

Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis

Nina Buscemi, Ben Vandermeer, Nicola Hooton, Rena Pandya, Lisa Tjosvold, Lisa Hartling, Sunita Vohra, Terry P Klassen, Glen Baker

Abstract

Objective To conduct a systematic review of the efficacy and safety of exogenous melatonin in managing secondary sleep disorders and sleep disorders accompanying sleep restriction, such as jet lag and shiftwork disorder.

Data sources 13 electronic databases and reference lists of relevant reviews and included studies; Associated Professional Sleep Society abstracts (1999 to 2003).

Study selection The efficacy review included randomised controlled trials; the safety review included randomised and non-randomised controlled trials.

Quality assessment Randomised controlled trials were assessed by using the Jadad Scale and criteria by Schulz et al, and non-randomised controlled trials by the Downs and Black checklist.

Data extraction and synthesis One reviewer extracted data and another reviewer verified the data extracted. The inverse variance method was used to weight studies and the random effects model was used to analyse data.

Main results Six randomised controlled trials with 97 participants showed no evidence that melatonin had an effect on sleep onset latency in people with secondary sleep disorders (weighted mean difference – 13.2 (95% confidence interval – 27.3 to 0.9) min). Nine randomised controlled trials with 427 participants showed no evidence that melatonin had an effect on sleep onset latency in people who had sleep disorders accompanying sleep restriction (– 1.0 (– 2.3 to 0.3) min). 17 randomised controlled trials with 651 participants showed no evidence of adverse effects of melatonin with short term use (three months or less).

Conclusions There is no evidence that melatonin is effective in treating secondary sleep disorders or sleep disorders accompanying sleep restriction, such as jet lag and shiftwork disorder. There is evidence that melatonin is safe with short term use.

Introduction

Sleep disorders affect approximately 20% of the American population.¹ A sleep disorder exists when-

ever a lower quality of sleep leads to impaired functioning or excessive sleepiness.²

Secondary sleep disorders are sleep problems associated with medical, neurological, or substance misuse disorders. Another category of sleep disorders arises from sleep restriction: inadequate sleep results from imposed or self imposed lifestyle and work schedules, such as air travel and shift work.¹

Complementary and alternative medicine has been used increasingly to manage sleep disorders. One of the most popular treatments of this type is melatonin, a hormone that is secreted by the pineal gland and is linked to the circadian rhythm.³

We conducted a systematic review of the efficacy and safety of exogenous melatonin in managing secondary sleep disorders and sleep disorders accompanying sleep restriction, such as jet lag and shiftwork disorder. Our findings can help to guide clinicians and patients in treatment decisions regarding the use of exogenous melatonin in the management of these conditions.

Methods

Search strategy

A health sciences librarian searched 13 electronic databases for relevant studies in English. The reference lists of relevant reviews, as well as a random sample of included studies, were reviewed to identify other potentially relevant studies. We hand searched abstracts of meetings of the Associated Professional Sleep Society from 1999 to 2003. See bmj.com for details. Finally, we re-searched Medline and EMBASE in early 2004 in order to identify recently published studies.

Study selection

To assess the efficacy of exogenous melatonin, we included randomised controlled trials that involved

University of Alberta/Capital Health Evidence-based Practice Centre, Department of Pediatrics, University of Alberta, Edmonton, AB, Canada T6G 2J3

Nina Buscemi
research associate

Ben Vandermeer
statistician

Nicola Hooton
project coordinator

Rena Pandya
project manager

Lisa Tjosvold
research librarian

Lisa Hartling
administrative director

Terry P Klassen
director

Complementary and Alternative Research and Education Program, Department of Pediatrics, University of Alberta

Sunita Vohra
director

Department of Psychiatry, University of Alberta

Glen Baker
professor and chair

Correspondence to: N Buscemi
nina.buscemi@ualberta.ca

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Search terms used are on bmj.com



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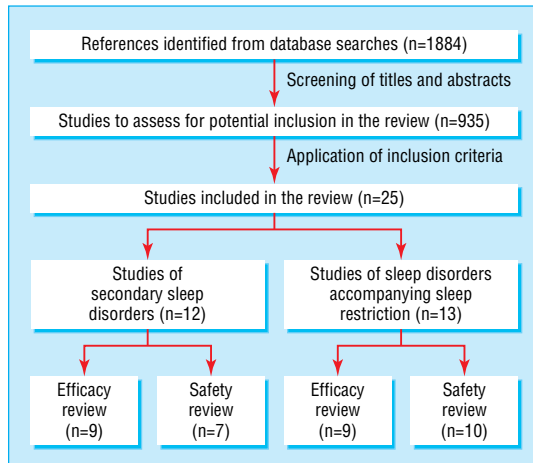


Fig 1 Retrieval and selection of studies of exogenous melatonin in management of secondary sleep disorders and sleep disorders accompanying sleep restriction

human participants who had a secondary sleep disorder or a sleep disorder accompanying sleep restriction; compared melatonin to placebo; and reported on one or more of: sleep onset latency (amount of time between lying down to sleep and onset of sleep), sleep efficiency (amount of time spent asleep as a percentage of total time spent in bed), sleep quality (perceived quality of sleep), wakefulness after sleep onset (amount of time spent awake in bed after first attainment of sleep), total sleep time (total time spent asleep while in bed), or percentage of time in rapid eye movement (REM) sleep. We listed our outcomes in order of importance, with sleep onset latency as primary outcome.

To assess the safety of exogenous melatonin, we included randomised and non-randomised trials meeting the first two criteria above and reporting on adverse events. A study population was considered to have a secondary sleep disorder if the participants, as a group, were defined by a specific chronic medical or psychiatric disorder and this disorder was likely to be the cause of the sleep disorder. (See bmj.com for details and the description of quality assessment and data extraction.)

Data analysis

Continuous outcomes were combined using a weighted mean difference, with the exception of sleep

quality, for which studies were combined by using a standardised mean difference. Dichotomous outcomes were combined by using a risk difference. All meta-analyses used a random effects model. A point estimate with corresponding 95% confidence interval was computed for each outcome, using the generic inverse variance function in RevMan 4.2.5 (Update Software, 2004).

All pooled estimates were assessed for heterogeneity, using the I^2 statistic.⁴ Publication bias graphs and calculations were produced with STATA 7.0 (Stata Corporation, 2001). (See bmj.com for details.)

Results

Figure 1 shows the flow of studies through the selection process.

Secondary sleep disorders

Efficacy

Nine trials (279 participants) were included in the efficacy analysis for secondary sleep disorders. The median quality score was 4 (interquartile range 2-4; maximum 5). Concealment of allocation was unclear in all studies except one,⁵ which had adequate allocation concealment. Only five studies described a funding source and for all of these studies, funding was received from public sponsors.⁶⁻¹⁰

Sleep onset latency

The six trials that compared sleep onset latency in placebo and melatonin groups produced a combined estimate that favoured melatonin but was not significant (weighted mean difference -13.2 (95% confidence interval -27.3 to 0.9) min) (fig 2).

See bmj.com for details and the results of subgroup and sensitivity analyses. Not enough studies examined sleep onset latency for publication bias to be tested on the basis of this outcome.

Other efficacy outcomes

Six trials reporting data for sleep efficiency showed a significant effect that favoured melatonin (weighted mean difference 1.9% (0.5 to 3.3); $I^2 = 0\%$); however, the effect seems not to be clinically important. See bmj.com for other efficacy outcomes.

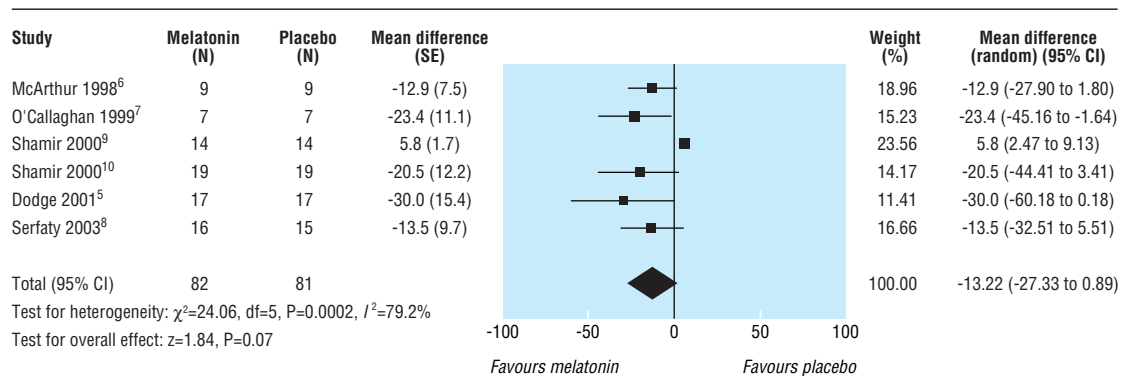


Fig 2 Sleep onset latency in people with secondary sleep disorders

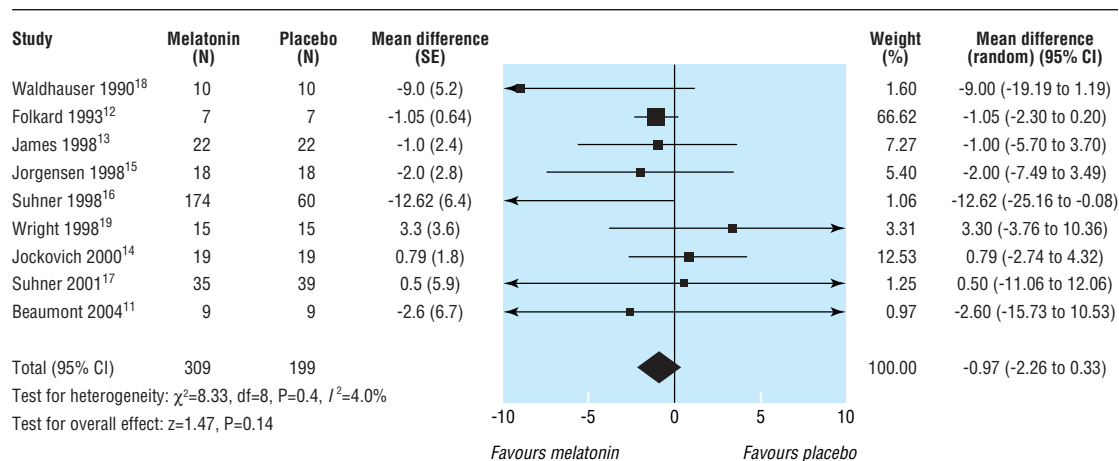


Fig 3 Sleep onset latency in people with sleep disorders accompanying sleep restriction

Safety

Seven studies with 164 participants were included in the safety analysis (see bmj.com). The quality of these studies was good (median quality index 21 (out of 29); range 20-22). The most commonly reported adverse events were headaches, dizziness, nausea, and drowsiness. The occurrence of these outcomes was similar for melatonin and placebo.

Sleep restriction

Efficacy

Nine trials (427 participants) were included in the efficacy analysis for sleep restriction (see bmj.com). The median quality score was 4 (interquartile range 3-4). Concealment of allocation was unclear in all studies except three,^{13 15 19} which had adequate allocation concealment. None of the studies described a funding source.

Sleep onset latency

Nine trials provided data on sleep onset latency. The studies produced a combined estimate that favoured melatonin but was not significant (weighted mean difference -1.0 (-2.3 to 0.3) min; $I^2=4.0\%$) (fig 3). There were no indications of publication bias. (See bmj.com for details and the results of subgroup and sensitivity analyses.)

Other efficacy outcomes

For sleep efficiency, the combined estimate from five trials showed no significant difference between melatonin and placebo (weighted mean difference 0.5% (-0.6 to 1.6); $I^2=20.9\%$). See bmj.com for other efficacy outcomes.

Safety

Of the 10 studies (487 participants) included in the safety analysis, all but one were randomised controlled trials. The methodological quality of these studies was good (median quality index 21 (out of 29); range 20-22). The most commonly reported adverse events were headache, dizziness, nausea, and drowsiness. The occurrence of these outcomes did not differ significantly for melatonin versus placebo.

Discussion

Our review showed that melatonin does not have a significant effect on sleep onset latency in secondary sleep disorders or sleep disorders accompanying sleep restriction or on sleep efficiency in people with sleep disorders accompanying sleep restriction. Although the increase in sleep efficiency in people with secondary sleep disorders was statistically significant with melatonin, the effect was small—1.9%—an increase of less than 10 minutes in the amount of time spent asleep for eight hours spent in bed. We considered this effect to be clinically unimportant.

Factors affecting heterogeneity

The effect of melatonin on sleep onset latency in studies of people with secondary sleep disorders was associated with substantial heterogeneity, which seemed to be highly influenced by the study by Shamir et al.¹⁰ This study was unique in that polysomnography was used to assess sleep outcomes and the method of concealing treatment allocation was reported and adequate. Although the estimation of sleep variables differs according to the assessment tool used to measure them,²⁰ the heterogeneity in results across studies is unlikely to be due to variation in assessment tool, as any differences between methods would have been cancelled out when absolute differences in the effect of treatment and placebo were obtained.

Failure to conceal treatment allocation adequately is associated with larger effect estimates.^{21 22} Allocation concealment may have been inadequate in the studies for which the adequacy of allocation concealment was unclear, which would tend to result in overestimation of treatment effect. Also, the heterogeneity across studies may have been due to publication or reporting bias, such that small studies with negative results were not published and therefore under-represented in the analysis; as this category included only nine studies, we could not verify this bias.

Other factors may have contributed to heterogeneity in results across studies of secondary sleep disorders. Formulations of melatonin vary in quality. In studies that reported the details of the intervention, the rate of release of melatonin varied from slow to fast, a

What is already known on this topic

Sleep disorders are a widespread problem and place a burden on society through their negative impact on quality of life, safety, productivity, and healthcare utilisation

Complementary and alternative therapies, such as melatonin, have been used increasingly to manage sleep disorders

What this study adds

There is no evidence that melatonin is effective in treating secondary sleep disorders or sleep disorders accompanying sleep restriction, such as jet lag or shiftwork disorder

There is evidence that melatonin is safe with short term use, but additional studies are needed to determine its long term safety

range of doses was used, and the duration of administration varied from days to weeks. Indeed, our results show that dosage and duration of melatonin administration explain a considerable amount of heterogeneity across studies.

Two other systematic reviews examining the use of melatonin for jet lag concluded that melatonin is effective in alleviating the symptoms of jet lag.^{23 24} These reviews examined the effect of melatonin on both the daytime fatigue and the sleep disturbance aspects of jet lag. Our review shows that melatonin does not affect either sleep onset latency or sleep efficiency in people with jet lag or people with shiftwork disorder. Our results do not provide evidence that melatonin is effective in alleviating sleep disturbance in jet lag, but we did not determine the effect of melatonin on measures of daytime fatigue.

Other limitations

The observations of this review are based mostly on studies with relatively short durations, so the efficacy and safety of melatonin reported here may reflect only its short term effects. Secondly, several studies did not report adequately on details of the intervention, such as content, quality, and formulation of the melatonin product under study, nor on methods of allocation concealment or source of funding, which casts doubt on the methodological quality of these studies, despite a good median Jadad score or Downs and Black quality index. Thirdly, non-English language reports were excluded from the review; however, we did not find strong evidence of publication bias, so it is unlikely that the inclusion of these reports would have altered our findings substantially.

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Ethical approval: Not required.

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