



**Title:** Benefits and Harms of Melatonin and Hypnotics in Preventing Jet Lag in Long-Haul Air Travelers

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**Clinical question:** Are melatonin and/or hypnotics effective preventive interventions for jet lag in long-haul travelers?

**Author recommendations:**

For long-distance air travelers who may benefit from jet lag mitigation, clinicians may prescribe melatonin or a hypnotic at specific times during the flight.

For melatonin, travelers can take 5 mg orally on the flight, between 5 p.m. and 9 p.m., at the same time before going to bed after arrival, and for a few days thereafter. Melatonin side effects are uncommon and generally mild. They may include drowsiness, headache, dizziness, or nausea.

**Evidence and recommendations:**

Quality of Evidence <sup>a</sup>	Strength of Recommendations <sup>b</sup>	Conclusion
Moderate	Weak	Evidence favors melatonin over placebo in travelers rapidly crossing multiple time zones

<sup>a</sup>Quality of evidence scale (GRADE): high, moderate, low, and very low.  
<sup>b</sup>Strength of recommendations scale (GRADE): strong, weak, or no recommendation. For more information on the GRADE rating system, see <http://www.gradeworkinggroup.org/index.htm>.

**PICO:**

<b>Population</b>	Healthy adults >18 years embarking on long-haul air travel Direction and duration of flight Number of time zones crossed
<b>Intervention</b>	Melatonin; hypnotics, e.g., zolpidem, zaleplon, eszopiclone With or without: adjusting sleep schedule, regulating bright light exposure Dose, frequency, duration Time initiated before travel
<b>Comparator</b>	No prophylaxis or placebo Adjusting sleep schedule or regulating bright light exposure only
<b>Primary outcome(s)</b>	Self-reported reduction in jet lag symptoms Columbia jet lag score Safety outcomes: all drug harms

### What are the parameters of our evidence search?

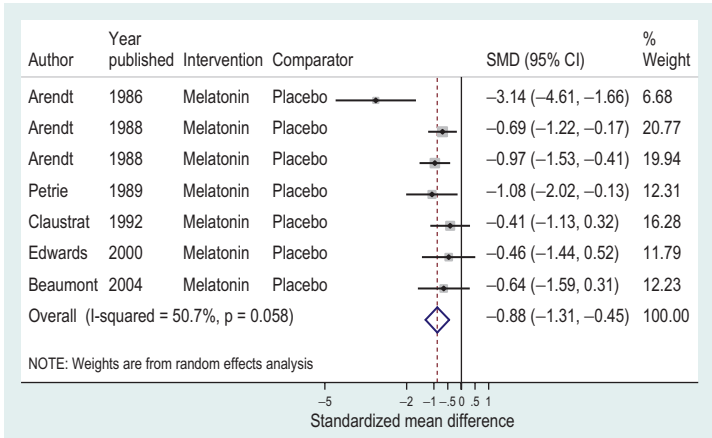
**Patients or population:** Healthy adults >18 years embarking on long-haul air travel

**Intervention:** Melatonin

**Comparison:** Placebo, adjusting sleep schedule, or regulating bright light exposure only; active comparators

**Outcome:** Self-reported reduction in jet lag symptoms over the days after arrival at destination

**Setting:** After long-haul jet travel crossing four time zones or more (eastward or westward)



**Figure 1** Effects of melatonin on jet lag.

TABLE 1 Melatonin vs. Placebo for Management of Jet Lag—Standardized Mean Difference

OUTCOME: SELF-REPORTED SEVERITY OF JET LAG ON A VISUAL ANALOG SCALE (0-100)						
Outcome	ILLUSTRATIVE COMPARATIVE RISKS (95% CI)		Pooled Outcome Standardized Mean Difference (95% CI)	Number of Participants (Studies)	Quality of Evidence (GRADE)	Comment
	Assumed Risk with Placebo	Corresponding Risk with Melatonin				
Reduction in self-reported jet lag symptoms on 0-100 VAS (0 = no symptoms; 100 = severe symptoms)	Mean VAS score in the placebo groups 46.4 (34.7, 58.1)	Mean VAS score in the intervention group 24.8 (14.8, 34.9)	-0.88 (-1.3, -0.5)	245 (6) <sup>1-6</sup>	Moderate	The evidence is of moderate quality primarily because of potential areas of bias. Across study results, there were reasonable precision, directness, and consistency

Notes: The comparative risks are reported as standardized mean differences with 97.5% one-sided confidence intervals. Studies in bold font have statistically significant differences in outcome. Because of rounding, the intervention and comparator numbers may not add up to the actual reported risk difference.  
 CI, Confidence interval; VAS, visual analog scale.

**Guidelines:** Practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders; 2007. Morgenthaler TI, Lee-Chiong T, Alessi C, et. al.<sup>7</sup> (AGREE II Score: unavailable) The strength of the recommendation is as applies to “standards.” The levels of evidence are levels 1 (validating cohort with well-validated reference standards) and 2 (smaller or exploratory cohort study or one that has incompletely validated reference standards).

- The benefits [of melatonin for treatment of jet lag] are well supported and the risks seem low.
- The most effective dose of melatonin for jet lag is unclear, though immediate-release formulations in doses between 0.5 to 5.0 mg may be effective in relieving jet lag symptoms.
- Melatonin preparations are not regulated by the US Food and Drug Administration. However, the medical literature has not produced evidence of significant risk derived from its use.

Medical guidelines for airline travel; 2003.<sup>8</sup> Aerospace Medical Association. (AGREE II Score: unavailable) There are no strength of recommendation or levels of evidence presented.

- The hormone melatonin ... purportedly helps travelers overcome jet lag. While the hypnotic activity of melatonin is generally accepted, its pure chronobiotic properties are still controversial.
- Melatonin is a dietary supplement and under no specific control.
- Travelers should get as much exposure as possible to natural light at the new destination. For example, when traveling from North America to Europe, one could get a short rest (2 hours is good, because it tends to respect the sleep cycle for light vs. deep sleep) and then spend the rest of the day outside, if possible.

**Author commentary:** This synopsis is based on a meta-analysis of six studies using patient-reported assessments of jet lag severity on a visual analog scale.<sup>1-6</sup> One study (Arendt 1988) contributed two comparisons (eastbound and westbound), while the other studies reported results pertinent only to eastbound travel.

The pooled estimate indicates that travelers who take melatonin report statistically significant lower jet lag effects over the days following long-haul jet travel. The component studies of this meta-analysis display a moderate amount of heterogeneity. This variability may be attributable to the small number of studies and/or the overall sample size. Across studies, the results are consistent, and both these and the pooled results are reasonably precise given the generally small sample sizes.

One study compared melatonin (N = 32, mean visual analog scale [VAS] = 30, standard error of the mean [SEM] = 2) with zolpidem (N = 35, mean VAS = 30, SEM = 4) and found no statistically significant differences in jet lag VAS outcomes.<sup>9</sup> This provides indirect evidence supporting the similar effectiveness of the two compounds for relief of jet lag symptoms. For zolpidem, 10 mg may be given for eastbound flights between 5 p.m. and 9 p.m. local time and, after arrival, daily for 4 days at bedtime for the occasional traveler. As zolpidem is a hypnotic drug, it is effective in facilitating in-flight sleep but may cause significant central nervous system adverse effects in more than 10% of those taking the drug.

Because of the unregulated nature of dietary supplements, it is imperative that all melatonin products are manufactured by a reputable source, ingredients are listed along with possible side effects, and manufacturer contact information is available.

In general, available guidelines are consistent with our findings.

**Update alerts:** Important new citations relevant to this topic are added here as they become available.

**Glossary:** AGREE II, Appraisal of Guidelines for Research and Evaluation; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; SEM, standard error of the mean; VAS, visual analog scale.

## REFERENCES

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