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## The use of melatonin in the treatment of jet lag – clinical review

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### Summary:

Jet lag is a circadian rhythm disorder, that occurs as a result of air travel across multiple time zones. Jet lag symptoms include: anxiety, constipation, diarrhea, confusion, dehydration, headache, irritability, nausea, indigestion, difficulty concentrating, sweating, coordination problems, dizziness, daytime sleepiness, malaise, and memory loss.

Melatonin, is a hormone that regulates the circadian rhythm by acting on MT1 and MT2 melatonin receptors. It is produced by pinealocytes in the pineal gland and released directly into the blood. Main therapeutic application of this medication is re-entraining disturbed circadian rhythms.

All the mentioned studies proved that melatonin is effective in the treatment of jet lag. None of the mentioned above trials didn't report any serious side effects caused by this medication therefore occasional short-term use of melatonin seems to be safe. Most people should start treatment of jet lag with taking 2-3 mg melatonin, and if necessary increase the dose to 5 mg. Melatonin is the most effective in alleviating symptoms of jet lag when it is given at bedtime on the day of the flight and in the next few days after arrival. Further research is needed to find out the optimal dosage of melatonin for treatment of jet lag, timing of its administration, time of initiation and duration of the treatment or possible side effects of this medication.

**Key words:** melatonin, jet lag, circadian rhythm

## **INTRODUCTION AND PURPOSE**

Jet lag is a circadian rhythm disorder, that occurs as a result of a rapid long-distance trans-meridian air travel across multiple time zones. The cause is the inability of the body of a traveler to immediate adjustment to new time zone, because of the significant time difference between origin and destination. Jet lag symptoms include: anxiety, constipation, diarrhea, confusion, dehydration, headache, irritability, nausea, indigestion, difficulty concentrating, sweating, coordination problems, dizziness, daytime sleepiness, malaise, and memory loss. Severity of symptoms depends on the number of time zones crossed and the direction of travel. The more time zones are crossed, the symptoms are more severe. Jet lag also tends to be more severe when traveling eastward compared with westward, due to less time to adjust to the change of time zone [1].

The aim of this study was to evaluate the efficacy of melatonin in the treatment of jet lag. Our study material consisted of publications, which were found in PubMed, ResearchGate and Google Scholar databases. In order to find the proper publications, the search has been conducted with the use of a combination of key words like: "melatonin", "jet lag", " circadian rhythm". The first step was to find proper publications from the last 40 years .The second step was to carry out an overview of the found publications.

## **DESCRIPTION OF THE STATE OF KNOWLEDGE**

Melatonin, N-acetyl-5-methoxytryptamine, is a hormone that regulates the circadian rhythm by acting on MT1 and MT2 melatonin receptors. It is produced by pinealocytes in the pineal gland and released directly into the blood. The synthesis of melatonin consists of four steps: tryptophan hydroxylase converts tryptophan to 5-hydroxytryptophan, that is converted in the next step to serotonin by aromatic amino acid decarboxylase. Then serotonin is converted to N-acetylserotonin by arylalkylamine N-acetyltransferase, that is converted in the last step to melatonin by hydroxyindole-O-methyltransferase. This process is timed by the suprachiasmatic nucleus, that is synchronized to the light-dark cycle via the retinohypothalamic tract. Darkness stimulate melatonin synthesis and its release into the blood. Thus, melatonin concentration increases at night. On the other hand light inhibit melatonin synthesis and its release into the blood. Thus, melatonin concentration falls during daylight. Main therapeutic application of this medication is re-entraining disturbed circadian rhythms. The most common side effects of melatonin are mild and include: drowsiness, dizziness, weakness, confusion, nausea and headache. This medication is contraindicated in pregnant or breast-feeding women and in those with liver problems. There are many studies that proved the role of melatonin in the treatment of jet lag [2].

Petrie et al. (1989) in their study investigated the effectiveness of the melatonin in the treatment of jet lag. 20 participants of their trial, that flew eastward and then westward, received 5 mg melatonin or placebo at bedtime 3 days before flight, on the day of the flight, and for 3 days after the flight. Symptoms of jet lag were assessed with the Profile of Mood States (POMS) and Visual Analogue Scale (VAS). Volunteers receiving melatonin reported less fatigue and inertia in comparison to those receiving placebo. They also took fewer days to establish a normal sleep pattern, reached normal energy levels and didn't feel tired during the day. Because of that this study proved that melatonin can alleviate jet lag and tiredness after long haul flights [3].

Petrie et al. (1993) in their study examined the efficacy of melatonin in the treatment of jet lag in 52 cabin crew members that flew westwards. The participants were randomly assigned to 3 groups; early melatonin (those who receive 5 mg melatonin at bedtime 3 days before flight, on the day of the flight and for 5 days after flight); late melatonin (those who receive placebo at bedtime for 2 days before flight, on the day of the flight, then 5 mg melatonin at bedtime for 5 days after flight); and placebo. Symptoms of jet lag were assessed with the Stanford Sleepiness Scale (SSS), Profile of Mood States (POMS) and Visual Analogue Scale (VAS). The late melatonin group reported both less sleep disturbance and significantly faster recovery of energy and alertness in comparison to early melatonin and placebo groups. Results of this study showed that melatonin may be used in alleviating symptoms of jet lag in cabin crew members [4].

Arendt et al. (1987) in their trial checked the role of melatonin in the treatment of jet lag. 17 participants of their trial, that flew eastwards, received 5 mg melatonin or placebo at bedtime 2 days before flight, on the day of the flight, and for 4 days after the flight. Symptoms of jet lag were assessed with the Visual Analogue Scale (VAS). The results of this study showed that the symptoms of jet lag were significantly less severe in those who received melatonin than in those who received placebo [5].

Arendt et al. (1988) in their double-blind cross-over study investigated the effectiveness of melatonin in the alleviation of symptoms of jet lag. 61 participants of their trial, that flew eastwards and then westwards, received 5 mg melatonin or placebo at bedtime 2 days before eastward flight, on the day of this flight, and for 4 days after arrival. Volunteers also received 5 mg melatonin or placebo for 4 days after westward flight. Symptoms of this disorder were assessed with the Visual Analogue Scale (VAS). Outcome of this trial revealed important role of melatonin in the treatment of jet lag [6].

Suhner et al. (1998a) in their double-blind, randomized, placebo-controlled study tried to determine the optimal dosage of melatonin for the treatment of jet lag. 320 participants of their study, that flew eastward over 6 to 8 time zones, received once a day at bedtime for 4 days after the flight different doses of melatonin: 0.5 mg immediate-release, 5 mg immediate-release, 2 mg controlled-release, or placebo. Symptoms of jet lag were assessed before the flight and during the melatonin intake with the Profile of Mood States (POMS), sleep diary, symptoms questionnaire and the Karolinska Sleepiness Scale (KSS). The results of this study proved that melatonin improved the self-rated sleep quality, shortened sleep latency, and reduced fatigue and daytime sleepiness of the participants after flight. A dose of 0.5 mg melatonin was almost as effective as the dose of 5.0 mg in the reduction of symptoms of jet lag, except sleep quality and sleep latency [7].

Suhner et al. (1998b) in their study checked the role of melatonin and zolpidem in the treatment of jet lag. 160 participants of their trial, that flew eastwards, received: 5 mg melatonin, 10 mg zolpidem, both medications, or placebo at bedtime on the day of the flight and then for 4 days after the flight. Symptoms of jet lag were assessed with the Profile of Mood States (POMS) and Visual Analogue Scale (VAS). Analysis of the results of this study showed that melatonin may be used for treatment of jet lag [8].

Claustrat et al. in their study also proved that melatonin may be used in the treatment of jet lag. 30 participants of their trial, that flew eastward, received 8 mg melatonin or placebo at bedtime on the day of the flight, and then for 3 days after the flight. Symptoms of this

disorder were assessed with the Visual Analogue Scale (VAS). Those volunteers that received melatonin reported less sleepiness, less tiredness, better mood and greater efficiency at work in comparison to those receiving placebo [9].

All the above mentioned studies proved that melatonin is effective in the treatment of jet lag. None of the mentioned above trials men didn't report any serious side effects caused by this medication therefore occasional short-term use of melatonin seems to be safe. However it is difficult to distinguish side effects from symptoms, therefore they could be inadequately assessed [1]. The trial of Suhner (1998a) showed that there is no significant difference in effectiveness between doses of 0,5 mg and 5 mg of melatonin, except faster falling asleep and better sleep quality after 5 mg. The study of Claustrat et al. didn't clearly proved that higher doses of melatonin such as 8 mg, are more effective in alleviating symptoms of jet lag in comparison to pharmacological dose of this medication – 5 mg [7]. Suhner et al. (1998a) study suggested that immediate-release formulation of melatonin is far more effective than its controlled-release formulation, because of faster action due to giving a higher concentration in the blood [7]. Most people should start treatment of jet lag with taking 2-3 mg melatonin, and if necessary increase the dose to 5 mg [1]. The effectiveness of melatonin was similar on westward and eastward flights. However the use of melatonin on eastward flights brings greater benefits due to more severe course of jet lag [1]. Melatonin differs from many medications in that the timing of administration is critical and determines the effect. The symptoms of jet lag could worsen when melatonin is given at the wrong time. The study of Petrie et al. (1993) demonstrated that melatonin is the most effective in alleviating symptoms of jet lag when it is given at bedtime on the day of the flight and in the next few days after arrival. Taking melatonin before the flight is not recommended because it does not hasten adjustment to time difference between origin and destination [4]. However further research is needed to find out the optimal dosage of melatonin for treatment of jet lag, timing of its administration, time of initiation and duration of the treatment or possible side effects of this medication [1].

## CONCLUSIONS

1. Melatonin may be used for the treatment of jet leg, due to its effectiveness proved by many studies. Occasional short-term use of melatonin seems to be safe.
2. Most people should start treatment of jet lag with taking 2-3 mg melatonin, and if necessary increase the dose to 5 mg.
3. Melatonin is the most effective in alleviating symptoms of jet lag when it is given at bedtime on the day of the flight and in the next few days after arrival.
4. The effectiveness of melatonin is similar on westward and eastward flights. However the use of melatonin on eastward flights brings greater benefits due to more severe course of jet lag.
5. Further research is needed to find out the optimal dosage of melatonin for treatment of jet lag, timing of its administration, time of initiation and duration of the treatment or possible side effects of this medication.

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