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Is melatonin useful for jet lag?

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Abstract

Jet lag syndrome is an exogenous circadian rhythm sleep disorder, frequently reported in travelers who cross multiple time zones in a short period of time. Oral melatonin -a pineal neurohormone normally produced during darkness and responsible for regulating the body's circadian rhythms- has been used as treatment for this condition. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified four systematic reviews including 11 randomized trials. We combined the evidence using meta-analysis and generated a summary of findings table following the GRADE approach. We concluded the use of oral melatonin probably reduces symptoms associated with jet lag syndrome. It is not clear whether its use produces adverse effects; however, these would be probably mild.

Problem

Jet lag syndrome is an exogenous circadian rhythm sleep disorder, frequently reported in travelers who cross multiple time zones in a short period of time. It is characterized by symptoms such as sleep disturbances, daytime fatigue, irritability, anxiety, nausea, diarrhea and sweating. This condition is caused by a desyncronization between the traveler´s endogenous circadian rhythm and the day-night cycle at the final destination, which tends to wear off with time. The severity of jet lag syndrome depends on the number of time zones and direction travelled.

The exogenous administration of oral melatonin -a pineal neurohormone normally produced during darkness and responsible for regulating the body´s circadian rhythms- has been used as treatment for jet lag syndrome. This oral supplement is sold as an inexpensive over-the-counter drug, and considered relatively safe to use.

Methods

We used Epistemonikos database, which is maintained by screening more than 30 databases, to identify systematic reviews and their included primary studies. With this information, we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages

- Melatonin probably reduces symptoms related to jet lag syndrome in travelers crossing more than five time zones.
- It is not clear whether the use of melatonin is associated with adverse effects (nausea, tiredness, drowsiness and headaches), because the certainty of the evidence is very low. If these adverse effects were to exist, they would be probably mild in nature.
- The risk-benefit and cost-benefit ratio would probably favour its use in the prevention and treatment of jet lag syndrome.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found four systematic reviews [1],[2],[3],[4] that included 11 randomized controlled trials reported in 16 references [5],[6],[7],[8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[18],[19],[20].
What types of patients were included	All studies involved healthy adults. One study [8] included members of the United States Air Force and a second one [13] involved airline staff. All other studies included different passengers who volunteered to participate. Ten studies assessed the use of melatonin in eastward flights [5],[6],[8],[9],[10],[11],[12],[16],[19],[20], while four did so for westward flights [5],[11],[12],[13].
What types of interventions were included	All studies used melatonin. Ten studies used 5 mg [5],[6],[8],[10],[11],[12],[13],[16],[19],[20]. One administered 10 mg [9]. Three studies assessed slow-release melatonin; one study 300 mg [8], one study used 0.5 mg followed by 2 mg [20] and one study 0.5 mg [16]. Similarly, while two studies administered melatonin before the flight [6],[12], six did so upon arrival [9],[10],[11],[16] ,[19],[20] and three did so both before and after flying [5],[8],[13]. All studies administered melatonin before the desired time of sleep onset at the final destination. In one study both groups received zolpidem in addition to melatonin [19]. All studies compared melatonin against placebo.
What types of outcomes were measured	The systematic reviews included the following outcomes: • General jet lag symptoms for eastward and westward flights. • Number of participants with more than 60% of jet lag symptoms in eastward flights. Additionally, some reviews reported two other outcomes related to exogenous circadian rhythm sleep disorders in general and not only jet lag [2]: • Sleep latency • Sleep quality Only one review conducted a meta-analysis of the following adverse effects [2]: headaches, drowsiness, tiredness, and nausea. These adverse effects were also compared to the use of melatonin studies in non-jet lag cases. All other reviews reported adverse effects without providing a pooled effect measure.

Summary of findings

The information on the use of melatonin is based on 11 randomized studies. Ten studies reported global jet lag symptoms [5],[6],[9],[10],[11],[12],[13],[16],[19],[20]. However, only four studies provided data in a way that could be added to a meta-analysis [5],[6],[9],[11]. Generally, all studies reported side effects, but only three did so systematically [10],[19],[20].

- Melatonin probably reduces the global symptoms associated to jet lag syndrome in travellers crossing more than five time zones. The certainty of the evidence is moderate.
- It is not clear whether the use of oral melatonin is associated to adverse effects (nausea, tiredness, drowsiness and headaches) because the certainty of the evidence is very low. However, no serious adverse effects were reported in any of the participants across the studies.

Melatonin for jet lag syndrome				
Population	Healthy individuals traveling across more than five time zones.			
Intervention	Melatonin			
Comparison	Placebo			
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT melatonin	**WITH melatonin**		
	Difference: patients per 1000			
Global jet lag symptoms (0 to 100 scale)	45 points per 1000	27 points per 1000	MD -17.74 (-23.98 to -11.50)	⊕⊕⊕◯[1] Moderate
	Difference: 18 points less (Margin of error: 12 to 24 points less)			
Adverse effects	Headaches, drowsiness, tiredness, confusion, and nausea. However, it is not clear whether there are significant differences among groups. A study that used zolpidem in addition to melatonin reported a greater number of adverse effects.			

MD: Mean difference.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article).

* The risk **WITHOUT melatonin** is based on the risk in the control group of the trials. The risk **WITH melatonin** (and its margin of error) is calculated from relative effect (and its margin of error).

[1] The certainty of the evidence was lowered one level due to the risk of bias because most studies did not adequately describe methods.

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

- This evidence applies to healthy adults who travel across more than five time zones.

About the outcomes included in this summary

- The outcomes included in this summary are those considered by the authors to be critical in the decision-making process regarding the use of melatonin in the prevention and treatment of jet lag.

Balance between benefits and risks, and certainty of the evidence

- The studies did not report serious adverse effects, or any consistently different effects to those patients using placebo. Considering the fact melatonin is probably a safe intervention the benefits of its use probably outweigh the risks.
- This does not apply to more serious adverse effects observed with the association of melatonin to hypnotics, other central nervous system stimulants, in the presence of other comorbidities, or when using any medication with a possible interaction with melatonin (e.g. anticonvulsants or warfarin).

What would patients and their doctors think about this intervention

- Most patients would be probably inclined in favour of the use of melatonin. In patients with a higher risk of adverse effects it may be necessary to individually assess the treatment decision.
- Some patients will consider jet lag symptoms too mild to treat. It is especially important to discuss the benefits and risks of the intervention in these cases.

Resource considerations

- This is a low-cost, time-limited intervention; in this way, it may be favourable regarding costs and benefits.
- In addition, if melatonin contributes to reducing the symptoms caused by jet lag, it is possible that it may also reduce the use of other symptom-relief medication, thus reducing the total costs.

Differences between this summary and other sources

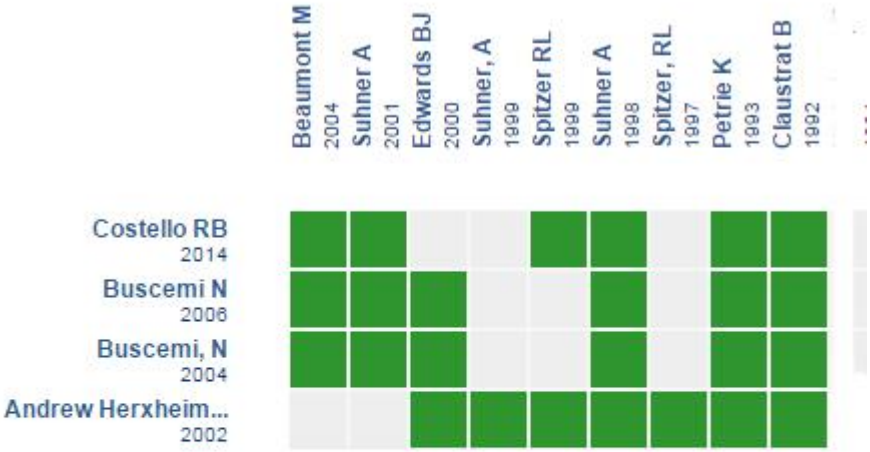
- The conclusions presented in this summary agree with most of the identified systematic reviews.
- Only one of the systematic reviews [4] argues the use of melatonin in secondary sleep disorders (including jet lag) is not effective. This review assessed the latency and quality of sleep, REM sleep time and wakefukness after sleep onset; however, it does not evaluate global jet lag symptoms, and groups jet lag syndrome as part of the secondary sleep disorder spectrum. Additionally, it does not include all of the studies included in this summary.
- The conclusions in this summary are consistent with the recommendations of the American Academy of Sleep Disorder [21], which state the administration of melatonin at the right time is indicated in the prevention and treatment of jet lag symptoms in travellers crossing multiple time zones. It also mentions that no serious adverse effects have been reported yet.

Could this evidence change in the future?

- The probability of future evidence changing the conclusions of this summary is low due to the certainty of the evidence.
- There are three ongoing or unpublished studies [22],[23],[24], which evaluate the use of melatonin in jet lag specifically [23],[24], or in transitory sleep disorders that include jet lag syndrome [22]. All of these studies could provide valuable information.
- It seems relevant to compare the use of melatonin with hypnotics or other interventions other than placebo.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

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Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here http://dx.doi.org/10.5867/medwave.2014.06.5997.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

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