of all neuro-		Control Group		Frequency and Duration
		active medications for at least 4		Enrolled:	7	1 capsule/day for 14 days
		weeks prior to the start of the study		Analyzed :	7	
		Sleep Disorder: Chronic insomnia				

Outcomes:
Time to Reach Peak
1.5 h
Peak [MLT] (Cmax)
64, 730 pg/mL

Author	Year	Population		Study Design	N	Intervention
Niederhofer, H	2003	Age (Years)		RCT		Formulation
Quality Score	17	*female*	17	Double-blind		Not specified
		mean:	15-18	Cross-over		Route of Administration
		range:		Treatment Group		Oral
		male		Enrolled:	20	Dosage and Timing
		mean	16	Analyzed:	20	MLT (0.1mg, 0.3mg) capsules 1/2hr before
		range:	14-18	Control Group		each individuals fixed bedtime
		Gender		Enrolled:	20	Frequency and Duration
		female:	10	Analyzed :	20	1capusle/day for 7 days
		male:	10			
		Co Medication: NS				
		Sleep Disorder: Chronic insomnia accompanying mental retardation				

Outcomes:
Time to Reach Peak
about 2h
Peak [MLT] (Cmax)
0.1mg: 79 pg/mL (range 63 - 118) , 0.3 mg: 234 pg/mL (range 144 - 301)

Author	Year	Population		Study Design	N	Intervention
Rajaratnam, SM	2002	Age (Years)		CCT		Formulation
Quality Score	17	mean (SD):	24.4(4.4)	Double-blind		Surged sustained released MLT
		range:	NS	Cross-over		Route of Administration
		Gender		Treatment Group		Oral
		female:	0	Enrolled:	8	Dosage and Timing
		male:	8	Analyzed:	8	1.5 mg MLT at 1600 h
		Co-Medication: None		Control Group		Frequency and Duration
		Sleep Disorder: None		Enrolled:	8	Daily dose for 8 days
				Analyzed :	8	

Outcomes:
Time to Reach Peak
3h
Peak [MLT] (Cmax) +/-NS
626 +/- 212 pg/mL

Author	Year	Population		Study Design	N	Intervention
Shah, J	1999	Age (Years)		RCT		Formulation
Quality Score	17	mean:	NS	Blindedness: NS		Not specified
		range:	60-73	Cross-over		Route of Administration
		Gender		Treatment Group		Oral
		female:	6	*low dose MLT*		Dosage and Timing, Frequency and Duration
		male:	6	Enrolled:	12	**Low dose MLT: 0.11mg at 2100hours on Day 1 or**
		Co-Medication: NS		Analyzed:	11	Day 15; High dose MLT: 0.44mg at 2100h
		Sleep Disorder: None		Control Group		on Day 1 or 15
				high dose MLT		
				Enrolled:	12	
				Analyzed :	11	

Outcomes:

Half-Life

~ 2 hours and did not change with dose

Time to Reach Peak +/-SD

Low dose MLT: 5.8 +/-1.6h, High dose MLT: 5.5 +/-1.0h

Peak [MLT] (Cmax) +/-SD

Low dose MLT: 56.9 +/- 50.8 pg/mL, High dose MLT: 179 +/-97.2 pg/mL

AUC +/- SD

AUC (0 - 12 hours): Low dose MLT: 288 +/-213 pg-h/mL, High dose MLT: 1069 +/-679 pg-h/mL

AUC (0 - infinity) (extrapolated): Low dose MLT: 318 +/-227 pg-h/mL, High dose MLT: 1234 +/- 856 pg-h/mL

Author	Year	Population		Study Design	N	Intervention
Shirawaka, S	2001	Age (Years)		CCT		Formulation
Quality Score	10	mean (SD):	23.4(1.5)	Blindedness: NS		Not specified
		range:	NS	Design: not clear		Route of Administration
		Gender		Treatment Group		Oral
		female:	0	Enrolled:	NS	Dosage and Timing
		male:	7	Analyzed:	NS	3mg MLT capsules 15 min prior to starting
		Co-Medication: NS		Control Group		polysomnographic recordings
		Sleep Disorder: None		Enrolled:	NS	Frequency and Duration
				Analyzed :	NS	1 capsule/day for 2 days

Outcomes:

Time to Reach Peak

2.25h

Peak [MLT] (Cmax)

1055.7 pg/mL

Author	Year	Population		Study Design	N	Intervention
Shirakawa, S	1998	Age (Years)		Not specified		Formulation
Quality Score	11	mean (SD):	31.1(1.1)	Treatment Group		Not specified
		range:	NS	Enrolled:	7	Route of Administration
		Gender		Analyzed:	7	Oral
		female:	0			Dosage and Timing
		male:	7			3 mg MLT at 0930 h
		Co-Medication: NS				Frequency and Duration
		Sleep Disorder: None				Single dose

Outcomes:
Time to Reach Peak
0.33h
Peak [MLT] (Cmax) +/-NS
3561 +/- 1201 pg/mL

Author	Year	Population		Study Design	N	Intervention
Van Den Heuvel, C	1999	Age (Years)		CCT		Formulation
Quality Score	15	mean (SD):	23.9(0.7)	Double-blind		Not specified
		range:	17-20	Cross-over		Route of Administration
		Gender		Treatment Group		Intravenous
		female:	4	Enrolled:	8	Dosage and Timing
		male:	4	Analyzed:	8	3, 10, or 30ug MLT at 1000h
		Co-Medication: None		Control Group		Frequency and Duration
		Sleep Disorder: None		Enrolled:	8	Single dose per experimental session
				Analyzed :	8	

Outcomes:
Time to Reach Peak
0.25h
Peak [MLT] (Cmax) +/- SE
3 ug: 14.75 +/- 4.67 pg/mL, 10 ug: 34.84 +/- 5.97 pg/mL, 30 ug: 132.19 +/- 25.74 pg/mL

Author	Year	Population		Study Design	N	Intervention
Wright, J	1986	Age (Years)		CCT		Formulation
Quality Score	17	mean:	NS	Double-blind		Not specified
		range:	22-46	Cross-over		Route of Administration
		Gender		Treatment Group		Oral
		female:	2	Enrolled:	12	Dosage and Timing
		male:	10	Analyzed:	12	2 mg MLT at 1700h
		Co-Medication: NS		Control Group		Frequency and Duration
		Sleep Disorder: None		Enrolled:	12	Daily for 4 weeks each (spring)
				Analyzed :	12	or 3 weeks (autumn) with 1 week washout

Outcomes:
Time to Reach Peak
1 h
Peak [MLT] (Cmax)
1500 pg/mL

Author	Year	Population		Study Design	N	Intervention
Zhdanova, I	2001	Age (Years)		RCT		Formulation
Quality Score	21	mean:	NS	Double-blind		Not specified
		range:	>50	Cross-over		Route of Administration
		Gender		Treatment Groups		Oral
		female:	NS	*0.1,.03, or 3.0mg*		Dosage and Timing
		male:	NS	Enrolled:	NS	0.1 mg, 0.3 mg, or 3.0 mg MLT, timing: NS
		Co-Medication: NS		Analyzed:	30	Frequency and Duration
		Sleep Disorder: Insomnia		Control Group		Single dose/day for each experimental session;
				Enrolled:	NS	treatment lasted 4 weeks
				Analyzed:	30	

Outcomes:
Time to Reach Peak
Within 2 hours of ingestion
Peak [MLT] (Cmax)
0.1 mg: 84 pg/mL (range 59 - 120) , 0.3 mg: 220 pg/mL(range 124 - 297) , 3.0 mg: 1370 pg/mL (range 957 - 2440)

Evidence Table C-2: References

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Evidence Table C-3: Melatonin and the Sleep Cycle: Study Characteristics

Abbreviations: **RCT**: Randomized Controlled Trial, **CCT**: Controlled Clinical Trial, **MLT**: Melatonin, **SD**: Standard Deviation, **SE**: Standard Error, **SEM**: Standard Error of the Mean, **IR**: Inter-quartile range, **NS**: Not Specified, **BL**: Bright Light, **DL**: Dim Light, **E-O**: Extra-Ocular, **Ocular**: Eye-directed including room/ambient, **SAD**: Seasonal Affective Disorder, **LEET**: Low Energy Emission Therapy, **SWS**: Slow-wave sleep

Author	Year	Population		Sample Size	N	Study Design	Intervention
Ando, K	1999	Age (Years)		Treatment Group		RCT	Treatment:
		Treatment group:		Enrolled :	6	Blindedness: NS	BL
Quality Score	19	Mean (SD):	34.4 (13.8)	Analyzed:	5	Parallel	Control:
		Range:	NS	Control Group			Placebo light
		Control Group:		Enrolled :	6		Mode of administration:
		Mean (SD):	32.6 (8.1)	Analyzed :	5		Ocular
		Range:	NS				Dosage and Timing:
		Gender:					BL: 500 lux; Placebo light: 0.1 lux for 3 hours. Clock time: NS
		Treatment group:					Frequency and Duration:
		Female:	1				One session/day for 12 days
		Male:	4				Sleep deprivation:
		Control Group:					No
		Female:	2				
		Male:	3				
		Sleep disorder: Delayed Sleep Phase Syndrome					

Author	Year	Population		Sample Size	N	Study Design	Intervention
Arnulf, I	2002	Age (Years)		Treatment Group		RCT	Treatment:
Quality Score	14	Mean (SD):	26 (5.9)	Enrolled :	18	Double-blind	Tryptophan-free amino acid drink
		Range:	18-38	Analyzed:	17	Cross-over	Control:
		Gender		Control Group			Placebo drink
		Female:	11	Enrolled :	18		Mode of administration:
		Male:	7	Analyzed :	17		Oral
		Sleep disorder: None					Dosage and Timing:
							Tryptophan-free drink in 250 ml of water at 1030 h
							Frequency and Duration:
							Single dose
							Sleep deprivation:
							No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Bougrine, S	1995	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	17	*Treatment group:*		Enrolled :	4	Blindedness: NS	BL during night shift
		Mean (SD):	NS	Analyzed:	4	Parallel	Control:
		Range:	20-30				BL after night shift
		Control group:		Control Group			Mode of administration:
		Mean (SD):	NS	Enrolled :	6		Ocular
		Range:	20-30	Analyzed :	6		Dosage and Timing:
		Gender					*BL during night shift: 2500-3000 lux for 3 hours (0200-0500 h); BL after night shift: 3 cycles for 3 hours (1200-1500h in 2 controls, 10:00-13:00h in 4 treatment)*
		Female:	NS				Frequency and Duration:
		Male:	NS				BL during night shift: One session/day for 3 days (Treatment Group) or for 5 days (Control Group);
		Sleep disorder: Shift-work disorder					BL after night shift: Three cycles
							Sleep deprivation:
							No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Boulos, Z	2002	Age (Years)		Treatment Group		RCT	Treatment:
Quality Score	19	*Treatment group:*		Enrolled :	10	Blindedness: NS	BL
		Mean (SD):	27 (3.68)	Analyzed:	8	Parallel	Control:
		Range:	21-34				DL
		Control Group:		Control Group			Mode of administration:
		Mean (SD):	24.9 (2.85)	Enrolled :	10		Ocular
		Range:	21-34	Analyzed:	8		Dosage and Timing:
		Gender					BL: 3000 lux; DL: 10 lux for 3 hours (1900-2200 h local time, 0100-0400 h departure time)
		Treatment group:					Frequency and Duration:
		Female:	6				One session/day for 2 days
		Male:	4				Sleep deprivation:
		Control Group:					No
		Female:	6				
		Male:	4				
		Sleep disorder: Jet-lag					

Author	Year	Population		Sample Size	N	Study Design	Intervention
Budnick, LD	1995	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	16	Median (IR):	35 (NS)	Enrolled :	13	Blindedness: NS	BL
		Range:	24-52	Analyzed:	9	Cross-over	Control:
		Gender		Control Group			DL
		Female:	2	Enrolled :	13		Mode of administration:
		Male:	11	Analyzed :	9		Ocular
		Sleep disorder: Shift-work disorder					Dosage and Timing: BL: 6000-12000 lux; DL: 1200-1500 lux on half of their 12h night shifts. Clock time: NS Frequency and Duration: One session/day for 3 months Sleep deprivation: No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Bunnell, D	1992	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	12	Mean (SD):	NS	Enrolled :	5	Blindedness: NS	BL
		Range:	20-28	Analyzed:	5	Cross-over	Control:
		Gender		Control Group			DL
		Female:	0	Enrolled :	5		Mode of administration:
		Male:	5	Analyzed:	5		Ocular
		Sleep disorder: None					Dosage and Timing: BL: 2500 lux; DL: < 100 lux for 2 h prior to sleep. Clock time: NS Frequency and Duration: One session/day for 2 nights Sleep deprivation: No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Burgess, H	2001	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	17	Mean (SE):	21.3 (2.7)	Enrolled :	16	Double-blind	BL
		Range:	NS	Analyzed:	14	Cross-over	Control:
		Gender		Control Group			DL
		Female:	8	Enrolled :	16		Mode of administration:
		Male:	8	Analyzed :	14		Ocular
		Sleep disorder: None					Dosage and Timing:
							BL: >3000 lux; DL: < 10 lux for 2 hours.
							Clock time: NS
							Frequency and Duration:
							Single session
							Sleep deprivation:
							No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Buxton, OM	2000	Age (Years)		Treatment Groups		CCT	Treatments:
Quality Score	14	Mean (SD):	23 (3)	*Morning nap:*		Blindedness: NS	Morning nap, Afternoon nap, Evening nap in darkness
		Range:	20-30	Enrolled	6	Parallel	Control:
		Gender		Analyzed :	6		No nap
		Female:	0	*Afternoon nap:*			Timing:
		Male:	25	Enrolled	6		Morning nap for 6 hours (0900-1500 h);
		Sleep disorder: None		Analyzed :	5		Afternoon nap for 6 hours (1400-2000 h);
				Evening nap:			Evening nap for 6 hours (1900-0100 h)
				Enrolled	6		Frequency and Duration:
				Analyzed :	6		Single session
				Control Group			Sleep deprivation:
							No
				Enrolled :	7		
				Analyzed :	6		

Author	Year	Population		Sample Size	N	Study Design	Intervention
Cajochen, C	2000	Age (Years)		Treatment Groups		RCT	Treatments:
Quality Score	16	Mean (SD):	27.8 (8.91)	Enrolled :	23	Blindedness: NS	Low level light, Middle level light, High level light
		Range:	18-44	Analyzed:	20	Parallel	Mode of administration:
		Gender		*Low level light*			Ocular
		Female:	1	Enrolled :	NS		Dosage and Timing:
		Male:	22	Analyzed:	NS		Low level light: 23 lux; Middle level light: 230 lux;
		Sleep disorder: None		*Middle level light*			High level light: 3190 lux for 6.5 hours.
				Enrolled :	NS		Clock time: NS
				Analyzed :	NS		Frequency and Duration:
				High level light			Single session
				Enrolled :	NS		Sleep deprivation:
				Analyzed :	NS		No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Cole, R	2002	Age (Years)		Treatment Group		RCT	Treatment:
Quality Score	23	*Treatment group:*		Enrolled :	29	Double-blind	BL
		Mean (SD):	25 (6.0)	Analyzed :	28	Parallel	Control:
		Range:	18-40	Control Group			DL
		Gender		Enrolled :	30		Mode of administration:
		Female:	27	Analyzed :	26		Ocular
		Male:	32				Dosage and Timing:
		Sleep disorder: Delayed Sleep Phase Syndrome					BL: 2700 lux; DL: 0.1 lux for 4 hours (before user-scheduled arising time); Clock time: NS
							Frequency and Duration:
							One session/day for 26 days
							Sleep deprivation:
							No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Costa, G	1997	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	15	Mean (SD):	NS	Enrolled :	5	Blindedness: NS	BL
		Range:	21-32	Analyzed:	5	Cross-over	Control:
		Gender		Control Group			DL
		Female:	4	Enrolled :	5		Mode of administration:
		Male:	1	Analyzed :	5		Ocular
		Sleep disorder: Shift-work disorder					Dosage and Timing: BL: 400-600 lux, 1500 lux, or 3200 lux DL: 40 lux; 4 periods of 40 min each at 2 hour-intervals. Clock time: NS Frequency and Duration: 4 sessions/night shift for 2 nights Sleep deprivation: No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Danilenko, KV	2000	Age (Years)		Treatment Group		RCT	Treatment:
Quality Score	14	Mean (SD):	24.0 (4.8)	Enrolled :	9	Blindedness: NS	Light Dawn signal
		Range:	NS	Analyzed:	5	Cross-over	Control:
		Gender		Control Group			Control signal
		Female:	0	Enrolled :	9		Mode of administration:
		Male:	9	Analyzed :	5		Ocular
		Sleep disorder: None					Dosage and Timing: Dawn signal: 0.003-0.1 lux for 2.5 h (0330-0600 h); Dawn watched for 1.5 h (0600-730 h); Control signal: 0.1 lux for 1.5 h (0600-0730 h). Sleep truncated at 0.1 lux (0600-0730 h) Frequency and Duration: One session/day for 9 days Sleep deprivation: No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Danilenko, KV	2003	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	16	Mean (SD):	24.9 (1.4)	Enrolled :	12	Blindedness: NS	Advanced sleep
		Range:	20-34	Analyzed:	10	Cross-over	Control:
		Gender		Control Group			Fixed sleep
		Female:	6	Enrolled :	12		Timing:
		Male:	4	Analyzed :	10		Advanced sleep: 2 h advance, Fixed sleep: 2330-0800 h
		Sleep disorder: None					Frequency and Duration: Sleep time advanced 20 min/day for 6 days.
							Sleep deprivation: Yes

Author	Year	Population		Sample Size	N	Study Design	Intervention
Daurat A	1996	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	16	Mean (SD):	23.6 (1.05)	Enrolled :	8	Blindedness: NS	Moderate BL
		Range:	NS	Analyzed:	8	Cross-over	Control:
		Gender		Control Group			DL
		Female:	0	Enrolled :	8		Mode of administration:
		Male:	8	Analyzed :	8		Ocular
		Sleep disorder: None					Dosage and Timing: BL: 1000-1500 lux; DL: 50 lux for 14 hours (1800-0800 h)
							Frequency and Duration: Single session
							Sleep deprivation: Yes

Author	Year	Population		Sample Size	N	Study Design	Intervention
Daurat, A	1997	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	16	Mean (SEM):	23.6 (1.05)	Enrolled :	10	Blindedness: NS	Moderate BL
		Range:	NS	Analyzed:	10	Cross-over	Control:
		Gender		Control Group			DL
		Female:	0	Enrolled :	10		Mode of administration:
		Male:	8	Analyzed :	10		Ocular
		Sleep disorder: None					Dosage and Timing:
							BL: 1000-2000 lux, DL: < 50 lux for 14 hours during the nocturnal part of sleepless period (18:00-08:00 h)
							Frequency and Duration:
							Single session
							Sleep deprivation:
							Yes

Author	Year	Population		Sample Size	N	Study Design	Intervention
Dijk, DJ	1989	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	16	Mean (SD):	23.1 (2.5)	Enrolled :	8	Blindedness: NS	BL
		Range:	NS	Analyzed:	8	Cross-over	Control:
		Gender		Control Group			DL
		Female:	0	Enrolled :	8		Mode of administration:
		Male:	8	Analyzed :	8		Ocular
		Sleep disorder: None					Dosage and Timing:
							BL: 2000 lux; DL: 1 lux for 3 hours (0600-0900)
							Frequency and Duration:
							Single session
							Sleep deprivation:
							No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Dollins, AB	1993	Age (Years)		Treatment Group		RCT	Treatment:
Quality Score	16	Mean (SEM):	23.0 (1.16)	Enrolled :	24	Blindedness: NS	Illuminated work stations at three different doses
		Range:	19-39	Analyzed:	21	Cross-over	Mode of administration:
		Gender		Control Group			Ocular
		Female:	0	Enrolled :	24		Dosage and Timing:
		Male:	24	Analyzed :	21		300 lux, 1500 lux, 3000 lux for 13.5 hours (1630-0800 h)
		Sleep disorder: None					Frequency and Duration:
							One session/day for 3 days
							Sleep deprivation:
							No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Ecker, AJ	2000	Age (Years)		Treatment Group B		CCT	Treatment:
Quality Score	10	Mean (SD):	28.5 (4.9)	Enrolled :	4	Blindedness: NS	Sleep restriction (Conditions B and C)
		Range:	NS	Analyzed:	4	Parallel	Control:
		Gender		Treatment Group C			Normal sleep
		Female:	5	Enrolled :	4		Timing:
		Male:	8	Analyzed :	4		Control: 8.2 h anchor sleep (2154-0606 h);
		Sleep disorder: None		Control Group			Condition B: 4.2 h anchor sleep (2354-0406 h);
				Enrolled :	5		Condition C: 4.2 h anchor sleep (2354-0406 h and a daily 1.2 h nap (1324-1440 h)
				Analyzed :	5		Frequency and Duration:
							One session/day for 10 days
							Sleep deprivation:
							Yes

Author	Year	Population		Sample Size	N	Study Design	Intervention
Gordijn, MC Quality Score	1998 19	Age (Years) Mean (SD): Range: Gender Female: Male: Sleep disorder: None	 39.3 (12.1) 23.6-56.5 6 6	Treatment Group Enrolled : Analyzed: Control Group Enrolled : Analyzed :	 12 12 12 12	CCT Blindedness: NS Cross-over	Treatment: BL Control: DL Mode of administration: Ocular Dosage and Timing: BL: 2500 lux; DL: < 10 lux (0600-09:00 h or 1800-21:00 h) Frequency and Duration: One session/day for 3 days during 3 weeks Sleep deprivation: No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Gordijn, MC Quality Score	1999 17	*Patients:* Age (Years) Mean (SD): Range: Gender Female: Male: *non-Patients:* Age (Years) Mean (SD): Range: Gender Female: Male: Sleep disorder: Patients had Nonseasonal Depression, which may or may not have been accompanied by a sleep disorder.	 38.3 (12.2) NS 5 5 38.7 (12.9) NS 3 5	Treatment Groups *Patients:* Enrolled : Analyzed: *non-Patients:* Enrolled : Analyzed: Control Groups *Patients:* Enrolled : Analyzed: *non-Patients:* Enrolled : Analyzed:	 10 8 8 8 10 8 8 8	CCT Blindedness: NS Cross-over	Treatment: BL Control: DL Mode of administration: Ocular Dosage and Timing: BL: 2500 lux, DL: < 10 lux. Morning: 0600-0900 h or Evening: 1800-2100 h) Frequency and Duration: One session/day for 3 days Sleep deprivation: No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Goh, VH	2001	Age (Years)		Treatment Group		RCT	Treatment:
Quality Score	18	Mean (SD):	NS	Enrolled :	7	Blindedness: NS	Total sleep deprivation
		Range:	20-30	Analyzed:	7	Parallel	Control:
		Gender		Control Group			Normal sleep
		Female:	0	Enrolled :	7		Timing:
		Male:	14	Analyzed :	7		Sleep deprivation: 34 hours (0800-1800 h the day after); Normal sleep: 8 hours (2400-0800)
		Sleep disorder: None					Frequency and Duration: Single session
							Sleep deprivation: Yes

Author	Year	Population		Sample Size	N	Study Design	Intervention
Goichot, B	1998	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	13	Mean (SD):	NS	Enrolled :	8	Blindedness: NS	Sleep after a night of sleep deprivation followed by daytime sleep
		Range:	23-30	Analyzed:	8	Cross-over	Control:
		Gender		Control Group			Normal sleep
		Female:	0	Enrolled :	8		Timing:
		Male:	8	Analyzed:	8		Sleep after a night of sleep deprivation: Daytime sleep: 0700-1500 h; Normal sleep: 8 hours of sleep (2300-0700 h)
		Sleep disorder: None					Frequency and Duration: Single session
							Sleep deprivation: Yes

Author	Year	Population		Sample Size	N	Study Design	Intervention
Higuchi, S	2003	Age (Years)		Treatment Group		RCT	Treatment:
Quality Score	15	Mean (SD):	24.7 (5.6)	Enrolled :	7	Blindedness: NS	Video display terminal with Bright display
		Range:	NS	Analyzed:	7	Cross-over	Control:
		Gender		Control Group			Video display terminal with Dark display
		Female:	0	Enrolled :	7		Mode of administration:
		Male:	7	Analyzed:	7		Ocular
		Sleep disorder: None					Dosage and Timing:
							Bright display: 45 lux, Dark display: 15 lux for 3 hours (2300-0200 h)
							Frequency and Duration:
							One session/day for 3 days
							Sleep deprivation:
							No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Horne, JA	1991	Age (Years)		Treatment Group		RCT	Treatment:
Quality Score	15	Mean (SD):	NS	Enrolled :	12	Single-blinded	BL
		Range:	19-26	Analyzed:	12	Cross-over	Control:
		Gender		Control Group			DL
		Female:	8	Enrolled :	12		Mode of administration:
		Male:	4	Analyzed:	12		Ocular
		Sleep disorder: None					Dosage and Timing:
							BL: 2000 lux; DL: NS lux for 12 hours (1800-0600 h)
							Frequency and Duration:
							10-min session/hour for 12 hours
							Sleep deprivation:
							Yes

Author	Year	Population		Sample Size	N	Study Design	Intervention
Horowitz, TS	2001	Age (Years)		Treatment Group		RCT	Treatment:
Quality Score	16	Mean (SD):	26.99 (6.22)	Enrolled :	26	Blindedness: NS	BL
		Range:	20-40	Analyzed:	25	Cross-over	Control:
		Gender		Control Group			DL
		Treatment group:		Enrolled :	28		Mode of administration:
		Female:	10	Analyzed:	27		Ocular
		Male:	16				Dosage and Timing:
		Control:					BL: 2500 lux for 6 hours (2300-0500 h);
		Female:	18				DL: 150 lux for 8 hours (2300-0700 h)
		Male:	10				Frequency and Duration:
		Sleep disorder: Shift-work disorder					One session/day for 4 days
							Sleep deprivation:
							No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Jelinkova-Vondrasova, D	1999	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	14	Mean (SD):	NS	Enrolled :	8	Blindedness: NS	Shift of the sleep period: 1) 3 h delay of the sleep period: 0100-0900 h,
		Range:	20-24	Analyzed:	8	Cross-over	2) 3-h advance of the sleep period: 2200-0600 h
		Gender		Control Group			Timing:
		Female:	5	Enrolled :	8		3-h delay of the sleep period: 0100-0900 h;
		Male:	3	Analyzed:	8		3-h advance of the sleep period: 2200 to 0600 h
		Sleep disorder: None					Frequency and Duration:
							One session/day for 6 days
							Sleep deprivation:
							No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Jimerson, DC Quality Score	1977 15	*Patients:* Age (Years) Mean (SD): Range: Gender Female: Male: *non-Patients:* Age (Years) Mean (SD): Range: Gender Female: Male: Sleep disorder: Patients suffered from Depression, which may or may not have been accompanied by a sleep disorder.	 NS 19-50 5 1 NS 19-65 2 4	Treatment Group *Patients:* Enrolled : Analyzed: *non-Patients:* Enrolled : Analyzed: Control Group *Patients:* Enrolled : Analyzed: *non-Patients:* Enrolled : Analyzed:	 6 5 8 5 6 5 8 5	CCT Blindedness: NS Cross-over	Treatment: Sleep deprivation Control: Normal sleep Timing: Sleep deprivation: 40 hours (0700-2300 h the day after); Normal sleep: 8 hours (2300-0700 h) Frequency and Duration: Single session Sleep deprivation: Yes

Author	Year	Population		Sample Size	N	Study Design	Intervention
Kelly, TL Quality Score	1997 17	Age (Years) Mean (SD): Range: Gender Female: Male: *LEET group* Age (Years) Mean (SD): Range: *BL* Age (Years) Mean (SD): Range: *BL + LEET* Age (Years)	 NS NS 0 45 24.8 (7.9) NS 22.5 (3.5) NS	Treatment Groups *LEET group* Enrolled : Analyzed: *BL* Enrolled : Analyzed: *BL + LEET* Enrolled : Analyzed: Control Group *DL* Enrolled : Analyzed:	 12 12 12 8 11 11 10 7	CCT Double-blind Parallel	Treatment: BL and LEET therapy (separately and combined) Control: DL Mode of administration: Ocular Dosage and Timing LEET: 20 min. prior to daytime sleep periods. BL: 3500-4300 lux, DL: 200-300 lux for 4 hours (2200-0200 h) Frequency and Duration: One session/day for 3 days Sleep deprivation: No

		Mean (SD): Range: *DL* Age (Years) Mean (SD): Range: Sleep disorder: Shift-work disorder	23.4 (4.1) NS 25.2 (7.7) NS				
Author	**Year**	**Population**		**Sample Size**	**N**	**Study Design**	**Intervention**
Koorengevel, KM Quality Score	2001 19	Age (Years) *Treatment group:* Mean (SD): Range: *Control group:* Mean (SD): Range: Gender *Treatment group:* Female: Male: *Control group:* Female: Male: Sleep disorder: Participants suffered from SAD, which may or may not be accompanied by a sleep disorder.	 39.6 (12.2) NS 43.4 (12.4) NS 11 4 10 4	Treatment Group Enrolled : Analyzed: Control Group Enrolled : Analyzed :	 15 13 14 11	CCT Double-blind Parallel	Treatment: Light therapy Control: Placebo (No light) Mode of administration: E-O (behind the knees) Dosage and Timing: 13000 lux for 3 hours (0800-1100 h) Frequency and Duration: One session/day for 5 days Sleep deprivation: No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Kubota, T	2002	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	18	Mean (SD):	24 (NS)	Enrolled :	9	Blindedness: NS	BL
		Range:	20-27	Analyzed:	9	Cross-over	Control:
		Gender		Control Group			DL
		Female:	0	Enrolled :	9		Mode of administration:
		Male:	9	Analyzed :	9		Ocular
		Sleep disorder: None					Dosage and Timing:
							BL: 5000 lux for 5 hours; DL: 10 lux for 5 hours (0000-0500 h)
							Frequency and Duration:
							Single session
							Sleep deprivation:
							Yes

Author	Year	Population		Sample Size	N	Study Design	Intervention
Lavoie, S	2003	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	17	Mean (SD):	26.1 (4.2)	Enrolled :	7	Blindedness: NS	BL
		Range:	22-35	Analyzed:	7	Parallel	Control:
		Gender		Control Group			DL
		Female:	8	Enrolled :	7		Mode of administration:
		Male:	6	Analyzed :	7		Ocular
		Sleep disorder: None					Dosage and Timing:
							BL: 3000 lux; DL: 15 lux for 4 hours (0030-0430 h)
							Frequency and Duration:
							Single session
							Sleep deprivation:
							Yes

Author	Year	Population		Sample Size	N	Study Design	Intervention
Lushington, K	2002	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	18	Mean (SD):	22.1 (3.0)	Enrolled :	13	Single-blind	Light
		Range:	13-34	Analyzed:	13	Cross-over	Control:
		Gender		Control Group			Placebo (No light)
		Female:	3	Enrolled :	13		Mode of administration:
		Male:	10	Analyzed :	13		E-O (behind the knee)
		Sleep disorder: None					Dosage and Timing:
							Light: 10000 lux for 3 hours (0100-0400 h)
							Frequency and Duration:
							One session/day for 3 nights
							Sleep deprivation:
							No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Morris, M	1990	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	17	Mean (SD):	27 (NS)	Enrolled :	8	Blindedness: NS	Continuous wakefulness
		Range:	NS	Analyzed:	8	Cross-over	Control:
		Gender		Control Group			Nightime sleep
		Female:	3	Enrolled :	8		Timing:
		Male:	5	Analyzed :	8		Continuous wakefulness: 24 hours; Nightime sleep: 2200-1000 h
		Sleep disorder: None					Frequency and Duration:
							Single session
							Sleep deprivation:
							Yes

Author	Year	Population		Sample Size	N	Study Design	Intervention
Partonen, T	1996	*Patients*		Treatment Group		RCT	Treatment:
Quality Score	19	Age (Years)		*Patients:*		Blindedness: NS	BL 1 hour
		Mean (SEM):	40.2 (2.2)	Enrolled :	7	Parallel	Control:
		Range:	23-55	Analyzed:	7		BL 15 minutes
		Gender		*non-Patients:*			Mode of administration:
		Female:	16	Enrolled :	5		Ocular
		Male:	0	Analyzed:	5		Dosage and Timing:
		non-Patients		Control Group			BL: 3300 lux for: 1 hour, or 15 minutes (between 06:00-08:00 h)
		Age (Years)		*Patients:*			Frequency and Duration:
		Mean (SEM):	41.6 (3.6)	Enrolled :	9		One session/day for 14 days during the winter
		Range:	24-64	Analyzed:	9		Sleep deprivation:
		Gender		*non-Patients:*			No
		Female:	13	Enrolled :	8		
		Male:	0	Analyzed:	8		
		Sleep disorder: Patients suffered from SAD, which may or may not be accompanied by a sleep disorder.					

Author	Year	Population		Sample Size	N	Study Design	Intervention
Rao, ML	1996	Age (Years)		Treatment Group		RCT	Treatment:
Quality Score	19	Median (IR):	25.5 (NS)	Enrolled :	12	Single-blind	SWS deprivation
		Range:	20-33	Analyzed:	12	Cross-over	Control:
		Gender		Control Group			Normal sleep
		Female:	0	Enrolled :	12		Timing:
		Male:	12	Analyzed :	12		SWS deprivation; Normal sleep for 12 hours (2100-0900 h)
		Sleep disorder: None					Frequency and Duration:
							One session/night for 2 nights
							Sleep deprivation:
							Yes

Author	Year	Population		Sample Size	N	Study Design	Intervention
Redwine, L	2000	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	17	Mean (SD):	35.8 (10.12)	Enrolled :	31	Blindedness: NS	Partial sleep deprivation
		Range:	25-65	Analyzed:	31	Cross-over	Control:
		Gender		Control Group			Uninterrupted sleep
		Female:	0	Enrolled :	31		Timing:
		Male:	31	Analyzed :	31		Partial sleep deprivation: Sleep time for 5 hours (2200-300 h); Control sleep: Sleep time for 9 hours (2200-0700 h).
		Sleep disorder: None					Frequency and Duration: One session/night for 2 nights
							Sleep deprivation: Yes

Author	Year	Population		Sample Size	N	Study Design	Intervention
Ross, JK	1995	Age (Years)		Treatment Group		RCT	Treatment:
Quality Score	17	Mean (SD):	NS	Enrolled :	8	Blindedness: NS	BL
		Range:	21-35	Analyzed:	7	Cross-over	Control:
		Gender		Control Group			DL
		Female:	0	Enrolled :	7		Mode of administration:
		Male:	14	Analyzed :	6		Ocular
		Sleep disorder: Shift-work disorder					Dosage and Timing: BL: 2500-3000 lux; DL: < 500 lux for 2 hours (1100-13:00 h)
							Frequency and Duration: One session/day for 7 days
							Sleep deprivation: No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Salin-Pascual RJ	1988	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	17	Mean (SD):	20.83 (2.97)	Enrolled :	12	Blindedness: NS	Sleep deprivation
		Range:	16-26	Analyzed:	12	Cross-over	Control:
		Gender		Control Group			Normal sleep
		Female:	3	Enrolled :	12		Timing:
		Male:	9	Analyzed :	12		Sleep deprivation: 36 hours of sleep-deprivation;
		Sleep disorder: None					Normal sleep: ~8 hours (1000-0600 h)
							Frequency and Duration:
							Single session
							Sleep deprivation:
							Yes

Author	Year	Population		Sample Size	N	Study Design	Intervention
Samel A	1993	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	15	Mean (SD):	23.0 (3.3)	Enrolled :	8	Blindedness: NS	Sleep-wake cycle advance
		Range:	20-29	Analyzed:	8	Cross-over	Control:
		Gender		Control Group			Normal sleep
		Female:	0	Enrolled :	8		Timing:
		Male:	8	Analyzed :	8		Sleep-wake advance: 7-h advance. Normal sleep: 9 hours. Clock-time: NS.
		Sleep disorder: None					Frequency and Duration:
							One session/day for 7 days
							Sleep deprivation:
							Yes

Author	Year	Population		Sample Size	N	Study Design	Intervention
von Treuer K	1996	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	14	Mean (SD):	NS	Enrolled :	9	Blindedness: NS	Sleep deprivation night
		Range:	17-29	Analyzed:	9	Cross-over	Control:
		Gender		Control Group			Control night
		Female:	0	Enrolled :	9		Timing:
		Male:	9	Analyzed :	9		Sleep deprivation: 36 hours (0700-2000 h the day after); Normal sleep: NS
		Sleep disorder: None					Frequency and Duration:
							Single session
							Sleep deprivation:
							Yes

Author	Year	Population		Sample Size	N	Study Design	Intervention
Wakamura, T	2000	Age (Years)		Treatment Group		RCT	Treatment:
Quality Score	17	Mean (SD):	20 (2)	Enrolled :	7	Blindedness: NS	BL
		Range:	18-23	Analyzed:	7	Cross-over	Control:
		Gender		Control Group			DL
		Female:	7	Enrolled :	7		Mode of administration:
		Male:	0	Analyzed :	7		Ocular
		Sleep disorder: None					Dosage and Timing:
							BL: 6000 lux; DL: 2000 lux (1800-bedtime h)
							Frequency and Duration:
							Single session
							Sleep deprivation:
							No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Wehr, TA	1991	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	14	Mean (SD):	NS	Enrolled :	8	Blindedness: NS	Summer photoperiod
		Range:	20-36	Analyzed:	7	Cross-over	Control:
		Gender		Control Group			Winter photoperiod
		Female:	0	Enrolled :	8		Dosage and Timing:
		Male:	8	Analyzed :	7		Summer photoperiod: 16 h of light and 8 hours of darkness for 1 week.
		Sleep disorder: None					Winter photoperiod: 10 h of light and 14 h of darkness for 4 weeks.
							Clock time: NS
							Frequency and Duration:
							Summer photoperiod: One session/day for 1 week
							Winter photoperiod: 1 session/day for 4 weeks
							Sleep deprivation:
							No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Weibel, L	1997	Age (Years)		Treatment Group		RCT	Treatments:
Quality Score	19	Mean (SD):	NS	Enrolled :	19	Non-blinded	Sleep period shift (day-active workers sleeping during the day)
		Range:	NS	Analyzed:	19	Cross-over	Control:
		Gender		Control Group			Normal sleep (day-active workers sleeping at night)
		Female:	0	Enrolled :	19		Timing:
		Male:	19	Analyzed :	19		Sleep period shift: 8 hours (0700-1500); Normal sleep: 8 hours (2300-0700 h)
		Sleep disorder: None					Frequency and Duration:
							Single session
							Sleep deprivation:
							Yes

Author	Year	Population		Sample Size	N	Study Design	Intervention
Yoon I	2000	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	8	Mean (SD):	NS	Enrolled :	17	Non-blinded	Light-1, Light-2
		Range:	20-41	Analyzed:	17	Cross-over	Control:
		Gender		Control Group			Baseline light
		Female:	NS	Enrolled :	17		Dosage and Timing:
		Male:	NS	Analyzed :	17		Light-1: 4000-6000 lux for 4 h (night shift) followed by 1h exposure to sunlight
		Sleep disorder: Shift-work disorder					or 10000 lux next morning; Light-2: Same light exposure without sunlight/10000 lux. Control: No light exposure. Clock time: NS
							Frequency and Duration:
							One session/day for 4 days
							Sleep deprivation:
							No

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Evidence Table C-4: Mechanisms by which Melatonin Produces Sleepiness: Study Characteristics

Abbreviations: RCT: randomized controlled trial, **CCT**: controlled clinical trial, **MLT**: melatonin, **FR**: fast-release, **SR**: slow-release, **SD**: standard deviation, SE: standard error, mg: milligrams,
h: hours, NS: not specified
Control Group received placebo unless otherwise indicated

Author	Year	Population		Sample Size	N	Study Design	Intervention
Almeida-Montes, LG Quality Score	2003 5	Age (Years) Mean (SD): Range: Gender Female: Male: Sleep Disorder: Insomnia	 50 (NS) 30-72 4 6	Treatment Group Enrolled : Analyzed: Control Group Enrolled : Analyzed :	 10 10 10 10	RCT Double-blind Cross-over	Formulation Sustained-release (SR) MLT Route of Administration Oral Dosage and Timing 0.3 mg or 1 mg of MLT one hour before bedtime Frequency and Duration One dose/day for 14 days

Author	Year	Population		Sample Size	N	Study Design	Intervention
Andrade, C Quality Score	2001 4	Age (Years) *Treatment group* Mean (SD): Range: *Control group* Mean (SD): Range: Gender *Treatment group* Female: Male: *Control group* Female: Male: Sleep Disorder: Insomnia	 59.7 (11.1) 43-85 51.4 (14.2) 23-70 4 14 5 10	Treatment Group Enrolled : Analyzed: Control Group Enrolled : Analyzed :	 18 18 15 15	RCT Double-blind Parallel	Formulation NS Route of Administration Oral Dosage and Timing 3 mg MLT taken at night Frequency 1 capsule/night for the first two nights, 2 capsules every alternate night thereafter up to 4 capsules/night Duration 21 patients (MLT n=11, PLB n= 10) received treatment for 8 days. 8 patients (MLT n= 5, PLB n= 3) received treatment for 10 days, and 4 patients (MLT n=2, PLB n=2) received treatment for 16 days.

Author	Year	Population		Sample Size	N	Study Design	Intervention
Dahlitz, M	1991	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	4	Mean (SD):	NS	Enrolled :	8	Double-blind	NS
		Range:	20-60	Analyzed:	8	Cross-over	Route of Administration
		Gender		Control Group			Oral
		Female:	0	Enrolled :	8		Dosage and Timing
		Male:	8	Analyzed :	8		5 mg MLT at 2200 h
		Sleep Disorder:					Frequency and Duration
		Delayed sleep phase syndrome					One dose/day for 4 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Edwards, BJ	2000	Age (Years)		Treatment Group		CCT	Formulation
Quality Score	22	*Treatment Group*		Enrolled :	14	Double-blind	Not specified
		mean (SD):	40(13)	Analyzed:	13	Parallel	Route of Administration
		range:	NS	Control Group			Oral
		Control Group		Enrolled :	17		Dosage and Timing
		mean (SD):	41(12)	Analyzed :	13		5mg MLT taken on the plane between 18:00-19:00h and between 22:00 and 23:00h, according to local time at destination and for the next three evenings.
		range:	NS				
		Gender					Frequency and Duration
		female:	3				2 capsules/day for first day and then 1 capsule/day for 2 days
		male:	28				
		Sleep Disorder: Jet-lag					

Author	Year	Population		Sample Size	N	Study Design	Intervention
Folklard, S	1993	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	3	Mean (SD):	29 (7)	Enrolled :	7	Double-blind	NS
		Range:	21-48	Analyzed:	7	Cross-over	Route of Administration
		Gender		Control Group			Oral
		Female:	2	Enrolled :	8		Dosage and Timing
		Male:	15	Analyzed :	8		5 mg MLT at 0642 h
		Sleep Disorder:					Frequency and Duration
		Night-shift disorder					One dose/day for 6 successive day sleeps taken between night shifts

Author	Year	Population		Sample Size	N	Study Design	Intervention
Holmes, A.L.	2002	Age (Years)		Treatment Group		CCT	Formulation
Quality Score	15	Mean (SD):	20.3 (0.6)	Enrolled :	12	Double-blind	NS
		Range:	19-25	Analyzed:	12	Cross-over	Route of Administration
		Gender		Control Group			Oral
		Female:	5	Enrolled :	12		Dosage and Timing
		Male:	7	Analyzed :	12		5 mg MLT at 1400 h
		Sleep Disorder:					Frequency and Duration
		Normal sleepers					Single dose

Author	Year	Population		Sample Size	N	Study Design	Intervention
Mishima, K	1997	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	16	Mean (SD):	22.5 (1.9)	Enrolled :	6	Single-blind	NS
		Range:		Analyzed:	6	Cross-over	Route of Administration
		Gender		Control Group			Oral
		Female:	0	Enrolled :	6		Dosage and Timing
		Male:	6	Analyzed :	6		3 mg or 9 mg MLT at 0930 h
		Sleep Disorder:					Frequency and Duration
		Normal sleepers					One dose/day for 2 days

Author	Year	Population		Sample Size	N	Study Design	Intervention
Petrie	1989	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	20	Mean (SD):	NS	Enrolled :	20	Double-blind	NS
		Range:	28-68	Analyzed:	20	Cross-over	Route of Administration
		Gender		Control Group			NS
		Female:	8	Enrolled :	20		Dosage and Timing
		Male:	12	Analyzed :	20		5 mg MLT between 1000 h and 1200 h local time
		Sleep Disorder: Jet Lag					Frequency and Duration
							One dose/day for 3 days (before flight, during flight, and once a day for 3 days after arrival)

Author	Year	Population		Sample Size	N	Study Design	Intervention
Satomura, T	2001	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	11	Mean (SD):	23.7(1.7)	Enrolled :	7	Single-blind	NS
		Range:	NS	Analyzed:	7	Cross-over	Route of Administration
		Gender		Control Group			Oral
		Female:	0	Enrolled :	7		Dosage and Timing
		Male:	7	Analyzed :	7		1 mg, 3 mg, or 6 mg MLT at 1330 h
		Sleep Disorder:					Frequency and Duration
		Normal sleepers					Single dose

Author	Year	Population		Sample Size	N	Study Design	Intervention
Terlo, L	1997	Age (Years)		Treatment Group		CCT	Formulation
Quality Score	19	Mean (SD):	28(2)	Enrolled :	10	Double-blind	NS
		Range:	NS	Analyzed:	10	Cross-over	Route of Administration
		Gender		Control Group			Oral
		Female:	0	Enrolled :	10		Dosage and Timing
		Male:	10	Analyzed :	10		0.1 mg, 0.5 mg or 1 mg MLT at 1600 h
		Sleep Disorder:					Frequency and Duration
		Normal sleepers					One dose/day for 4 non-consecutive days

Author	Year	Population		Sample Size	N	Study Design	Intervention
Zhdanova, I	1995	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	18	Mean (SD):	26.5(1.3)	Enrolled :	6	Double-blind	NS
		Range:	25-64	Analyzed:	6	Cross-over	Route of Administration
		Gender		Control Group			Oral
		Female:	0	Enrolled :	6		Dosage and Timing
		Male:	6	Analyzed :	6		0.3 mg, or 1.0 mg MLT at 1800 h or between 2000 h - 21:00 h
		Sleep Disorder:					Frequency and Duration
		Normal sleepers					One dose/day for 9 days

Evidence Table C-4: References

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Evidence Table C-5: Effect of Melatonin on Normal Sleepers: Study Characteristics

Abbreviations: **RCT**: randomized controlled trial, **CCT**: controlled clinical trial, **MLT**: melatonin, **FR**: fast-release, **SR**: slow-release, **SD**: standard deviation, **SE**: standard error, **mg**: milligrams, **h**: hours, **NS**: not specified
Control group received placebo unless otherwise indicated

Author	Year	Population		Sample Size	N	Study Design	Intervention
Attenburrow M	1996	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	17	mean:	53.9	Enrolled :	15	Double-blind	Not specified
		range:	41-67	Analyzed:	12	Cross-over	Route of Administration
		Gender		Control Group			Not specified
		female:	11	Enrolled :	15		Dosage and Timing
		male:	4	Analyzed :	12		0.3 or 1.0mg MLT two hours before bedtime (2200-2300h)
							Frequency and Duration
							0.3 or 1.0mg/night for 3 nights

Author	Year	Population		Sample Size	N	Study Design	Intervention
Baskett, J	2003	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	25	mean:	NS	Enrolled :	20	Double-blind	Not specified
		range:	60-84	Analyzed:	14	Cross-over	Route of Administration
		Gender					Oral
		female:	16				Dosage and Timing
		male:	4	Control Group			5mg MLT at bedtime
				Enrolled :	20		Frequency and Duration
				Analyzed :	14		I capsule/day for 4 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Cajochen, C	1998	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	18	mean (SD):	27(5)	Enrolled :	10	Single-blind	Not specified
		range:	NS	Analyzed:	10	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	0	Enrolled :	10		Dosage and Timing
		male:	10	Analyzed :	10		5 mg of MLT, timing:NS
							Frequency and Duration
							1 capsule/week for 2 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Cajochen, C	1997	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	16	mean:	NS	Enrolled :	8	Double-blind	Not specified
		range:	23-32	Analyzed:	8	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	0	Enrolled :	8		Dosage and Timing
		male:	8	Analyzed :	8		5 mg MLT at 1800h
							Frequency and Duration
							Single dose

Author	Year	Population		Sample Size	N	Study Design	Intervention
Dollins, A.B.	1994	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	18	mean (SD):	23.05(4.22)	Enrolled :	20	Double-blind	Not specified
							Route of Administration
		range:	18-24	Analyzed:	20	Cross-over	Oral
		Gender		Control Group			Dosage and Timing
		female:	0	Enrolled :	20		0.1, 0.3, 1.0 or 10mg MLTat 1145h
		male:	20	Analyzed :	20		Frequency and Duration
							I capsule/day for 5 days

Author	Year	Population		Sample Size	N	Study Design	Intervention
Ferini-Strambi	1993	Age (Years)		Treatment Group		CCT	Formulation
Quality Score	14	mean (SD):	25.3(3.6)	Enrolled :	6	Single-blind	Not specified
		range:	NS	Analyzed:	6	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	0	Enrolled :	6		Dosage and Timing
		male:	6	Analyzed :	6		100mg MLT at 1030h
							Frequency and Duration
							1 tablet on nights 4 and 7

Author	Year	Population		Sample Size	N	Study Design	Intervention
Holmes, A.L.	2002	Age (Years)		Treatment Group		CCT	Formulation
Quality Score	15	mean (SD):	20.3(0.6)	Enrolled :	12	Double-blind	Not specified
		range:	19-25	Analyzed:	12	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	5	Enrolled :	12		Dosage and Timing
		male:	7	Analyzed :	12		5 mg MLT at 1400h
							Frequency and Duration
							Single dose

Author	Year	Population		Sample Size	N	Study Design	Intervention
James, S.P	1987	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	17	mean:	29.9	Enrolled :	11	Double-blind	Not specified
		range:	21-40	Analyzed:	10	Cross-over	Route of Administration
		Gender		Control Group			Not specified
		female:	3	Enrolled :	11		Dosage and Timing
		male:	7	Analyzed :	10		1mg or 5mg MLT at 2245h
							Frequency and Duration
							1mg or 5mg/day for 3 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Luboshitzky R	2000	Age (Years)		Treatment Group		CCT	Formulation
Quality Score	19	mean (SD):	23.9(2.4)	Enrolled :	6	Double-blind	Not specified
		range:	NS	Analyzed:	6	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	0	Enrolled :	6		Dosage and Timing
		male:	6	Analyzed :	6		6 mg MLT at 1700h
							Frequency and Duration
							6mg/day for 1 month

Author	Year	Population		Sample Size	N	Study Design	Intervention
Matsumomo M	1999	Age (Years)		Treatment Group		CCT	Formulation
Quality Score	19	mean (SD):	23.7(1.3)	Enrolled :	6	Single-blind	Not specified
		range:	NS	Analyzed:	6	Cross-over	Route of Administration
		Gender		Control Group			Not specified
		female:	0	Enrolled :	6		Dosage and Timing
		male:	6	Analyzed :	6		10 mg of MLT at 1000h
							Frequency and Duration
							Single dose

Author	Year	Population		Sample Size	N	Study Design	Intervention
Mishima, K	1997	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	16	mean (SD):	22.5(1.9)	Enrolled :	6	Single-blind	Not specified
		range:	NS	Analyzed:	6	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	0	Enrolled :	6		Dosage and Timing
		male:	6	Analyzed :	6		3mg or 9mg MLT capsule at 0930h
							Frequency and Duration
							1 caspsule/day for 2 days

Author	Year	Population		Sample Size	N	Study Design	Intervention
Nave, R	1995	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	19	mean (SD):	24.6(2.7)	Enrolled :	12	Double-blind	Not specified
		range:	NS	Analyzed:	12	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	12	Enrolled :	12		Dosage and Timing
		male:	0	Analyzed :	12		3mg or 6mg MLT at 1600h and 1730h
							Frequency and Duration
							Single dose/week for 5 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Nickelson, T	1989	Age (Years)		Treatment Group		CCT	Formulation
Quality Score	16	female mean (SD):	30.0(7.9)	Enrolled :	12	Double-blind	Not specified
		male mean (SD):	30.4(6.2)	Analyzed:	12	Parallel	Route of Administration
		female range:	23-46	Control Group			Oral
		male range:	20-39	Enrolled :	13		Dosage and Timing
		Gender		Analyzed :	13		50mg of MLT at 0900h or 1900h
		female:	11				Frequency and Duration
		male:	14				1 capsule/day for 1 week

Author	Year	Population		Sample Size	N	Study Design	Intervention
Pires, M.L	2001	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	10	mean:	NS	Enrolled :	6	Double-blind	Not specified
		range:	22-24	Analyzed:	6	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	0	Enrolled :	6		Dosage and Timing
		male:	6	Analyzed :	6		0.3 and 1.0 mg MLT at 3 fixed times:1800, 2000, and 2100 hour
							Frequency and Duration
							3 doses/day of each dose over 9 sessions

Author	Year	Population		Sample Size	N	Study Design	Intervention
Reid, K	1996	Age (Years)		Treatment Group		CCT	Formulation
Quality Score	15	mean (SD):	20.3(2.4)	Enrolled :	16	Double-blind	Not specified
		range:	NS	Analyzed:	16	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	0	Enrolled :	16		Dosage and Timing
		male:	16	Analyzed :	16		5 mg MLT capsule at 1400h
							Frequency and Duration
							Single dose

Author	Year	Population		Sample Size	N	Study Design	Intervention
Satomura, T	2001	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	11	mean (SD):	23.7(1.7)	Enrolled :	7	Single-blind	Not specified
		range:	NS	Analyzed:	7	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	0	Enrolled :	7		Dosage and Timing
		male:	7	Analyzed :	7		1mg, 3mg, 6mg of MLT at 13:30 h
							Frequency and Duration
							Single dose

Author	Year	Population		Sample Size	N	Study Design	Intervention
Seabra, M.L.	2000	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	20	mean (SD):	29(1)	Enrolled :	30	Double-blind	Not specified
		range:	25-55	Analyzed:	30	Parallel	Route of Administration
		Gender		Control Group			Oral
		female:	0	Enrolled :	10		Dosage and Timing
		male:	40	Analyzed :	10		10 mg MLT one hour before sleep time (approx. 2200h)
							Frequency and Duration
							1 capusule/day for 28 days

Author	Year	Population		Sample Size	N	Study Design	Intervention
Terlo, L	1997	Age (Years)		Treatment Group		CCT	Formulation
Quality Score	19	mean (SD):	28(2)	Enrolled :	10	Double-blind	Not specified
		range:	NS	Analyzed:	10	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	0	Enrolled :	10		Dosage and Timing
		male:	10	Analyzed :	10		0.1, 0.5 or 1mg MLT tablet at 16:00h
							Frequency and Duration
							1 tablet/day for 4 non-consecutive days

Author	Year	Population		Sample Size	N	Study Design	Intervention
Zhdanova, I	1995	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	18	mean (SD):	26.5(1.3)	Enrolled :	6	Double-blind	Not specified
		range:	25-64	Analyzed:	6	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	0	Enrolled :	6		Dosage and Timing
		male:	6	Analyzed :	6		0.3mg and 1.0mg at 1800h or between 2000h and 2100h
							Frequency and Duration
							Single dose for 9 sessions

Author	Year	Population		Sample Size	N	Study Design	Intervention
Zhdanova, I	1996	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	16	mean (SD):	28.5(1.8)	Enrolled :	12	Double-blind	Not specified
		range:	NS	Analyzed:	12	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	0	Enrolled :	12		Dosage and Timing
		male:	12	Analyzed :	12		0.3 or 1.0mg MLT at 2100h, 2-4 hours before habitual bedtime
							Frequency and Duration
							1 tablet/day for 2 days

Author	Year	Population		Sample Size	N	Study Design	Intervention
Zisapel, N	1997	Age (Years)		Treatment Group		CCT	Formulation
Quality Score	17	mean (SD):	28(2)	Enrolled :	10	Double-blind	Not specified
		range:	NS	Analyzed:	10	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	0	Enrolled :	10		Dosage and Timing
		male:	10	Analyzed :	10		2mg MLT at 1100h
							Frequency and Duration
							1 tablet/day for 3 non-consecutive days

Evidence Table C-5: References

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Evidence Table C-6: Melatonin and the Temperature Rhythm: Study Characteristics

RCT: Randomized Control Trial, CCT: Controlled Clinical Trial, MLT: Melatonin, SD: Standard Deviation, SE: Standard Error, SEM: Standard Error of the Mean, NS: Not Specified, BL: Bright Light, DL: Dim Light, E-O: Extra-Ocular, Ocular: Eye-directed including room/ambient, SAD: Seasonal Affective Disorder, LEET: Low Energy Emission Therapy

Author	Year	Population		Sample Size	N	Study Design	Intervention
Ando, K	1999	Age (Years)		Treatment Group		RCT	Treatment:
Quality Score	19	*Treatment group:*		Enrolled :	6	Blindedness: NS	BL
		Mean (SD):	34.4 (13.8)	Analyzed:	5	Parallel	Control:
		Range:	NS	Control Group			Placebo light
		Control Group:		Enrolled :	6		Mode of administration:
		Mean (SD):	32.6 (8.1)	Analyzed :	5		Ocular
		Range:	NS				Dosage and Timing:
		Gender:					BL: 500 lux; Placebo light: 0.1 lux for 3 hours. Clock time: NS
		Treatment group:					Frequency and Duration:
		Female:	1				One session/day for 12 days
		Male:	4				Sleep deprivation:
		Control Group:					No
		Female:	2				
		Male:	3				
		Sleep disorder: Delayed Sleep Phase Syndrome					

Author	Year	Population		Sample Size	N	Study Design	Intervention
Bunnell, D	1992	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	12	Mean (SD):	NS	Enrolled :	5	Blindedness: NS	BL
		Range:	20-28	Analyzed:	5	Cross-over	Control:
		Gender		Control Group			DL
		Female:	0	Enrolled :	5		Mode of administration:
		Male:	5	Analyzed:	5		Ocular
		Sleep disorder: None					Dosage and Timing:
							BL: 2500 lux; DL: < 100 lux for 2 h prior to sleep. Clock time: NS
							Frequency and Duration:
							One session/day for 2 days
							Sleep deprivation:
							No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Burgess, H	2001	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	17	Mean (SE):	21.3 (2.7)	Enrolled :	16	Double-blind	BL
		Range:	NS	Analyzed:	14	Cross-over	Control:
		Gender		Control Group			DL
		Female:	8	Enrolled :	16		Mode of administration:
		Male:	8	Analyzed :	14		Ocular
		Sleep disorder: None					Dosage and Timing:
							BL: >3000 lux; DL: < 10 lux for 2 hours. Clock time: NS
							Frequency and Duration:
							Single session
							Sleep deprivation:
							No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Cagnacci, A	1993	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	15	Mean (SD):	NS	Enrolled :	7	Blindedness: NS	BL
		Range:	23-34	Analyzed:	7	Cross-over	Control:
		Gender		Control Group			DL
		Female:	7	Enrolled :	7		Mode of administration:
		Male:	0	Analyzed:	7		Ocular
		Sleep disorder: None					Dosage and Timing:
							BL: 3000 lux for 4 hours (2100-0100);
							DL: 10 lux for 8 hours (1700-0115 h)
							Frequency and Duration:
							Single session
							Sleep deprivation:
							No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Cajochen, C	2000	Age (Years)		Treatment Groups		RCT	Treatments:
Quality Score	16	Mean (SD):	27.8 (8.91)	Enrolled :	23	Blindedness: NS	Low level light, Middle level light, High level light
		Range:	18-44	Analyzed:	20	Parallel	Mode of administration:
		Gender		*Low level light*			Ocular
		Female:	1	Enrolled :	NS		Dosage and Timing:
		Male:	22	Analyzed:	NS		Low level light: 23 lux; Middle level light: 230 lux;
		Sleep disorder: None		*Middle level light*			High level light: 3190 lux for 6.5 hours. Clock time: NS
				Enrolled :	NS		Frequency and Duration:
				Analyzed :	NS		Single session
				High level light			Sleep deprivation:
				Enrolled :	NS		No
				Analyzed :	NS		

Author	Year	Population		Sample Size	N	Study Design	Intervention
Costa, G	1997	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	15	Mean (SD):	NS	Enrolled :	5	Blindedness: NS	BL
		Range:	21-32	Analyzed:	5	Cross-over	Control:
		Gender		Control Group			DL
		Female:	4	Enrolled :	5		Mode of administration:
		Male:	1	Analyzed :	5		Ocular
		Sleep disorder: Shift-work disorder					Dosage and Timing:
							BL: 400-600 lux, 1500 lux, or 3200 lux DL: 40 lux.
							4 periods of 40 min each at 2 hour-intervals. Clock time: NS
							Frequency and Duration:
							4 sessions/night shift for 2 nights
							Sleep deprivation:
							No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Danilenko, KV	2000	Age (Years)		Treatment Group		RCT	Treatment: Dawn signal (Bright light)
Quality Score	14	Mean (SD): Range: Gender Female: Male: Sleep disorder: None	24.0 (4.8) NS 0 9	Enrolled : Analyzed: Control Group Enrolled : Analyzed :	9 5 9 5	Blindedness: NS Cross-over	Control: Control signal (Dim Light) Mode of administration: Ocular Dosage and Timing: Dawn signal watched for 1.5 h (0600-730 h); Control signal (0.1 lux) watched for 1.5 h (0600-0730 h); Frequency and Duration: One session/day for 9 days Sleep deprivation: No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Daurat, A	1996	Age (Years)		Treatment Group		CCT	Treatment: Moderate BL
Quality Score	16	Mean (SD): Range: Gender Female: Male: Sleep disorder: None	23.6 (1.05) NS 0 8	Enrolled : Analyzed: Control Group Enrolled : Analyzed :	8 8 8 8	Blindedness: NS Cross-over	Control: DL Mode of administration: Ocular Dosage and Timing: BL: 1000-1500 lux; DL: 50 lux for 14 hours (1800-0800 h) Frequency and Duration: Single session Sleep deprivation: Yes

Author	Year	Population		Sample Size	N	Study Design	Intervention
Daurat, A	1997	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	16	Mean (SEM):	23.6 (1.05)	Enrolled :	10	Blindedness: NS	Moderate BL
		Range:	NS	Analyzed:	10	Cross-over	Control:
		Gender		Control Group			DL
		Female:	0	Enrolled :			Mode of administration:
		Male:	8	Analyzed :	10		Ocular
		Sleep disorder: None			10		Dosage and Timing:
							BL: 1000-2000 lux, DL: < 50 lux for 14 hours during the nocturnal part of sleepless period (1800-0800 h)
							Frequency and Duration:
							Single session
							Sleep deprivation:
							Yes

Author	Year	Population		Sample Size	N	Study Design	Intervention
Eastman, CI Quality Score	2000 11	Age (Years) *Experiment 1:* Mean (SD): Range: *Experiment 2:* Mean (SD): Range: Gender *Experiment 1:* Female: Male: *Experiment 2:* Female: Male: Sleep disorder: None	 25 (5.0) NS 25 (5.0) NS 4 12 0 4	*Experiment 1:* Treatment Group Enrolled : Analyzed: Control Group Enrolled : Analyzed : *Experiment 2:* Treatment Group Enrolled : Analyzed: Control Group Enrolled : Analyzed :	 16 14 16 14 4 3 4 3	CCT Blindedness: NS Cross-over	*Experiment 1:* Treatment condition: BL Controls: 1) DL, 2) Medium intensity light Mode of administration: BL: E-O (behind the knee); DL: Ocular; Medium intensity light: Ocular Dosage and Timing: E-O light: 13,000 lux; Ocular light: either 10-20 lux; or 1000 lux for 3 hours (0300 to 0600 h) Frequency and Duration: One session/day for 2 days Sleep deprivation: Yes *Experiment 2:* Treatment condition: BL Controls: 1) DL, 2) Medium intensity light Mode of administration: BL: E-O; DL and Medium intensity light: Ocular Dosage and Timing: E-O light: 13000 lux; Ocular light: either 10-20 lux or 1000 lux for 3 hours (0600 to 0900 h or 0100 to 0400 h) Frequency and Duration: One session/day for 2 days Sleep deprivation: Yes

Author	Year	Population		Sample Size	N	Study Design	Intervention
Fletcher, A	1999	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	18	Mean (SD):	20.5 (1.2)	Enrolled :	16	Blindedness: NS	Heat administered with electric blanket
		Range:	18-23	Analyzed:	16	Cross-over	Control:
		Gender		Control Group			No heat administered with electric blanket
		Female:	7	Enrolled :	16		Dosage and Timing:
		Male:	9	Analyzed:	16		Heat blanket: 32V, 138W from 2230 h to terminal awakening
		Sleep disorder: None					Clock time: NS
							Frequency and Duration:
							Single session
							Sleep deprivation:
							No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Gordijn, MC	1998	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	19	Mean (SD):	39.3 (12.1)	Enrolled :	12	Blindedness: NS	BL
		Range:	23.6-56.5	Analyzed:	12	Cross-over	Control:
		Gender		Control Group			DL
		Female:	6	Enrolled :	12		Mode of administration:
		Male:	6	Analyzed :	12		Ocular
		Sleep disorder: None					Dosage and Timing:
							BL: 2500 lux; DL: < 10 lux (0600-0900 h or 1800-2100 h)
							Frequency and Duration:
							One session/day for 3 days
							Sleep deprivation:
							No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Gordijn, MC	1999	*Patients:*		Treatment Group		CCT	Treatment:
Quality Score	17	Age (Years)		*Patients:*		Blindedness: NS	BL
		Mean (SD):	38.3 (12.2)	Enrolled :	10	Cross-over	Control:
		Range:	NS	Analyzed:	8		DL
		Gender		*non-Patients:*			Mode of administration:
		Female:	5	Enrolled :	8		Ocular
		Male:	5	Analyzed:	8		Dosage and Timing:
		non-Patients:		Control Group			BL: 2500 lux, DL: < 10 lux.
		Age (Years)		*Patients:*			Morning: 0600-0900 h
		Mean (SD):	38.7 (12.9)	Enrolled :	10		or Evening: 1800-2100 h)
		Range:	NS	Analyzed:	8		Frequency and Duration:
		Gender		*non-Patients:*			One session/day for 3 days
		Female:	3	Enrolled :	8		Sleep deprivation:
		Male:	5	Analyzed:	8		No
		Sleep disorder: Patients suffered from Nonseasonal Depression, which may or may not be accompanied by a sleep disorder					

Author	Year	Population		Sample Size	N	Study Design	Intervention
Higuchi, S	2003	Age (Years)		Treatment Group		RCT	Treatment:
Quality Score	15	Mean (SD):	24.7 (5.6)	Enrolled :	7	Blindedness: NS	Video display terminal with Bright display
		Range:	NS	Analyzed:	7	Cross-over	Control:
		Gender		Control Group			Video display terminal with Dark display
		Female:	0	Enrolled :	7		Mode of administration:
		Male:	7	Analyzed:	7		Ocular
		Sleep disorder: None					Dosage and Timing:
							Bright display: 45 lux, Dark display: 15 lux for 3 hours (2300-0200 h)
							Frequency and Duration:
							One session/day for 3 days
							Sleep deprivation:
							No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Horne, JA	1991	Age (Years)		Treatment Group		RCT	Treatment: BL
Quality Score	15	Mean (SD): Range: Gender Female: Male: Sleep disorder: None	NS 19-26 8 4	Enrolled : Analyzed: Control Group Enrolled : Analyzed:	12 12 12 12	Single-blinded Cross-over	Control: DL Mode of administration: Ocular Dosage and Timing: BL: 2000 lux; DL: NS lux for 12 hours (1800-0600 h) Frequency and Duration: 10-min session/hour for 12 hours Sleep deprivation: Yes

Author	Year	Population		Sample Size	N	Study Design	Intervention
Horowitz, TS	2001	Age (Years)		Treatment Group		RCT	Treatment: BL
Quality Score	16	Mean (SD): Range: Gender *Treatment group:* Female: Male: *Control:* Female: Male: Sleep disorder: Shift-work disorder	26.99 (6.22) 20-40 10 16 18 10	Enrolled : Analyzed: Control Group Enrolled : Analyzed:	26 25 28 27	Blindedness: NS Cross-over	Control: DL Mode of administration: Ocular Dosage and Timing: BL: 2500 lux for 6 hours (2300-0500 h); DL: 150 lux for 8 hours (2300-0700 h) Frequency and Duration: One session/day for 4 days Sleep deprivation: No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Kelly, TL	1997	Age (Years)		Treatment Groups		CCT	Treatment:
Quality Score	17	Mean (SD):	NS	*LEET group*	12	Double-blind	BL and LEET therapy (separately and combined)
		Range:	NS	Enrolled :	12	Parallel	Control:
		Gender		Analyzed:			DL
		Female:	0	*BL*			Mode of administration:
		Male:	45	Enrolled :	12		Ocular
		LEET group		Analyzed:	8		Dosage and Timing
		Age (Years)		*BL + LEET*			LEET: 20 min. prior daytime sleep periods. BL: 3500-4300 lux, DL: 200-300 lux for 4 hours (2200-0200 h)
		Mean (SD):	24.8 (7.9)	Enrolled :	11		
		Range:	NS	Analyzed:	11		
		BL		Control Group			
		Age (Years)		*DL*			Frequency and Duration:
		Mean (SD):	22.5 (3.5)	Enrolled :	10		One session/day for 3 days
		Range:	NS	Analyzed:	7		Sleep deprivation:
		BL + LEET					No
		Age (Years)					
		Mean (SD):	23.4 (4.1)				
		Range:	NS				
		DL					
		Age (Years)					
		Mean (SD):	25.2 (7.7)				
		Range:	NS				
		Sleep disorder: Shift-work disorder					

Author	Year	Population		Sample Size	N	Study Design	Intervention
Kubota, T	2002	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	18	Mean (SD):	24 (NS)	Enrolled :	9	Blindedness: NS	BL
		Range:	20-27	Analyzed:	9	Cross-over	Control:
		Gender		Control Group			DL
		Female:	0	Enrolled :	9		Mode of administration:
		Male:	9	Analyzed :	9		Ocular
		Sleep disorder: None					Dosage and Timing:
							BL: 5000 lux for 5 hours; DL: 10 lux for 5 hours (0000-0500 h)
							Frequency and Duration:
							Single session
							Sleep deprivation:
							Yes

Author	Year	Population		Sample Size	N	Study Design	Intervention
Lavoie, S	2003	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	17	Mean (SD):	26.1 (4.2)	Enrolled :	7	Blindedness: NS	BL
		Range:	22-35	Analyzed:	7	Parallel	Control:
		Gender		Control Group			DL
		Female:	8	Enrolled :	7		Mode of administration:
		Male:	6	Analyzed :	7		Ocular
		Sleep disorder: None					Dosage and Timing:
							BL: 3000 lux; DL: 15 lux for 4 hours (0030-0430 h)
							Frequency and Duration:
							Single session
							Sleep deprivation:
							Yes

Author	Year	Population		Sample Size	N	Study Design	Intervention
Lushington, K	2002	Age (Years)		Treatment Group		CCT	Treatment:
Quality Score	18	Mean (SD):	22.1 (3.0)	Enrolled :	13	Single-blind	Light
		Range:	13-34	Analyzed:	13	Cross-over	Control:
		Gender		Control Group			Placebo (No light)
		Female:	3	Enrolled :	13		Mode of administration:
		Male:	10	Analyzed :	13		E-O (behind the knee)
		Sleep disorder: None					Dosage and Timing:
							Light: 10000 lux for 3 hours (0100-0400 h)
							Frequency and Duration:
							One session/day for 3 days
							Sleep deprivation:
							No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Morita, T	1996	Age (Years)		Treatment Group		RCT	Treatment conditions: Daylight; Warm-white light Control: DL Mode of administration: Ocular Dosage and Timing: Daylight: 1000 lux (Color temperature: 6500 K); Warm-white light: 1000 lux (Color temperature: 3000 K) for 5 hours (2100-0200 h); 3) DL: 50 lux (1900-0200 h and 0800-0900 h) Frequency and Duration: Single session Sleep deprivation: No
Quality Score	16	Mean (SD): Range: Gender Female: Male: Sleep disorder: None	20.0 (0.63) 19-21 0 5	Enrolled : Analyzed: Control Group Enrolled : Analyzed :	5 5 5 5	Blindedness: NS Cross-over	

Author	Year	Population		Sample Size	N	Study Design	Intervention
Strassman, RJ	1991	Age (Years)		Treatment Group		CCT	Treatment: BL Control: DL Mode of administration: Ocular Dosage and Timing: BL: > 2500 lux; DL: > 100 lux for 9 hours (2200-0700 h) Frequency and Duration: Single session Sleep deprivation: Yes
Quality Score	14	Mean (SE): Range: Gender Female: Male: Sleep Disorder: None	26.4 (1.90) 20-36 0 17	Enrolled : Analyzed: Control Group Enrolled : Analyzed :	17 9 17 9	Blindedness: NS Cross-over	

Author	Year	Population		Sample Size	N	Study Design	Intervention
Wakamura, T	2000	Age (Years)		Treatment Group		RCT	Treatment: BL
Quality Score	17	Mean (SD): Range: Gender Female: Male: Sleep disorder: None	20 (2) 18-23 7 0	Enrolled : Analyzed: Control Group Enrolled : Analyzed :	7 7 7 7	Blindedness: NS Cross-over	Control: DL Mode of administration: Ocular Dosage and Timing: BL: 6000 lux; DL: 2000 lux (1800-bedtime h) Frequency and Duration: Single session Sleep deprivation: No

Author	Year	Population		Sample Size	N	Study Design	Intervention
Wright, KP Jr	1997	Age (Years)		Treatment Group		RCT	Treatment condition: BL
Quality Score	17	Mean (SD): Range: Gender Female: Male: Sleep disorder: Sleep restriction	19.2 (NS) 18-25 0 46	Enrolled : Analyzed: Control Group Enrolled : Analyzed :	46 40 46 40	Blindedness: NS Cross-over	Control: DL Mode of administration: Ocular Dosage and Timing: BL: 2000 lux; DL: > 100 lux for 12 h (2000-0800) Frequency and Duration: Single session Sleep deprivation: Yes

Evidence Table C-6: References

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Evidence Table C-7: Effect of Melatonin on People with Sleep Disorders: Study Characteristics

Abbreviations: **RCT**: randomized controlled trial, **CCT**: controlled clinical trial, **MLT**: melatonin, **FR**: fast-release, **SR**: slow-release, **SD**: standard deviation, **SE**: standard error, **mg**: milligrams, **h**: hours, **NS**: not specified
Control group received placebo unless otherwise indicated

Author	Year	Population		Sample Size	N	Study Design	Intervention
Almeida-Montes, LG	2003	Age (Years)		Treatment Group		RCT	Formulation
		mean:	50	Enrolled :	10	Double-blind	Sustained-release
Quality Score	5	range:	30-72	Analyzed:	10	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	4	Enrolled :	10		Dosage and Timing
		male:	6	Analyzed :	10		0.3 mg or 1 mg MLT one hour before bedtime
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: Insomnia					I capsule/day for 14 days

Author	Year	Population		Sample Size	N	Study Design	Intervention
Andrade, C	2001	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	4	*Treatment group*		Enrolled :	18	Double-blind	Not specified
		mean (SD):	59.7(11.1)	Analyzed:	18	Parallel	Route of Administration
		range:	43-85	Control Group			Oral
		Control group		Enrolled :	15		Dosage and Timing
		mean (SD):	51.4(14.2)	Analyzed :	15		3mg MLT taken at night
		range:	23-70				Frequency
		Gender					I capsule/night for first two nights, 2 capsules every
		Treatment group					alternate night thereafter; up to 4 capsules/night
		female:	4				Duration
		male:	14				21 patients (melatonin n=11, placebo n= 10) received
		Control group					treatment for 8 days; 8 patients (melatonin n= 5,
		female:	5				placebo n= 3) received treatment for 10 days; and 4
		male:	10				patients (melatonin n=2 placebo n=2) received treatment
		Ethnicity: NS					for 16 days
		Sleep Disorder: Insomnia					

Author	Year	Population		Sample Size	N	Study Design	Intervention
Baskett, J	2003	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	5	mean:	NS	Enrolled :	20	Double-blind	Not specified
		range:	60-84	Analyzed:	14	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	10	Enrolled :	20		Dosage and Timing
		male:	10	Analyzed :	14		5mg MLT at bedtime
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: Sleep maintenance problems					I capsule/day for 4 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Beaumont, M	2004	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	3	mean (SD):	35.3(8.1)			Double-blind	Not specified
		range:	19-47	Enrolled :	9	Parallel	Route of Administration
		Gender		Analyzed:	NS		Not specified
		female:	9	Control Group			Dosage and Timing
		male:	18	Enrolled :	9		5mg MLT on day 1 at 1700h and on days 2 and 3 at 2300h
		Ethnicity: 15 Caucasians, 9 Hispanics *and 3 African Americans*		Analyzed :	NS		Frequency and Duration 5mg/day for 3 days
		Sleep Disorder: Jet lag					

Author	Year	Population		Sample Size	N	Study Design	Intervention
Camfield, P	1995	Age (Years)		Treatment Group		N of 1RCT	Formulation
Quality Score	4	mean:	8.8	Enrolled :	6	Double-blind	Not specified
		range	3 to 13	Analyzed:	6	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	2	Enrolled :	6		Dosage and Timing
		male:	4	Analyzed :	6		0.5 or 1.0mg MLT at 1800h
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: Fragmented sleep patterns accompanying developmental disabilities					For each two week interval of 10 week trial, children received MLT or PLB first week with alternative agent given on second week

Author	Year	Population		Sample Size	N	Study Design	Intervention
Dahlitz, M	1991	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	4	mean:	NS	Enrolled :	8	Double-blind	Not specified
		range:	20-60	Analyzed:	8	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	0	Enrolled :	8		Dosage and Timing
		male:	8	Analyzed :	8		5mg MLT at 2200h
		Ethnicity: Caucasian					Frequency and Duration
		Sleep Disorder: Delayed sleep phase syndrome					1 capsule/day for 4 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Dawson, D	1998	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	3	mean (SD):	65.67(1.68)	Enrolled :	12	Double-blind	Not specified
							Route of Administration
		range:	>55	Analyzed:	12	Cross-over	Oral (MLT patch placed on the gums)
		Gender		Control Group			Dosage and Timing
		female:	NS	Enrolled :	12		0.5mg MLT at 1900h
		male:	NS	Analyzed :	12		Frequency and Duration
		Ethnicity: NS					0.5mg/day for 4 consecutive days
		Sleep Disorder: Sleep maintenance insomnia					

Author	Year	Population		Sample Size	N	Study Design	Intervention
Dodge, N	2000	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	4	mean:	NS	Enrolled :	20	Double-blind	Not specified
		range:	1-12 yrs	Analyzed:	17	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	NS	Enrolled :	20		Dosage and Timing
		male:	NS	Analyzed :	17		5mg MLT at 2000h
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: Sleep disturbance accompanying severe developmental disability					5mg/day for weeks 2-3 and 5-6 of 6 week study

Author	Year	Population		Sample Size	N	Study Design	Intervention
Ellis, C	1994	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	4	mean (SD):	46(11)	Enrolled :	15	Double-blind	Not specified
		range:	32-67	Analyzed:	15	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	6	Enrolled :	15		Dosage and Timing
		male:	9	Analyzed :	15		5mg MLTat 2000h
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: Psychophysiological insomnia					5mg/day for 7 consecutive days

Author	Year	Population		Sample Size	N	Study Design	Intervention
Folklard, S	1993	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	3	mean (SD):	29(7)	Enrolled :	7	Double-blind	Not specified
		range:	21-48	Analyzed:	7	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	2	Enrolled :	8		Dosage and Timing
		male:	15	Analyzed :	8		5mg MLTat 0642h
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: Night-shift disorder					1 capsule/day for 6 successive day sleeps taken between night shifts

Author	Year	Population		Sample Size	N	Study Design	Intervention
Garfinkel, D	1995	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	4	mean:	76	Enrolled :	12	Double-blind	Controlled-release MLT
		range:	68-93	Analyzed:	12	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	5	Enrolled :	12		Dosage and Timing
		male:	7	Analyzed :	12		2 mg MLT two hours before desired bedtime
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: Long-term insomnia					1 tablet/day for 3 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Haimov, I	1995	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	3	mean (SD):	73.1(3.9)	Enrolled :	8	Double-blind	Sustained-release and fast-release MLT
		range:	NS	Analyzed:	8	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	4	Enrolled :	8		Dosage and Timing
		male:	4	Analyzed :	8		2 mg FR MLT, 2 mg sustained-release MLT or 1 mg sustained-release MLT two hours before desired bedtime
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: Insomnia					I tablet/day of 2mg FR and 2mg sustained-release MLT for 1 week and tablet/day of 1mg sustained-release MLT for 2 months

Author	Year	Population		Sample Size	N	Study Design	Intervention
James, M	1997	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	5	mean (SD):	29(8)	Enrolled :	24	Double-blind	Not specified
		range:	20-41	Analyzed:	22	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	5	Enrolled :	24		Dosage and Timing
		male:	17	Analyzed :	22		6 mg MLT 0.5h before each consecutive day sleep
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: Night-shift disorder					6mg/day for 4 treatment cycles lasting 4-6 consecutive night shifts

Author	Year	Population		Sample Size	N	Study Design	Intervention
James, SP	1990	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	3	mean:	33.4	Enrolled :	10	Double-blind	Not specified
		range:	20-57	Analyzed:	10	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	6	Enrolled :	10		Dosage and Timing
		male:	4	Analyzed :	10		1 mg or 5mg MLT given 15 minutes before bedtime
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: Insomnia					1mg or 5mg MLT/day for 1 week

Author	Year	Population		Sample Size	N	Study Design	Intervention
Jockovich, M	2000	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	3	mean:	28.2	Enrolled :	19	Double-blind	Not specified
		range:	NS	Analyzed:	19	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	15	Enrolled :	19		Dosage and Timing
		male:	4	Analyzed :	19		1 mg MLT 0.5-1h before daytime sleep
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: Night-shift disorder					1 caplet/day for 3 consecutive days

Author	Year	Population		Sample Size	N	Study Design	Intervention
Jorgensen	1998	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	4	mean:	32	Enrolled :	20	Double-blind	Not specified
		range:	25-40	Analyzed:	18	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	2	Enrolled :	20		Dosage and Timing
		male:	16	Analyzed :	18		10 mg MLT the morning after each night shift
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: Night-shift disorder					1 tablet/day for varied amount of time

Author	Year	Population		Sample Size	N	Study Design	Intervention
Kayumov, L	2001	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	3	female; mean (SD):	30.8(12.4)	Enrolled :	22	Double-blind	Not specified
		male; mean (SD):	35.6(14.0)	Analyzed:	19	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	7	Enrolled :	22		Dosage and Timing
		male:	15	Analyzed :	19		5 mg MLT, timing: NS
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: Delayed sleep phase syndrome					5mg/day for 4 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
McArthur, A	1998	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	3	mean (SD):	10.1(1.5)	Enrolled :	9	Double-blind	Immediate-release MLT
		range:	4-17 yrs	Analyzed:	9	Cross-over	Route of Administration
		Gender		Control Group			Oral or by gastrostomy tube
		female:	9	Enrolled :	9		Dosage and Timing
		male:	0	Analyzed :	9		Dosage based on individual body weight, range 2.5-7.5 mg given one hour before bedtime
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: Sleep dysfunction accompanying Rett syndrome					I capsule/day for 4 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
O'cahllaghan	1999	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	4	median:	11	Enrolled :	7	Double-blind	Not specified
		range:	Feb-28	Analyzed:	7	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	4	Enrolled :	7		Dosage and Timing
		male:	3	Analyzed :	7		5 mg MLT 30 minutes before usual bedtime
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: Delayed sleep onset accompanying tuberous sclerosis					1 capsule/day for 2 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Serfaty, M	2002	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	5	mean (SD):	84.2(7.6)	Enrolled :	44	Double-blind	Slow release MLT
		range:	NS	Analyzed:	25	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	9	Enrolled :	44		Dosage and Timing
		male:	16	Analyzed :	25		6 mg MLT tablet at usual bedtime
		Ethnicity: Not specified					Frequency and Duration
		Sleep Disorder: Sleep disorder associated with dementia					1 tablet/day for 2 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Serfaty, M	2003	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	2	mean (SD):	39.9(11.8)	Enrolled :	NS	Double-blind	Slow-release MLT
		range:	NS	Analyzed:	NS	Parallel	Route of Administration
		Gender		Control Group			Oral
		female:	17	Enrolled :	NS		Dosage and Timing
		male:	14	Analyzed :	NS		6 mg MLT tablet at usual bedtime
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: Sleep disorder accompanying depression					1 tablet/day for 4 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Shamir, E	2000	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	4	mean (SD):	42.3(13.1)	Enrolled :	14	Double-blind	Controlled-release MLT
		range:	25-64	Analyzed:	14	Cross-over	Route of Administration
		Gender		Control Group			Not specified
		female:	3	Enrolled :	14		Dosage and Timing
		male:	11	Analyzed :	14		2mg MLT taken two hours before the desired bedtime
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: Poor sleep quality					2 mg MLT/day for 3 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Shamir, E	2000	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	4	mean (SD):	42(5)	Enrolled :	27	Double-blind	Controlled-release MLT
		range:	24-67	Analyzed:	19	Cross-over	Route of Administration
		Gender		Control Group			Not specified
		female:	7	Enrolled :	27		Dosage and Timing
		male:	12	Analyzed :	19		2mg MLT taken two hours before the desired bedtime
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: DSM-IV insomnia accompanying schizophrenia					2 mg MLT/day for 3 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Singer, C	2003	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	4	mean (SD):	77.4 (8.9)	Enrolled :	104	Double-blind	Immediate-release MLT
		range:	NS	Analyzed:	104	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	88	Enrolled :	52		Dosage and Timing
		male:	69	Analyzed :	47		10 mg MLT taken one hour before habitual bedtime
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: Sleep disturbance accompanying Alzheimer's disease					1 capsule/day for 8 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Smits, M.G	2003	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	5	mean (SD):		Enrolled :	27	Double-blind	Fast-release MLT
		Treatment Group	9.2 (2.1)	Analyzed:	27	Cross-over	Route of Administration
		Control Group	10.1 (1.7)	Control Group			Oral
		range:	NS	Enrolled :	35		Dosage and Timing
		Gender		Analyzed :	35		5mg MLT at 1900h
		Treatment Group					Frequency and Duration
		female:	7				1 dose/ day for 4 weeks
		male:	20				
		Control Group					
		female:	6				
		male:	29				
		Ethnicity: White					
		Sleep Disorder: Idiopathic chronic sleep-onset insomnia					

Author	Year	Population		Sample Size	N	Study Design	Intervention
Suhner, A	1998	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	4	mean:	NS	Enrolled :	240	Double-blind	Not specified
		range:	NS	Analyzed:	174	Parallel	Route of Administration
		Gender		Control Group			Not specified
		female:	148	Enrolled :	80		Dosage and Timing
		male:	172	Analyzed :	60		0.5mg FR, 5mg FR, 2mg CR MLT or PLB at bedtime
		Ethnicity: NS					on the first day post-flight at 23:10 (+/- 1.52h) and on the
		Sleep Disorder: Jet-lag					following days at 23:29 (+/- 1.12h)
							Frequency and Duration
							1 dose/day for 4 days following eastward flight

Author	Year	Population		Sample Size	N	Study Design	Intervention
Suhner, A	2001	Age (Years) of Compliant (137)		Treatment Group		RCT	Formulation
							Not specified
Quality Score	4	mean:	41.3	Enrolled :	40	Double-blind	Route of Administration
		range:	18-68	Analyzed:	35	Parallel	Not specified
		Gender of Compliant (137)		Control Group			Dosage and Timing
							5mg MLT taken on the return flight
		female:	67	Enrolled :	40		(eastbound)
		male:	70	Analyzed :	39		between 1700h and 2100h local time at the place
		Ethnicity: NS					of departure depending on the flight schedule
		Sleep Disorder: Jet-lag					Frequency and Duration
							1 dose/day for four consecutive days post-flight

Author	Year	Population		Sample Size	N	Study Design	Intervention
Waldhauser	1990	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	2	mean (SD):	26.4(4.8)	Enrolled :	10	Double-blind	Not specified
		range:	NS	Analyzed:	10	Parallel	Route of Administration
		Gender		Control Group			Oral
		female:	10	Enrolled :	10		Dosage and Timing
		male:	10	Analyzed :	10		80mg MLTat 2100h
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: Induced insomnia					Single dose

Author	Year	Population		Sample Size	N	Study Design	Intervention
Wright, SW	1998	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	4	mean:	38.6	Enrolled :	20	Double-blind	Not specified
		range:	32-45	Analyzed:	15	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	3	Enrolled :	20		Dosage and Timing
		male:	12	Analyzed :	15		5 mg MLT thirty minutes before bedtime in the evening
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: Night-shift disorder					5mg/night for 3 nights following shift work

Author	Year	Population		Sample Size	N	Study Design	Intervention
Zhdanova, I	2001	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	2	mean:	NS	Enrolled :	NS	Double-blind	Not specified
		range:	NS	Analyzed:	30	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	NS	Enrolled :	NS		Dosage and Timing
		male:	NS	Analyzed :	30		0.1 mg, 0.3 mg, or 3.0 mg MLT, timing: NS
		Ethnicity: NS					Frequency and Duration
		Sleep Disorder: Insomnia					1 capsule/day for 4 days at home and then for 3 days as inpatients of the MIT Clinical Research Center.

Evidence Report C-7: References

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Evidence Table C-8: Safety of Malatonin: Study Characteristics

Abbreviations: **RCT**: randomized controlled trial, **CCT**: controlled clinical trial, **MLT**: melatonin, **FS**: fast-release, **SR**: slow-release, **SD**: standard deviation, **SE**: standard error, **mg**: milligrams, **h**: hours, **NS**: not specified
Control group received placebo unless otherwise indicated

Author	Year	Population		Sample Size	N	Study Design	Intervention
Andrade, C	2001	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	25	*Treatment Group*		Enrolled :	18	Double-blind	Not specified
		mean (SD):	59.7(11.1)	Analyzed :	18	Parallel	Route of Administration
		range:	43-85	Control Group			Oral
		Control Group		Enrolled :	15		Dosage and Timing
		mean (SD):	51.4(14.2)	Analyzed :	15		3mg MLT taken at night
		range:	23-70				Frequency
		Gender					I capsule/first two nights, 2 capsules every alternate night thereafter upto 4 capsules/night thereafter
		Treatment Group					
		female:	4				Duration
		male:	14				21 patients (melatonin n=11, placebo n= 10) received treatment for 8 days; 8 patients (melatonin n= 5, placebo n= 3) received treatment for 10 days; and 4 patients (melatonin n=2 placebo n=2) received treatment for 16 days
		Control Group					
		female:	5				
		male:	10				
		Sleep Disorder: insomnia					

Author	Year	Population		Sample Size	N	Study Design	Intervention
Arendt, J	1984	Age (Years)		Treatment Group		CCT	Formulation
Quality Score	19	mean:	NS	Enrolled :	12	Double-blind	Not specified
		range:	22-46	Analyzed :	12	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	2	Enrolled :	12		Dosage and Timing
		male:	10	Analyzed :	12		2mg MLT at 1700h
		Sleep Disorder: None					Frequency and Duration
							2mg/day for 4 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Baskett, J	2003	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	25	mean:	NS	Enrolled :	20	Double-blind	Not specified
		range:	60-84	Analyzed:	14	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	16	Enrolled :	20		Dosage and Timing
		male:	4	Analyzed :	14		5mg MLT at bedtime
							Frequency and Duration
							I capsule/day for 4 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Claustrat, B	1992	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	19	mean (SD):		Enrolled :	15	Double-blind	Not specified
		Treatment group	36.3(8.9)	Analyzed :	15	Cross-over	Route of Administration
		Control group	35.7(6.4)	Control Group			Oral
		range:	NS	Enrolled :	15		Dosage and Timing
		Gender		Analyzed :	15		8 mg MLT at 2200h
		female:					Frequency and Duration
		Treatment group	7				1 capsule/day for 4 days
		Control group	5				
		male:					
		Treatment group	8				
		Control group	10				
		Sleep Disorder: Jet-lag					

Author	Year	Population		Sample Size	N	Study Design	Intervention
Dahlitz, M	1991	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	24	mean:	NS	Enrolled :	8	Double-blind	Not specified
		range:	20-60	Analyzed :	8	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	0	Enrolled :	8		Dosage and Timing
		male:	8	Analyzed :	8		5mg MLTat 2200h
		Sleep Disorder: Delayed sleep					Frequency and Duration
		phase insomnia					1 capsule/day for 4 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Dodge, N	2000	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	22	mean:	NS	Enrolled :	20	Double-blind	Not specified
		range:	1-Dec	Analyzed :	17	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	NS	Enrolled :	20		Dosage and Timing
		male:	NS	Analyzed :	17		5mg MLT at 2000h
		Sleep Disorder: Sleep disturbance accompanying severe developmental disability					Frequency and Duration 5mg/day on weeks 2-3 and 5-6 of a 6 week study

Author	Year	Population		Sample Size	N	Study Design	Intervention
Edwards, BJ	2000	Age (Years)		Treatment Group		CCT	Formulation
Quality Score	22	*Treatment Group*		Enrolled :	14	Double-blind	Not specified
		mean (SD):	40(13)	Analyzed:	13	Parallel	Route of Administration
		range:	NS	Control Group			Oral
		Control Group		Enrolled :	17		Dosage and Timing
		mean (SD):	41(12)	Analyzed :	13		5mg MLT taken on the plane between 18:00-19:00h and between 22:00 and 23:00h, according to local time at destination and for the next three evenings.
		range:	NS				
		Gender					Frequency and Duration 2 capsules/day for first day and then 1 capsule/day for 2 days
		female:	3				
		male:	28				

Author	Year	Population		Sample Size	N	Study Design	Intervention
Ellis, C	1194	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	20	mean (SD):	46(11)	Enrolled :	15	Double-blind	Not specified
		range:	32-67	Analyzed :	15	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	6	Enrolled :	15		Dosage and Timing
		male:	9	Analyzed :	15		5mg MLT at 2000h

		Sleep Disorder: Psychophysiological insomnia					Frequency and Duration 1 capsule/day for 7 consecutive days

Author	Year	Population		Sample Size	N	Study Design	Intervention
Fraschini, F	1999	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	18	mean:	32.5	Enrolled :	5	Double-blind	Not specified
		range:	NS	Analyzed :	5	Cross-over	Route of Administration
		Gender		Control Group			Not specified
		female:	1	Enrolled :	5		Dosage and Timing
		male:	4	Analyzed :	5		5mg, 10mg or 100mg MLT, timing: NS
		Sleep Disorder: None					Frequency and Duration 1 dose/day for 1 to 3 days

Author	Year	Population		Sample Size	N	Study Design	Intervention
Garfinkel, D	1995	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	24	mean:	76	Enrolled :	12	Double-blind	Controlled-release MLT
		range:	68-93	Analyzed :	12	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	5	Enrolled :	12		Dosage and Timing
		male:	7	Analyzed :	12		2 mg MLT two hours before desired bedtime
		Sleep Disorder: Long-term insomnia					Frequency and Duration 1 tablet/night for three weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Hood, E	1999	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	12	mean:	NS	Enrolled :	15	Double-blind	Not specified
		range:	NS	Analyzed :	9	Cross-over	Route of Administration
		Gender		Control Group			Not specified
		female:	NS	Enrolled :	15		Dosage and Timing
		male:	NS	Analyzed :	9		1mg MLT at bedtime
		Sleep Disorder: None					Frequency and Duration 1mg/day for 4 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
James, M	1998	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	23	mean (SD):	29(8)	Enrolled :	24	Double-blind	Not specified

		range:	20-41	Analyzed :	22	Cross-over	Route of Administration Oral Dosage and Timing 6 mg MLT 30 minutes before each consecutive day sleep Frequency and Duration 6mg/day for 8-12 consecutive night shifts
		Gender		Control Group			
		female:	5	Enrolled :	24		
		male:	17	Analyzed :	22		
		Sleep Disorder: Night-shift disorder					

Author	Year	Population		Sample Size	N	Study Design	Intervention
Jan, E	1994	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	21	mean:	NS	Enrolled :	15	Double-blind	Not specified
		range:	6mon-13yr	Analyzed :	15	Cross-over	Route of Administration
		Gender		Control Group			Not specified
		female:	2	Enrolled :	15		Dosage and Timing
		male:	13	Analyzed :	15		2-5mg MLT at desired bedtime
		Sleep Disorder: Severe sleep problems					Frequency and Duration 2-5mg/day for 7-10 days

Author	Year	Population		Sample Size	N	Study Design	Intervention
Jean-Louis, G	1998	Age (Years)		Treatment Group		CCT	Formulation
Quality Score	21	mean (SD):	68.8(15.8)	Enrolled :	10	Double-blind	Not specified
		range:	NS	Analyzed :	NS	Cross-over	Route of Administration
		Gender		Control Group			Not specified
		female:	6	Enrolled :	10		Dosage and Timing
		male:	4	Analyzed :	NS		6mg MLT two hours before bedtime
		Sleep Disorder: Sleep disturbance accompanying mild cognitive impairment					Frequency and Duration 6mg/day for 10 days

Author	Year	Population		Sample Size	N	Study Design	Intervention
Jockovich, M	2000	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	22	mean:	28.2	Enrolled :	19	Double-blind	Not specified
		range:	NS	Analyzed :	19	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	15	Enrolled :	19		Dosage and Timing
		male:	4	Analyzed :	19		1 mg MLT thirty to sixty minutes before daytime sleep
		Sleep Disorder: Night-shift disorder					Frequency and Duration 1 tablet/day for 3 consecutive days

Author	Year	Population		Sample Size	N	Study Design	Intervention
Jorgensen	1998	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	22	mean:	32	Enrolled :	20	Double-blind	Not specified
		range:	25-40	Analyzed :	18	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	2	Enrolled :	20		Dosage and Timing
		male:	16	Analyzed :	18		10 mg MLT the morning after each night shift
		Sleep Disorder: Night-shift disorder					Frequency and Duration
							1 tablet/day for varied amount of time

Author	Year	Population		Sample Size	N	Study Design	Intervention
Kayumov, L	2001	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	22	mean (SD):		Enrolled :	22	Double-blind	Not specified
		female:	30.8(12.4)	Analyzed :	19	Cross-over	Route of Administration
		male:	35.6(14.0)	Control Group			Oral
		Gender		Enrolled :	22		Dosage and Timing
		female:	7	Analyzed :	19		5 mg MLT, timing: NS
		male:	15				Frequency and Duration
		Sleep Disorder: Delayed sleep phase syndrome					5mg/day for 4 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Matsumomo M	1999	Age (Years)		Treatment Group		CCT	Formulation
Quality Score	19	mean (SD):	23.7(1.3)	Enrolled :	6	Single-blind	Not specified
		range:	NS	Analyzed :	6	Cross-over	Route of Administration
		Gender		Control Group			Not specified
		female:	0	Enrolled :	6		Dosage and Timing
		male:	6	Analyzed :	6		10 mg MLT at 1000h
							Frequency and Duration

Not specified

Author	Year	Population		Sample Size	N	Study Design	Intervention
McArthur, A	1998	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	21	mean (SD):	10.1(1.5)	Enrolled :	9	Double-blind	Immediate-release melatonin
		range:	4-17 yrs	Analyzed :	9	Cross-over	Route of Administration
		Gender		Control Group			Oral or by gastrostomy tube
		female:	9	Enrolled :	9		Dosage and Timing
		male:	0	Analyzed :	9		Dosage based on individual body weight, range 2.5-7.5mg taken one hour before bedtime
		Sleep Disorder: Sleep dysfunction accompanying Rett syndrome					Frequency and Duration I capsule/day for 4 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Monti, J	1999	Age (Years)		Treatment Group		CCT	Formulation
Quality Score	21	mean:	NS	Enrolled :	10	Single-blind	Not specified
		range:	66-86	Analyzed :	10	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	2	Enrolled :	10		Dosage and Timing
		male:	8	Analyzed :	10		3 mg MLT taken in the evenings
		Sleep Disorder: Insomnia					Frequency and Duration 3mg/day for 14 days

Author	Year	Population		Sample Size	N	Study Design	Intervention
Naguib, M	1999	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	25	mean:	29.7	*5mg and 15mg MLT*		Double-blind	Not specified
		range:	19-44	Enrolled :	25	Cross-over	Route of Administration
		Gender		Analyzed :	25		Oral
		female:	75	Control Group			Dosage and Timing
		male:	0	Enrolled :	25		5mg and 15 mg MLT taken approximately one and a half hours before induction of general
		Sleep Disorder: None		Analyzed :	25		

							anaesthesia Frequency and Duration Single dose

Author	Year	Population		Sample Size	N	Study Design	Intervention
O'Callaghan, F	1999	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	20	median:	11	Enrolled :	7	Double-blind	Not specified
		range:	Feb-28	Analyzed :	7	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	4	Enrolled :	7		Dosage and Timing
		male:	3	Analyzed :	7		5 mg MLT thirty minutes before usual bedtime
		Sleep Disorder: Sleep disorder accompanying Tuberous Sclerosis					Frequency and Duration 1 capsule/day for 2 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Paccoti, P	1987	Age (Years)		Treatment Group		CCT	Formulation
Quality Score	18	mean:	NS	Enrolled :	6	Double-blind	Not stated
		range:	22-32	Analyzed :	6	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	0	Enrolled :	6		Dosage and Timing
		male:	6	Analyzed :	6		100mg MLT, timing: NS
		Sleep Disorder: None					Frequency and Duration Single dose

Author	Year	Population		Sample Size	N	Study Design	Intervention
Petrie	1989	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	20	mean:	NS	Enrolled :	20	Double-blind	Not specified
		range:	28-68	Analyzed :	20	Cross-over	Route of Administration
		Gender		Control Group			Not specified
		female:	8	Enrolled :	20		Dosage and Timing
		male:	12	Analyzed :	20		5 mg MLT taken between 1000h and 1200h local time
		Sleep Disorder: Jet-lag					Frequency and Duration

							One dose for 3 days before flight, during flight, and once a day for 3 days after arrival

Author	Year	Population		Sample Size	N	Study Design	Intervention
Petrie	1993	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	20	mean (SD):	34.9(7.7)	*Early MLT*		Double-blind	Not specified
		range:	25-52	Enrolled :	NS	Parallel	Route of Administration
		Gender		Analyzed :	NS		Oral
		female:	26	*Late MLT*			Dosage and Timing
		male:	26	Enrolled :	NS		5 mg MLT taken between 0700h-0800h
		Sleep Disorder: Jet lag		Analyzed :	NS		Frequency and Duration
				Control Group			5 mg early MLT for 8 days, 5mg late MLT for 5 days
				Enrolled :	NS		
				Analyzed :	NS		

Author	Year	Population		Sample Size	N	Study Design	Intervention
Seabra, M.L.	2000	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	20	mean (SD):	29(1)	Enrolled :	30	Double-blind	Not specified
		range:	25-55	Analyzed :	30	Parallel	Route of Administration
		Gender		Control Group			Oral
		female:	0	Enrolled :	10		Dosage and Timing
		male:	40	Analyzed :	10		10 mg MLT taken one hour before sleep time (approximately 2200h)
		Sleep Disorder: None					Frequency and Duration
							1 capsule/day for 28 days

Author	Year	Population		Sample Size	N	Study Design	Intervention
Serfaty, M	2002	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	22	mean (SD):	84.2(7.6)	Enrolled :	44	Double-blind	Slow-release
		range:	NS	Analyzed :	25	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	9	Enrolled :	44		Dosage and Timing
		male:	16	Analyzed :	25		6 mg MLT taken at usual bedtime

		Sleep Disorder: Sleep disturbance accompanying dementia				Frequency and Duration 1 tablet/day for two weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Shamir, E	2000	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	22	mean (SD):	74.0 (9.5)	Enrolled :	10	Double-blind	Not specified
		range:	55-91	Analyzed :	10	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	11	Enrolled :	9		Dosage and Timing
		male:	8	Analyzed :	9		2 mg MLT taken at 2000h
		Sleep Disorder: None					Frequency and Duration 2 mg/day for 4 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Shamir, E	2001	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	24	mean (SD):	64.2(14.3)	Enrolled :	10	Double-blind	Controlled-release
		range:	28-82	Analyzed :	8	Cross-over	Route of Administration
		Gender		Control Group			Not specified
		female:	11	Enrolled :	12		Dosage and Timing
		male:	11	Analyzed :	12		2.5 mg MLT, timing: NS
		Sleep Disorder: Jet-lag					Frequency and Duration 2.5 mg/day for 6 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Smits, MG	2003	Age (Years)		3 treatments		RCT	Formulation
Quality Score	25	mean (SD):		FR =0.5mg, 5mg		Double-blind	Fast-release and controlled-release
		Treatment group	9.2 (2.1)	CR= 2mg		Parallel	Route of Administration
		Control group	10.1 (1.7)	Treatment Groups			Oral
		range:	NS	Enrolled :	NS		Dosage and Timing
		Gender		Analyzed :	NS		5 mg MLT at 1900h
		Treatment group		Control Group			Frequency and Duration 5mg/day for 4 weeks
		female:	20	Enrolled :	NS		
		male:	6	Analyzed :	NS		

		Control group					
		female:	6				
		male:	29				
		Sleep Disorder:					
		Idiopathic chronic					
		sleep-onset insomnia					

Author	Year	Population		Sample Size	N	Study Design	Intervention
Suhner, A	1998	Age (Years)		3 treatment groups		RCT	Formulation
Quality Score	20	mean:	36	0.5 mg FR MLT		Double-blind	Controlled-release or Fast-release
		range:	20-65	5.0 mg FR MLT		Parallel	Route of Administration
		Gender		2 mg CR MLT			Not specified
		female:	148	Treatment Groups			Dosage and Timing
		male:	172	Enrolled :	NS		0.5 mg FR, 5.0 mg FR, 2 mg CR at
		Sleep Disorder: Jet-lag		Analyzed :	NS		bedtime after an eastward flight
				Control Group			on the first day post-flight at 2310(+/-
				Enrolled :	NS		1.52h) and on the following
				Analyzed :	NS		days at 2329h(+/-1.12h)
							Frequency and Duration
							One dose/day for 4 days after eastward flight

Author	Year	Population		Sample Size	N	Study Design	Intervention
Suhner, A	2001	Age (Years) of Compliant (137)		Treatment Group		RCT	Formulation
							Not specified
Quality Score	19	mean:	41.3	Enrolled :	40	Double-blind	Route of Administration
		range:	18-68	Analyzed :	35	Parallel	Not specified
		Gender of Compliant (137)		Control Group			Dosage and Timing
							5mg MLT or 10mg zolpidem taken
		female:	67	Enrolled :	40		on the
		male:	70	Analyzed :	39		return flight (eastbound) between
		Sleep Disorder: Jet-lag					1700h and 2100h local
							time at the place of departure
							depending on the flight schedule
							Frequency and Duration
							4 consecutive days post-flight at bedtime.

Author	Year	Population		Sample Size	N	Study Design	Intervention
Van Wieringen	2001	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	21	mean (SD):	33.4(10.7)	Enrolled :	40	Double-blind	Not specified
		range:	NS	Analyzed :	29	Parallel	Route of Administration
		Gender		Control Group			Oral
		female:	59	Enrolled :	41		Dosage and Timing
		male:	22	Analyzed :	21		5mg MLT taken five hours before individual melatonin onset time
		Sleep Disorder: Delayed melatonin onset as well as fatigue and sleep disturbance					Frequency and Duration 1 tablet/day for 4 weeks

Author	Year	Population		Sample Size	N	Study Design	Intervention
Wright, SW	1998	Age (Years)		Treatment Group		RCT	Formulation
Quality Score	17	mean:	38.6	Enrolled :	20	Double-blind	Not specified
		range:	32-45	Analyzed :	15	Cross-over	Route of Administration
		Gender		Control Group			Oral
		female:	3	Enrolled :	20		Dosage and Timing
		male:	12	Analyzed :	15		5 mg MLT taken 30 minutes before bedtime in the evening
		Sleep Disorder: Night-shift disorder					Frequency and Duration 5mg/night for 3 nights following shift work

Author	Year	Population		Sample Size	N	Study Design	Intervention
Wright, J	1986	Age (Years)		Treatment Group		CCT	Formulation
Quality Score	17	mean:	NS	Enrolled :	6	Double-blind	Not specified
		range:	22-46	Analyzed :	6	Cross-over	Route of Administration
		Gender		Control Group			Not specified
		female:	2	Enrolled :	6		Dosage and Timing
		male:	10	Analyzed :	6		2mg MLT at 1700h
							Frequency and Duration 2mg/day for 4 weeks

Evidence Table C-8: References

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Evidence Table C-9: Melatonin Compared to Other Pharmacological Treatments for Sleep Disorders: Study Characteristics

Abbreviations: **RCT**: randomized controlled trial, **CCT**: controlled clinical trial, **MLT**: melatonin, **FR**: fast-release, **SR**: slow-release, **SD**: standard deviation, **SEM**: standard error of the mean, **mg**: milligrams, **h**: hours, **NS**: not specified

Author	Year	Population		Sample Size	N	Study Design	Intervention
Author	**Year**	**Population**		**Sample Size**	**N**	**Study Design**	**Intervention**
Ferini-Strambi, L	1993	Age (Years)		MLT Group		CCT	Comparison:
Quality Score	14	Mean (SD):	25.3 (3.6)	Enrolled :	6		MLT vs.Triazolam vs. PLB
		Range:	NS	Analyzed:	6	Double-blind	Route of administration:
		Gender:		Triazolam Group			Oral
		Female:	0	Enrolled :	6	Cross-over	Dosage and Timing:
		Male:	6	Analyzed :	6		MLT: 100 mg; Triazolam: 0.125 mg; PLB (NS) at 2230 h
		Sleep disorder: None		Placebo Group			
				Enrolled :	6		Frequency and Duration:
				Analyzed :	6		Single dose

Author	Year	Population		Sample Size	N	Study Design	Intervention
Author	**Year**	**Population**		**Sample Size**	**N**	**Study Design**	**Intervention**
Holmes, A	2002	Age (Years)		MLT Group		CCT	Comparison:
Quality Score	15	Mean (SEM):	20.3 (0.6)	Enrolled :	12	Double-blind	MLT vs. Zopiclone vs. PLB (Lactose)
		Range:	19-25	Analyzed:	12	Cross-over	Route of administration:
		Gender		Zopiclone Group			Oral
		Female:	5	Enrolled :	12		Dosage and Timing:
		Male:	7	Analyzed :	12		MLT: 5 mg; Zopiclone: 7.5 mg; PLB: 10 mg at 1400 h
		Sleep disorder: None		PLB Group			
				Enrolled :	12		Frequency and Duration:
							Single dose

Author	Year	Population		Sample Size	N	Study Design	Intervention
Author	**Year**	**Population**		**Sample Size**	**N**	**Study Design**	**Intervention**
Satomura, T	2001	Age (Years)		MLT Group		RCT	Comparison:
Quality Score	11	Mean (SD):	23.7 (1.7)	Enrolled :	7	Double-blind	MLT vs.Triazolam vs. PLB (Lactose)
		Range:	NS	Analyzed:	7	Cross-over	Route of administration:
		Gender:		Triazolam Group			Oral
		Female:	0	Enrolled :	7		Dosage and Timing:
		Male:	7	Analyzed :	7		MLT: 1 mg, 3 mg, 6 mg; Triazolam: NS; PLB: NS at 1330 h
		Sleep disorder: None		PLB Group			
				Enrolled :	7		Frequency and Duration:
				Analyzed :	7		Single dose

Author	Year	Population		Sample Size	N	Study Design	Intervention
Suhner, A	2001	Age (Years)		MLT Group		RCT	Comparison:
Quality Score	20	Mean (SD):	41.3 (NS)	Enrolled :	35	Double-blind	MLT vs. Zolpidem vs. PLB
		Range:	18-68	Analyzed:	34	Parallel	Route of administration:
		Gender:		Zopiclone Group			Oral
		Female:	67	Enrolled :	34		Dosage and Timing:
		Male:	70	Analyzed :	34		MLT: 5 mg; Zolpidem: 10 mg; PLB: NS between 1700-2100 h at
		Sleep disorder: Jet-lag		PLB Group			departure time and then at local bedtime
				Enrolled :	39		(Clock time: NS)
				Analyzed :	37		Frequency and Duration:
							Single dose during flight and then once daily at bedtime for 4
							consecutive days

Evidence Table C-9 References

1. Ferini-Strambi L, Zucconi M, Biella G et al. Effect of melatonin on sleep microstructure: preliminary results in healthy subjects. Sleep 1993;16(8):744-7.

2. Holmes AL, Gilbert SS, Dawson D. Melatonin and zopiclone: the relationship between sleep propensity and body temperature. Sleep 2002;25(3):301-6.

3. Satomura T, Sakamoto T, Shirakawa S et al. Hypnotic action of melatonin during daytime administration and its comparison with triazolam. Psychiatry Clin Neurosci 2001;55(3):303-4.

4. Suhner A, Schlagenhauf P, Hofer I et al. Effectiveness and tolerability of melatonin and zolpidem for the alleviation of jet lag. Aviat Space Environ Med 2001;72(7):638-46.

Appendix D: Technical Expert Panel

The following is a list of the members of the TEP with a brief description of some of their professional affiliations and areas of expertise:

(1) Dr. Irvin Mayers, Divisional Director of Pulmonary Medicine, University of Alberta (expertise in pulmonary medicine and sleep disorders)

(2) Ms. Shirley Heschuk, Lecturer, University of Alberta (expertise in Pharmacy Law and Ethics, Non-Prescription Drugs, Nutrition, and CAM)

(3) Dr. Constance Chik, Professor and Program Director of the Division of Endocrinology and Metabolism, University of Alberta (expertise in neuroendocrinology and pineal cell biology)

(4) Dr. Christina Benishin, Associate Professor of Physiology, University of Alberta (expertise in pharmacology, physiology, and CAM)

(5) Dr. Gary Hnatko, Associate Professor of Psychiatry, University of Alberta (expertise in psychiatry and sleep disorders)

(6) Dr. Carina Majaesic, Pediatric Pulmonologist, University of Alberta Hospital (expertise in pulmonary medicine and immunology)

(7) Dr. Nalaka Gooneratne, Assistant Professor, University of Pennsylvania (expertise in sleep and pulmonary critical care)

(8) Dr. Irina Zhdanova, Associate Professor, Boston University (expertise in melatonin and sleep disorders)

(9) Dr. Manisha Witmans, Pediatric Pulmonologist, University of Alberta Hospital (expertise in sleep disorders)

(10) Dr. Larry Pawluk, Associate Clinical Professor of Psychiatry, University of Alberta (expertise in pharmacology and sleep disorders)

(11) Dr. Catherine E. Ulbricht, Executive Director of Natural Standard Research Collaboration, Senior Attending Pharmacist Massachusetts General Hospital (expertise in CAM and pharmacology)

(12) Dr. Ethan Basch, Chief Editor, Natural Standard Research Collaboration (expertise in CAM)

(13) Dr. Adrianne E. Rogers, Professor of Pathology and Public Health, Boston University School of Medicine; Editorial Board Member of Natural Standard Research Collaboration (expertise in toxicology and pathology)

(14) Dr. Paul Hammerness, Investigator, Pediatric Psychopharmacolgy Unit, Child and Adolescent Psychiatry, Massachusetts General Hospital; Editor and Author, Natural Standard Research Collaboration (expertise in CAM)

(15) Dr. Serguei Aksentsev, Author, Natural Standard Research Collaboration (expertise in CAM)

(16) Dr. Alan Carroll, Associate Clinical Professor, Department of Psychiatry, University of Alberta (expertise in psychiatry and neurodevelopment)