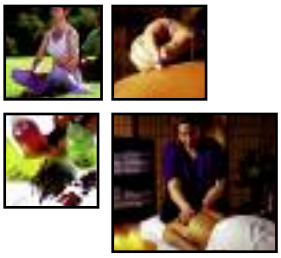

Melatonin for Jet Lag: *Does it Work?*

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For many years melatonin has been used to prevent jet lag. Is there any scientific proof that it works?

Endogenous melatonin is synthesized from tryptophan in the pineal gland. The formation and release of melatonin is stimulated by darkness and inhibited by light. The production of melatonin is regulated by postsynaptic receptors originating in the superior cervical ganglion, which innervate the pineal gland. The suprachiasmatic nucleus of the hypothalamus, considered to be the anatomic site for the biologic clock, receives stimuli from the retina and, during dark hours, forwards a stimulus to the superior cervical ganglion and pineal gland, resulting in melatonin secretion. With the onset of darkness, activation of the sympathetic system and norepinephrine release is followed by the stimulation of postsynaptic pineal adrenoreceptors and the enhancement of melatonin synthesis.

Does it work? A Cochrane review[1]

Arendt, et al[2]

Eight participants flying from San Francisco eastwards to London took 5 mg of melatonin q.d. for three days before their flight and nine participants took placebo at 18:00 local time and then at bedtime (22:00 to 24:00) for the first four days after their return to Britain.

Jet lag was significantly less severe among subjects who had taken melatonin, as rated by a visual analogue scale (VAS), on the seventh day after the flight.

Arendt, et al[3]

Six to seven days following a flight from the United Kingdom to Australia and to New Zealand and then back, 52 participants self-rated their jet lag using a VAS.

Mean jet lag ratings for both eastward and westward flights were better after supplementation with melatonin than with placebo.

Petrie, et al[4]

Twenty participants flew eastward from Auckland to London on a 26 hour flight. They returned on a similar westward flight three weeks later. Participants were randomized to receive either melatonin or placebo on the outward flight and the other substance on the return flight. Each took 5 mg of melatonin or placebo between 10:00 and 12:00 local time for three days before each flight and on the day of the flight and then between 22:00 and 24:00, destination time, for three days after arrival.

VAS ratings for jet lag and tiredness were significantly less for the participants taking melatonin. This group took significantly fewer days to establish a normal sleep pattern, to reduce daytime fatigue and to reach normal energy levels. They also had more vigour-activity and less tiredness based on their profile of mood states ratings.

Nickelsen, et al[5]

Thirty-six participants flew westward from Frankfurt to North America and two weeks later in the reverse direction. Three subgroups of 12 were created, according to the time shift of:

- Six to seven hours
- Eight to nine hours
- 10 to 11 hours

After the westbound flight, participants took either 5 mg of melatonin or placebo at bedtime for seven days. After the eastbound flight, they took the same dose for five days.

Overall, subjective jet lag ratings were better in all three melatonin subgroups after both the west- and eastbound flights, but the differences compared to placebo were not statistically significant.

Claustrat, et al[6]

On the day of flight and at bedtime for the following three days, 30 participants received 8 mg of melatonin or

placebo. A significant difference was observed only for evening sleepiness and morning tiredness scores.

Petrie, et al[7]

Three treatment groups of 52 airline staff, who had returned to New Zealand from London via Los Angeles, were created:

1. Melatonin, 5 mg, taken at a time corresponding to evening/night at the place of destination from three days before arrival until five days after arrival
2. Placebo for three days before flight then 5 mg of melatonin q.d. for five days
3. Placebo

A retrospective VAS ratings on the sixth day showed that participants in the first group had significantly lower scores of jet lag compared to both the second and placebo groups. The late melatonin group had significantly less sleep disturbance than did the placebo group and recovered their energy and alertness faster than the early melatonin group, which reported a worse overall recovery than did the placebo group.

Five participants in the early melatonin group reported minor side-effects of sleep difficulties, drowsiness, headaches and feeling depressed. Melatonin, taken after arrival, resulted in reduced feelings of jet lag and a more rapid recovery of sleep and energy levels.

Suhner, et al[8]

Two-hundred and thirty-four subjects flying eastwards from the US to Europe and from Europe to Asia were divided into three groups:

1. Melatonin, 0.5 mg fast-release (FR) formulation
2. Melatonin, 5 mg FR and 2 mg controlled-release (CR) formulation
3. Placebo

All medications were taken daily at bedtime for four days after the flight.

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The group taking 5 mg of FR melatonin reported shortened sleep latency, reduced fatigue, reduced daytime sleepiness and a significant improvement in their self-rated sleep quality.

A physiological dose of 0.5 mg was almost as effective as a pharmacological dose of 5 mg. Only sleep quality and sleep latency were significantly greater with the 5 mg dose.

Suhner, et al[9]

Four groups of 137 participants flying eastwards from America to Switzerland were created:

1. Melatonin (5 mg)
2. Zolpidem (10 mg)
3. Combination melatonin (5 mg) and zolpidem (10 mg)
4. Placebo

The medication was taken between 17:00 and 21:00 local time on the day of flight and then for four days post-flight at bedtime.

The zolpidem group reported significantly better sleep quality, less jet lag and rated zolpidem as the most effective jet lag medication.

The combination of melatonin and zolpidem were not as well tolerated as melatonin alone. Confusion, nausea and morning sleepiness were reported to be highest in the combination group.

Spitzer, et al[10]

Two-hundred and fifty-seven Norwegian physicians visited New York for five days and then travelled back to Oslo, Norway in an eastward direction. On the returning flight, they were randomized to receive either:

- melatonin, 5 mg h.s.,
- melatonin, 0.5 mg h.s.,
- melatonin, 0.5 mg, taken on a shifting schedule, or
- placebo.

Medications were administered on the day of travel and continued daily for five days post-flight. No significant difference in jet lag score was found between the treatment groups. The limitations were that participants had come from Norway to New York and stayed there for only five days before returning to Norway. The baseline used was not asymptomatic.

Table 1

Rare side-effects of melatonin use

- Disorientating "rocking" feeling
- Reduced glucose tolerance and insulin sensitivity
- Autoimmune hepatitis
- Tachycardia
- Mild GI upset
- Neurological effects (including seizures)
- Lowered BP
- Allergic reactions/anaphylaxis
- Palpitations
- Chest pains
- Increased triglyceride and VLDL-C levels
- Depression

Edwards, et al[11]

Thirty-one sports officials or sports scientists flew from London to Eastern Australia and took either 5 mg of melatonin, or placebo on the plane at the time corresponding to 18:00 to 19:00 in Eastern Australia, then at 22:00 to 23:00 on the evening of arrival in Eastern Australia and for three more evenings post-flight.

Subjective jet lag VAS and responses to a jet lag questionnaire were measured four times daily for six days post-flight. No significant differences in jet lag ratings, sleep disturbances or morning alertness were found between the two groups over the six days. The authors conclude that melatonin had no benefit in alleviating jet lag in individuals who followed a busy schedule after arrival (as a result of which light exposure was erratic) or in those who consumed alcohol in the evenings after arrival.

Caffeine vs. melatonin

In a study by Beaumont, *et al*[12] 27 participants who flew from Texas to France were given either:

- 300 mg of slow release caffeine (SRC) over a five day period after their flight at 08:00, or
- 5 mg of melatonin or placebo to be taken once on the day before their flight at 17:00, on the day of their flight at 16:00 and then for three days after their flight at 23:00.

The participants were prohibited from sleeping during the flight so that they remained awake for 33 hours from last awakening in Texas to first sleep in France.

Participants woke up earlier, slept for less time and complained of more awakenings than did the melatonin group. The melatonin group fell asleep earlier and slept longer than did the placebo group. No significant difference was found among the three groups for subjective daytime sleepiness, except on day one where the SRC group was sleepier than the melatonin group, but was less sleepy on subsequent days compared to baseline. The melatonin group felt sleepier on day one, but not on day two and three as compared to baseline.

Rare side-effects

Table 1 lists the more uncommon side-effects of melatonin use.

Melatonin levels may rise with the use of CYP1A2 inhibitors, caffeine, fluvoxamine and fluoxetine. Levels may decrease with the use of CYP1A2 inducers, cigarettes and nifedipine. Melatonin may potentiate the effects of sedatives.

Caution is advised with driving, operating heavy machinery, pregnancy and lactation and when combined with warfarin use.

Dosage

Melatonin (0.5 mg to 5 mg) should be started on the day of travel as close as possible to the target bedtime at the place of destination and then taken every 24 hours at bedtime for several days after arrival. Dx

References

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For additional references, please contact **diagnosis@sta.ca.**