

MELATONIN FOR THE PREVENTION AND TREATMENT OF JET LAG

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Date of most recent amendment: 27 August 2002

Date of most recent substantive amendment: 13 December 2001

This review should be cited as: Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2003. Oxford: Update Software.

ABSTRACT

Background

: Jet-lag commonly affects air travellers who cross several time zones. It results from the body's internal rhythms being out of step with the day-night cycle at the destination. Melatonin is a pineal hormone that plays a central part in regulating bodily rhythms and has been used as a drug to re-align them with the outside world.

Objectives

: To assess the effectiveness of oral melatonin taken in different dosage regimens for alleviating jet-lag after air travel across several time zones.

Search Strategy

: We searched the Cochrane Controlled Trials Register, MEDLINE, EMBASE, PsychLit and Science Citation Index electronically, and the journals 'Aviation, Space and Environmental Medicine' and 'Sleep' by hand. We searched citation lists of relevant studies for other relevant trials. We asked principal authors of relevant studies to tell us about unpublished trials. Reports of adverse events linked to melatonin use outside randomised trials were searched for systematically in 'Side Effects of Drugs' (SED) and SED Annuals, 'Reactions Weekly', MEDLINE, and the adverse drug reactions databases of the WHO Uppsala Monitoring Centre (UMC) and the US Food & Drug Administration.

Selection Criteria

: Randomised trials in airline passengers, airline staff or military personnel given oral melatonin, compared with placebo or other medication. Outcome measures should consist of subjective rating of jet-lag or related components, such as subjective wellbeing, daytime tiredness, onset and quality of sleep, psychological functioning, duration of return to normal, or indicators of circadian rhythms.

Data collection and analysis

: Ten trials met the inclusion criteria. All compared melatonin with placebo; one in addition compared it with a hypnotic, zolpidem. Nine of the trials were of adequate quality to contribute to the assessment, one had a design fault and could not be used in the assessment. Reports of adverse events outside trials were found through MEDLINE, 'Reactions Weekly', and in the WHO UMC database.

Main Results

: Nine of the ten trials found that melatonin, taken close to the target bedtime at the destination (10pm to midnight), decreased jet-lag from flights crossing five or more time zones. Daily doses of melatonin between 0.5 and 5mg are similarly effective, except that people fall asleep faster and sleep better after 5mg than 0.5mg. Doses above 5mg appear to be no more effective. The relative ineffectiveness of 2mg slow-release melatonin suggests that a short-lived higher peak concentration of melatonin works better. Based on the review, the number needed to treat (NNT) is 2. The benefit is likely to be greater the more time zones are crossed, and less for westward flights.

The timing of the melatonin dose is important: if it is taken at the wrong time, early in the day, it is liable to cause sleepiness and delay adaptation to local time.

The incidence of other side effects is low. Case reports suggest that people with epilepsy, and patients taking warfarin may come to harm from melatonin.

Reviewers' conclusions

: Melatonin is remarkably effective in preventing or reducing jet-lag, and occasional short-term use

appears to be safe. It should be recommended to adult travellers flying across five or more time zones, particularly in an easterly direction, and especially if they have experienced jet-lag on previous journeys. Travellers crossing 2-4 time zones can also use it if need be.

The pharmacology and toxicology of melatonin needs systematic study, and routine pharmaceutical quality control of melatonin products must be established. The effects of melatonin in people with epilepsy, and a possible interaction with warfarin, need investigation.

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Herxheimer A, Petrie KJ Melatonin for the prevention and treatment of jet lag (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2003. Oxford: Update Software.

BACKGROUND

Jet-lag is a common complaint of travellers who fly across a number of time zones (Winget 84). The symptoms of jet-lag are primarily daytime fatigue and sleep disturbance, but also include loss of mental efficiency, weakness and irritability (Comperatore 90). Jet-lag is caused by desynchronisation between the body's circadian system and the new day-night cycle at the traveller's destination. The sleep loss caused by the travel itself often contributes to jet-lag. After a flight through six or more time zones most travellers will take 4-6 days to re-establish a normal sleeping pattern and not to feel tired during the day. The severity of jet-lag symptoms largely depends on the number of time zones crossed and the direction of travel. They are worse the greater the number of zones crossed. Westbound travel generally causes less disruption, as it is easier to lengthen than to shorten the natural circadian cycle.

Melatonin is a hormone released by the pineal gland during darkness. Exposure to bright light cuts off melatonin release; the onset of dim light triggers resumption of release. It seems to play a key role in regulating the body's circadian rhythms and has been used therapeutically to re-entrain disturbed circadian rhythms. Exogenous melatonin tends to produce a phase advance when it is taken in the late afternoon (Lewy 92, 95), since its effect is additive with that of endogenous melatonin. However, taken in the early morning, exogenous melatonin causes a phase delay by antagonising the effect of bright light.

OBJECTIVES

This review aims to evaluate whether melatonin taken by mouth can prevent or alleviate jet-lag associated with air travel across several time zones. The review also examines the evidence for the effectiveness of different dosage regimens.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised trials

Types of participants

Airline passengers, airline staff or military personnel.

Types of intervention

Oral melatonin, compared with placebo or other medication, taken before during and/or after travel.

Types of outcome measures

The primary outcome measure is subjective rating of jet-lag, and components or correlates of this, such as fatigue, daytime tiredness, onset of sleep at destination, onset and quality of sleep, psychological functioning, duration of return to normal, and measures indicating the phase of circadian rhythms.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: [Cochrane Depression, Anxiety and Neurosis Group](#) search strategy

We searched the Cochrane Controlled Trials Register, MEDLINE, EMBASE and PsychLit electronically, using the terms melatonin, jet-lag, jet lag, aviation, air travel, airtravel. The Science Citation Index was searched to identify trials that had cited the studies. The journals 'Aviation, Space and Environmental Medicine' and 'Sleep' from 1986 -1999 were searched by hand, including the conference abstracts published there. We searched citation lists of relevant studies for other relevant trials. We asked principal authors of relevant studies to tell us about unpublished trials.

We also searched for reports of suspected adverse effects of melatonin that were not reported in the studies retrieved in the above searches.

We checked Martindale 99, Meyler's Side Effects of Drugs (SED 96), and Side Effects of Drugs Annuals (SEDA) up to vol 22 (1999); searched 'Reactions Weekly' from 1990 to 1999, using the annual indexes to find all items mentioning melatonin;

obtained the reports mentioning melatonin from the WHO Uppsala Monitoring Centre and the US Food and Drug Administration's Special Nutritionals Adverse Events Monitoring System (SN/AEMS) (<http://vm.cfsan.fda.gov/cgi-in/aems.cgi?QUERY=melatonin>);

and searched MEDLINE using the MESH term 'Melatonin-adverse effects'.

We did not search EMBASE because that is used in the production of SED and SEDA.

METHODS OF THE REVIEW

All relevant RCTs were considered and the full reports obtained, as was subsequent published correspondence about them. Several authors were contacted and asked for supplementary information.

The trials that met the inclusion criteria are referred to in this review by the year of publication followed by the first author's name, eg '87 Arendt', except when they are mentioned informally in the text. This has been done so that they can be listed in chronological order in the Table of characteristics of included studies, to make it easier for readers to see how the design of the studies has developed over the years. The other references are cited and listed in the conventional style.

*Quality assessment: allocation concealment and blinding was looked for, described and evaluated
Methods of measurement used in the trials are described and their relevance, validity and reproducibility discussed

*Data were extracted independently by each author; differences were reconciled

*Data synthesis: the following comparisons are made -

- (1) melatonin v. placebo;
- (2) treatment with melatonin only after arrival at destination ('post' regimen) v. treatment before, during and after travel ('pre+post' regimen);
- (3) eastward flights v. westward flights (with placebo and with melatonin);
- (4) passengers v. airline staff v. military personnel;
- (5a) low doses (5mg or less) v. high (8mg or more);
- (5b) low doses v. very low doses (0.5mg);
- (5c) rapid-release melatonin v. slow-release melatonin;
- (6) short (48 hr or less) v. long (over 48 hr) treatment.

A meta-analysis was performed of visual analogue scores of jet-lag symptoms from 5 trials that were sufficiently similar in design.

Adverse events noted in the course of the trials are summarised and assessed.

Reports of adverse events linked with melatonin in other contexts, i.e. outside RCTs, were screened. Those that were considered potentially relevant to the use of melatonin for jet-lag are summarised and evaluated. To be considered potentially relevant, reports had to be related to use of melatonin for 14 days or less, or use for jet-lag, and to include enough contextual information about the event to raise reasonable suspicion that melatonin might have contributed to it.

DESCRIPTION OF STUDIES

Nine trials, published between 1986 and 1999, met the inclusion criteria. All compared melatonin with placebo, and one (98 Suhner b) in addition included a comparison with zolpidem, a hypnotic. One study, in US soldiers on an overseas rapid deployment mission, was excluded because it tested their adaptation to night operations at the destination in the Middle East, and not adaptation to the new time zone (Comperatore 96).

One trial (93 Petrie) directly compared a 'pre+post' with an 'post' regimen, in airline cabin staff who had travelled through several time zones in the preceding 9 days. Of the other 8 trials, four examined a 'pre+post', and four a 'post' regimen. All were performed in civilian travellers.

In all nine trials the clock time at which melatonin was taken after arrival at the destination remained the same each day: the time of administration was not changed 1-3 hours per day, to take account of the way in which the body clock is expected to adjust (Lewy 95).

Two trials (87 Arendt, 91 Nickelsen) included assays of cortisol and of melatonin to measure circadian phase.

The four trials of the 'post' regimen, all in travellers, differed in size (92 Nickelsen n=36; 97 Spitzer, n=257; 98 Suhner a, n=234; 98 Suhner b, n=137) and in design.

The Nickelsen study focused more on endogenous cortisol and melatonin rhythmicity than on symptoms of jet-lag. Suhner's first trial (98a) compared two doses of fast-release melatonin with an intermediate dose of slow-release melatonin and placebo after an eastward flight from Switzerland to Asia, or America to Switzerland. The volunteers completed sleep logs, a symptoms questionnaire and the Profile of Mood States (POMS) daily for 3 days before and 4 days after the flight; subjective sleepiness was assessed three times a day. In Suhner's second trial (98b) melatonin was of subsidiary interest: the prime focus was on zolpidem with which melatonin was compared, and the results for melatonin and placebo are not reported in detail. The Spitzer trial compared three different regimens of melatonin with placebo in Norwegians (mainly physicians) who were returning to Oslo after having visited New York for 5 days.

METHODOLOGICAL QUALITY

The design and performance of all ten trials seem to have satisfactorily minimised selection bias, performance bias, attrition bias and detection bias (Cochrane Handbook 99). All except that of Claustrat are described as double-blind, but none of the reports includes a statement on allocation concealment, on how closely alike in appearance, etc, the test treatments were, or whether participants could ever examine or see different treatments side by side.

None of the reports state what the participants were told about the trial they were entering, and what effects they would have been led to expect. The prior expectations of the participants could well have influenced the effects and symptoms that they experienced and reported.

None of the trial reports give details of the source of the melatonin used and most do not state the pharmaceutical form used.

Nickelsen's trial was underpowered because it was not possible to use a cross-over design. The authors also note that they could not control how closely their volunteers followed the protocol in respect of regular bedtimes, abstention from alcohol, etc.

In Spitzer's trial the participants had come from Norway to New York and after 5 days would not have fully adjusted to New York time before they flew back. They would therefore have been expected to suffer less jet-lag than thoroughly adapted transatlantic travellers, so that a reduction of jet-lag by melatonin would have been more difficult to detect in this trial. For this reason the results of this trial are not considered in comparisons (4) and (5).

The reporting of adverse events in the trials is mostly rudimentary and inadequate. In some the participants were asked specifically, in most only spontaneously mentioned events are noted. The number of reported adverse events is often not explicitly related to the number of individuals who experienced them.

Other reports of adverse events span a huge range in quality, from the detailed and unambiguous to many that are fragmentary and uninterpretable, with most at the latter end of the range.

RESULTS

Comparison (1): melatonin v. placebo [Table 01](#)

In nine of the ten trials melatonin reduced the symptoms of jet-lag. In one trial (Spitzer) no effects were found, but this can be attributed to a faulty design (see above). For 5 trials in travellers (87 & 88 Arendt, 89 Petrie, 91 Nickelsen, 92 Claustrat), totalling 237 flights, a global visual analogue jet-lag score is reported. We have converted these scores to a single scale from 0 to 100. Table 1 shows the results: the weighted mean score after melatonin was 25, after placebo 48, (excluding the 18 westward flights in Nickelsen's trial). The meta-analysis, which allows for the differing variances in the trials, shows a bigger difference in score of 37.3 (95% CI 39.8 - 34.9). This is highly significant, both statistically and practically. In the only two trials that reported results for individuals (and not merely group means), 16 out of 24 people (67%) given placebo experienced jet-lag after an eastward transatlantic flight (87 Arendt, 92 Claustrat), while only 4 out of 22 (18%) did so after 5mg melatonin. On this basis, one of every two people taking melatonin would benefit. The group means reported in the other trials are consistent with such an estimate.

Various components or aspects of the jet-lag syndrome were assessed in the trials, but the results cannot be combined because the methods of measurement and reporting differed.

SLEEPINESS was rated and reported on in three trials: Claustrat found significantly less morning tiredness and less evening sleepiness for up to 6 days with melatonin than with placebo; 98 Suhner (a) found melatonin takers less tired from the second day on; in 93 Petrie cabin crew taking late melatonin were less sleepy than those on placebo or 'early+late' melatonin.

SLEEP LATENCY was reported by 87 Arendt as significantly shorter with melatonin than with placebo for 6 days after the flight, and SLEEP QUALITY likewise; Suhner (a) found the differences in latency and quality greatest on day 2; the Claustrat trial found no clear difference in latency, but used a coarse and insensitive scale.

The Profile of Mood States used by 89 Petrie showed that in comparison with the placebo group, melatonin increased 'vigour/ activity' and lessened fatigue. 98 Suhner (a) noted that fatigue scores were similar for 5mg and 0.5mg melatonin, both less than for placebo. 89 Petrie reports three useful subjective estimates of RECOVERY: how many days it took a) for the sleep pattern to return to normal, b) for energy likewise, c) for daytime tiredness to disappear. All three became normal sooner with melatonin.

SYMPTOMS are reported in several trials, but there is no certain way of deciding whether a symptom is due to jet-lag, to melatonin or to something else. When a symptom occurs more often after melatonin than after placebo, causation in an individual case remains in doubt.

Comparison (2): 'post' regimen v. 'pre+post' regimen

The 93 Petrie trial in airline cabin crew was the only one that directly compared a 'pre+post' with a 'post' regimen, as well as with placebo. In the 'pre+post' group overall recovery after the flight was worse than in the placebo group, whereas the 'post' melatonin group had less jet-lag and sleep disturbance than the placebo group. In this trial however the circadian rhythms in the participants were so disordered that the timing of the pre-flight doses must have been very variable in their circadian phase.

All three trials of the 'pre+post' regimen in civilian travellers found less jet-lag and better sleep quality in the melatonin group. In the trial in soldiers, melatonin helped circadian adaptation and maintained sleep durations of 7-8 hours at the destination, while on placebo sleep was 5-7 hours. In cognitive tests done soon after waking, the melatonin group made about half as many errors as the placebo group. Symptoms of jet-lag were not directly assessed.

Of the four trials of the 'post' regimen, 98 Suhner (a) found that melatonin very clearly improved self-rated sleep quality, shortened sleep latency and reduced fatigue and daytime sleepiness. Two other trials found trends in the same direction that either did not reach statistical significance (92 Nickelsen) or are not adequately reported (98 Suhner b). 97 Spitzer found no differences between the treatment groups, most likely because the participants' baseline rhythms had not adapted to the time zone from which they left.

These data suggest that the 'pre+post' regimens have no important advantage over 'post' regimens that might outweigh the inconvenience of dosing before the day of travel, but they have not been directly

compared in ordinary travellers.

Comparison (3): eastward flights v. westward flights

Two trials have compared eastward with westward flights as a part of their design. The Auckland - London trial (89 Petrie) did so, but is not suitable for this comparison as the travellers crossed 12 time zones and it takes over 24 hours to complete the journey. Nickelsen's volunteers flew from Frankfurt to North America, returning at least 2 weeks later; they did not cross over. In this study jet-lag was worse after the eastward flight (overall VAS, combining results with melatonin and with placebo : eastward 5.9, westward 3.0). Jet-lag scores were modestly lower on melatonin than on placebo in both directions.

Comparison (4): passengers v. airline staff

Seven of the 8 trials were in travellers, one in airline cabin crew (93 Petrie). Both groups showed some benefit from melatonin, but their duties and activities at the destination differed. For the travellers these were undefined and very diverse. The airline cabin crew entered the trial with very disordered circadian rhythms, and this probably made it harder to achieve and detect any improvement in jet-lag. Even so a benefit was shown.

Comparison (5a): low doses (5mg or less) v. high (8mg or more)

One trial, that of Claustrat, compared melatonin 8mg with placebo. Nothing in the results of this trial suggests a greater effect than was seen with lower dosage.

Comparisons (5b, 5c): low doses v. very low doses (0.5mg): rapid-release melatonin v. slow-release melatonin

Suhner (a) compared doses of 5mg and 0.5mg in ordinary (fast-release tablets) and 2mg in a slow-release tablet. The 5mg dosage improved self-rated sleep quality, shortened sleep latency, and reduced fatigue and daytime sleepiness after intercontinental flight. The lower dosage of 0.5mg was almost as effective; only the hypnotic properties of melatonin, sleep quality and sleep latency were greater with the 5mg dosage. The 2mg slow-release form was less effective than either of the fast-release tablets.

Comparison (6): short (48 hr or less) v. long (over 48 hr) treatment

All nine trials were of treatment for longer than 2 days; none examined a treatment duration of two days or less.

Reported symptoms/ side effects

Eight RCT reports note symptoms, but only Suhner's two studies looked for symptoms systematically. The first (Suhner a) found no statistically significant differences in the incidence of symptoms between melatonin and placebo. Some symptoms - daytime sleepiness, dizziness, headache and loss of appetite - were most frequent on day 1 after the flight and became less frequent on the next 3 days of treatment; these were probably symptoms of jet-lag. In Suhner (b) the zolpidem+melatonin group felt significantly sleepier in the morning, while the melatonin group felt least sleepy. The combination group also felt significantly more confused and more nauseated than all other treatment groups. Ear/ nose/ throat problems were most frequent in melatonin users; pruritus was least frequent in this group.

Most adverse events or symptoms in the other six studies can be regarded as no more than sketchy qualitative pointers. However, hypnotic effects after melatonin occurred in 5 of the studies, affecting about 10% of the participants. Others included headache or 'heavy head' (2 studies), disorientation (88 Arendt), nausea, and gastrointestinal problems. One individual experienced difficulty in swallowing and breathing within 20 minutes of taking the first dose of 0.5mg melatonin, symptoms which subsided after 45 minutes (97 Spitzer). This person stopped taking the capsules, but agreed to take another single dose on another occasion to see if the symptoms would recur. They did, but were somewhat milder. All the adverse events reported in the trials occurred during treatment and appear to have been short-lived.

Reports of adverse effects from sources other than clinical trials [Table 02](#)

Potentially relevant adverse events have been reported (from sources other than clinical trials in jet-lag) in 6 published papers and 19 unpublished case records from the WHO Uppsala Monitoring Centre (UMC). The reports obtained from the website of the US FDA SN/AEMS lacked essential details and could not be used. Table 2 lists the 25 single cases by the systems affected - CNS, circulation, blood clotting, skin. (Cases identified only by a number and a country are from the UMC register.) Many of the reports do not state whether or not the individual concerned was healthy, or for what purpose melatonin had been taken.

The reports that are in our view worth noting by potential users of melatonin are marked with an asterisk. They concern people with epilepsy, patients taking warfarin or another oral anticoagulant, and anyone getting a skin rash after using melatonin.

Four types of events that may signal a true effect of melatonin deserve investigation. Possible effects on

mental function, sleep, seizure activity, and the circulation are complex, likely to vary greatly with circadian phases, and will be difficult to elucidate. The simplest possibility to study, and perhaps the most urgent, is that melatonin potentiates warfarin. The reports of fixed drug eruption, an allergic manifestation, appear to be convincing and must be taken seriously.

DISCUSSION

Nine of the ten trials found that melatonin taken close to bedtime at the destination decreased jet-lag from journeys crossing five or more time zones. The one study that did not (97 Spitzer) was handicapped by starting from an inappropriate baseline. No differences were detected between daily doses of 0.5 and 5mg melatonin, except that people fall asleep faster and sleep better after 5mg than 0.5mg. A higher dose (92 Claustrat) is not clearly more effective than 5mg. The relative ineffectiveness of 2mg slow-release melatonin (98 Suhner a) suggests that a pulse of melatonin, briefly giving a higher concentration in the blood, works better.

The effect on jet lag shown in the meta-analysis is striking. The benefit is likely to be even greater for flights across more time zones, but less for westward flights.

No trials have directly assessed the use of melatonin with other strategies for reducing jet-lag, but an additive effect would seem likely. Light exposure and light avoidance at the destination have to be scheduled appropriately in order to support the adaptation process to the new time zone. This schedule depends on the number of time zones crossed and the direction of flight. Tables and computer programmes exist that give guidelines when to seek and when to avoid light. Furthermore, the rapid adoption of the new daily pattern at the traveller's destination in terms of meal times, exercise and sleep periods will also aid overall adaptation. The value of melatonin to travellers using sensible re-entrainment principles needs to be established in future research. The effects of caffeine and alcohol intake during the flight on adaptation also deserve study.

There may also be a difference between arrival home and arrival away. The literature on the psychology of physical symptoms would lead one to expect more reported jet-lag symptoms after arrival home than arrival away, because people tend to notice symptoms less when their attention is drawn outwards in a new and more exciting environment (Pennebaker 82). Future studies (but not intervention studies) should examine whether this is true for jet-lag.

The melatonin literature has a number of gaps in terms of the type of people who may benefit from the medication. So far only limited data exist on elderly travellers, and none on the effect of melatonin on jet lag in children. Children typically have the highest circulating melatonin levels of any age group, and this seems likely to be important in their normal development. It has been suggested that an excess of melatonin may be related to delay in the development of reproductive function (Zhdanova 00), but it seems very unlikely that short-term use of a low dose would affect this. Rather melatonin use should be avoided in children because of a general lack of data on either benefits or safety in this population.

It should be noted that individuals differ greatly in the experience of jet-lag, with some travellers extremely affected while others who may have flown the same route may report no jet-lag symptoms. This suggests that individual differences may strongly influence the effectiveness of melatonin. This also remains an unexplored area of research.

The sleep disturbance and circadian dysrhythmia that characterise jet-lag have the potential to be treated with melatonin in combination with other hypnotic medicines. To date only one trial (98 Suhner b) has tested this, using the non-benzodiazepine hypnotic zolpidem. The study found that melatonin plus zolpidem, while reducing sleep disturbance after a transmeridian flight, also produced a significantly higher rate of side effects than in groups taking zolpidem or melatonin alone. No trial combining melatonin with a benzodiazepine hypnotic has yet been published.

Possible adverse effects of melatonin have not been adequately assessed, and many symptoms are difficult to distinguish from symptoms or manifestations of jet-lag itself.

Melatonin differs from most or all other drugs in that the timing of the dose is critical and determines the effect: given at the wrong time it will delay circadian adaptation to local time (Lewy 92, 95). Adverse effects that may occur during treatment for a few days appear to be transient, as would be expected from its pharmacokinetics. The most common risk factor seems likely to be taking melatonin at the wrong time of the day at too high a dose - which in addition to causing a phase shift in the wrong direction would cause excessive daytime sleepiness, particularly if combined with another soporific drug. However, the published and unpublished case reports we have examined suggest that some serious adverse effects may occur, albeit rarely.

The pharmacology and toxicology of melatonin and pharmaceutical aspects of its formulation have not been systematically studied, very likely because the drug cannot be patented and the cost of the work cannot readily be recouped from sales of the drug. Such data are needed in the public interest, to enable melatonin of assured good quality to be provided.

REVIEWER'S CONCLUSIONS

Implications for practice

Melatonin is remarkably effective in preventing or reducing jet-lag, and occasional short-term use by adults appears to be safe. Doses between 0.5mg and 5mg appear to be similarly effective, apart from the greater hypnotic effect of higher doses. For many people 5mg may be a higher dose than necessary: 2 or 3mg may therefore be preferable to start with. It is effective when taken at bedtime on the day of arrival at the destination, and on the following 2-5 days at the same time. Taking melatonin before the day of travel does not hasten or improve adaptation to local time at the destination and is not recommended.

Melatonin should be recommended to adult travellers crossing five or more time zones, especially if they have experienced jet-lag on previous journeys. People making such a journey for the first time may reasonably take it if jet-lag might seriously interfere with their activity at the destination - whether this is work or leisure. Travellers crossing 2-4 time zones can also use it if need be. The use of melatonin on the day of travel and for up to four days after arrival could greatly increase the effectiveness and efficiency of short-term business or diplomatic travel, and military deployment. The major barrier to the use of melatonin is that in most countries it is not licensed and cannot be easily obtained. It is in the public interest that the necessary safety testing is done as soon as possible, and quality controls are established, so that it can be legally marketed.

Reports of adverse events possibly related to use of melatonin suggest that two categories of people should not use the drug without an informed discussion with someone who has read this review: those with epilepsy, and anyone taking warfarin or another oral anticoagulant. In the absence of data of the value and the safety of melatonin in children, its use in them should be avoided.

Implications for research

The toxicological work and the methods of pharmaceutical quality control required for licensing and regulatory control of melatonin are urgently needed.

Data on safety in practice, including possible interactions with other drugs in common use (including alcohol and caffeine) should be collected systematically. Interactions between melatonin and vitamin K antagonists such as warfarin may threaten life and need experimental study now.

Studies are needed to find out whether melatonin is useful and safe in children and in old people, and if so how it would best be used.

Future trials should report the results not only as group means, but also in terms of the proportion of people helped and not helped.

Further suggestions are made above in the discussion.

ACKNOWLEDGEMENTS

We thank Andrea Suhner, Iain Chalmers and Paul Montgomery for valuable comments, Jeffrey Aronson for advice on searching for published ADR reports, and the staff of the WHO Uppsala Monitoring Centre for providing unpublished reports from their database.

POTENTIAL CONFLICT OF INTEREST

None [AH]; Keith Petrie has undertaken two of the trials reviewed.

TABLES

Characteristics of included studies

Study 87 Arendt

Methods Double-blind. Treatment allocated according to a computer programme, decoded only after data collection was complete.

Participants 17 volunteers (10 women, 7 men) aged 29-68 years flying from San Francisco or Los Angeles eastwards to London (8 time zones) after having stayed in California for 14 days.

Interventions Oral melatonin 5mg + 300mg lactose in gelatine capsule (n=8) or lactose 300mg (n=9) taken at 18.00 local time on day of departure and 2 preceding days, and then at bedtime (22.00 - 24.00) for the first 4 days after return to the UK. ['pre+post']

Outcomes Activity patterns measured by wrist meters (n=16), oral temperature, mood self-rating, psychological tests, sleep duration and quality, rating of subjective feelings of jet lag. Urine assays for major metabolite of melatonin and of cortisol.

Notes

Allocation concealment A

Study 88 Arendt

Methods Double-blind cross-over study

Participants 52 of 61 participants flying from the UK to Australia & New Zealand and back completed the crossover.

Interventions Melatonin 5mg or placebo. For eastward flights this was taken for 2 days before the flight at the local time, which corresponded to 2am at the destination time zone, and for 4 days after arrival at the local bedtime ['pre+post']. For westward flights melatonin or placebo was taken at the local bedtime for 4 days after arrival

Outcomes Self-rated jet lag (VAS), symptoms

Notes This study is briefly reported by Skene 1989 in congress proceedings

Allocation concealment B

Study 89 Petrie

Methods Double-blind, placebo controlled, cross-over trial

Participants 20 volunteers (8 women, 12 men) aged 28 to 68, flying eastward from New Zealand to London through 12 time zones on a 26-hour flight. They returned on a similar westward flight 3 weeks later.

Interventions Gelatin capsule of melatonin 5mg + lactose, or lactose daily at between 10.00 and 12.00 local time for 3 days before each flight and on the day of flight, then between 22.00 and 24.00 (destination time) for 3 days after their arrival. Participants were randomised to receive melatonin either on the outward or the return flight ['pre+post']

Outcomes Feelings of jet lag and tiredness assessed by analogue scales, profile of mood states questionnaire, hours of sleep. On 10th day after arrival, retrospective rating of jet lag, estimate of how many days it had taken for sleep pattern and energy to return to normal. The participants recorded possible side effects

Notes

Allocation concealment B

Study 91 Nickelsen

Methods Double-blind

Participants 36 volunteers (26M 10F) flying westward from Frankfurt to USA and 2 weeks later in the reverse direction. In 12 the time shift was 6-7 hr, in 12 8-9 hr, in 12 10-11 hr.

Interventions After the westbound flight participants took melatonin 5mg or placebo at bedtime for 7 consecutive days. After the eastbound flight they took the same dose for 5 days ['post']

Outcomes	Sleepiness self-rated on Stanford scale, log of rest/ activity schedule
Notes	
Allocation concealment	B
Study	92 Claustrat
Methods	Double-blind
Participants	30 healthy volunteers flying from North America to France, having stayed in N America for 7 days or longer
Interventions	Melatonin 8mg capsule (n=15; 8 men) or placebo (n=15; 10 men) on the day of flight and at bedtime on the following 3 days ['post']
Outcomes	Sleepiness, mood, sleep, tiredness, efficiency at work, sleep latency, global effectiveness, symptoms
Notes	Three volunteers performed a double-blind cross-over trial within the study
Allocation concealment	B
Study	93 Petrie
Methods	Double-blind
Participants	52 international airline cabin crew (26 M, 26 F) returning to New Zealand from London via Los Angeles to complete a 9-day tour of duty
Interventions	3 treatment groups: melatonin (5mg daily at a time corresponding to evening/night at the destination) from 3 days before arrival until 5 days after arrival) n=14 ['pre+post']; melatonin (placebo for 3 days then melatonin 5mg daily for 5 days) ['post']. n=15; and placebo, n=15.
Outcomes	Self-rated jet lag (VAS), tiredness, drowsiness; SSS (Stanford sleepiness scale), POMS (Profile of Mood States)
Notes	
Allocation concealment	A
Study	97 Spitzer
Methods	Double-blind
Participants	257 volunteers travelling eastwards across 6 time zones
Interventions	Melatonin 5mg or 0.5mg at bedtime or early evening on day of flight and then for 5 further days ['post']
Outcomes	Jet lag measured by new Columbia Jet Lag scale
Notes	Insufficient adaptation in the new time zone before performing the study on the return flight
Allocation concealment	B
Study	98 Suhner a
Methods	Double-blind
Participants	320 volunteers (age range 20 - 65 years; 172 men) from the University of Zurich travel clinic, flying eastwards through six to eight time zones. Exclusion criteria: use of a beta-blocker or hypnotic, psychiatric disorder, severe sleep disorder, leukaemia, endocrine disorder, melanoma, severe allergy, pregnancy. 142 travelled from America to Europe, 92 from Europe to Asia. These numbers exclude 86 people who were either non-compliant or withdrew for a medical reason.
Interventions	a) Melatonin 0.5mg b) melatonin 5mg c) melatonin 2mg controlled-release d) placebo. All were taken daily at bedtime for the first 4 days after the flight ['post'].

Outcomes	Sleep quality and daytime sleepiness (sleep logs and Karolinska sleepiness scale), mood (POMS) and symptoms (questionnaire). Compliance was assessed using the electronic Medication Event Monitoring System [MEMS] and a questionnaire. Symptoms were noted
Notes	Participants were asked to maintain a regular sleep-wake cycle during the baseline and the four testing days and to limit their nicotine, caffeine and alcohol consumption to normal levels
Allocation concealment	A
Study	98 Suhner b
Methods	Double-blind; computer randomisation
Participants	160 volunteer travellers (80 men) flying eastwards from America to Switzerland across 6 to 9 time zones after a stay of at least 7 days in America. 137 completed the study.
Interventions	Four groups: a) melatonin 5mg, b) zolpidem 10mg, c) both, or d) placebo, using the double dummy technique. The medication was taken between 5 and 9 pm local time on the day of the flight and then for 4 days at bedtime ['post']
Outcomes	Sleep quality, profile of mood states, symptoms, wrist activity monitoring (n=80), subjective rating of jet lag, and of efficacy of the medication. Compliance was assessed electronically (MEMS) and by questionnaire. 23 participants who missed one or more doses were excluded from the analysis. Symptoms were noted
Notes	
Allocation concealment	A

Characteristics of excluded studies

Study	Reason for exclusion
Arendt 95, 97a, 97b	These three broad reviews only briefly summarise the authors' controlled and uncontrolled studies and puts together the results for 474 subjects given melatonin and 112 given placebo; of these 86 took part in both arms of a crossover study. Randomisation is not mentioned.
Comperatore 96	The study examined the effect of melatonin on sleep loss and cognitive impairment in soldiers engaging in night operations immediately on arrival in the Middle East after flying eastwards across eight time zones. Neither adaptation to local time, nor jet lag was assessed

ADDITIONAL TABLES

Table 01 Global jet-lag rating (Visual Analogue Scale, VAS): 0= no jet-lag; 100= maximum

Trial	Number of flights	Melatonin	Placebo	Diff M - P (S. E.)	Notes
87 Arendt	Placebo 9, Melatonin 8	9.8 SD 0.8	55.4 SD 4.5	-45.6 (2.2)	
88 Arendt [crossover study]	Placebo 52, Melatonin 52	18.1 SD 15.5	40.5 SD 15.5	-22.6 (4.6)	Within-subject comparisons
89 Petrie [NZ-London-NZ, crossover study]	Placebo 20, Melatonin 20	35.8 SD 16.5	56.7 SD 24.5	-20.9 (0.66)	Eastward & westward results not reported separately
Claustrat	Placebo 15, Melatonin 15	28.0 SD 7.4	47.7 SD 12.2	-19.7 (3.7)	
Nickelsen - eastward	Placebo 9,	52.3 SD	66.3 SD	-14 (9.8)	Not statistically significant

flights	Melatonin 9	21.7	19.7	
TOTAL participants & Weighted Means	Placebo 105, Melatonin 104	25.3	48.1	-22.8
[Nickelsen - westward flights]	[Placebo 9, Melatonin 9]	26	35	-9

Table 02 Single case reports of possible adverse effects reported in cases outside RCTs

Case no/ Ref	Effects and comment	Days use	Sex / Age
BRAIN			
1 Force 97	transient psychotic episode [possible overdose]	?	F 73
2 Dalton 00	mixed affective state in depressed woman - withdrawn from clinical trial of M for insomnia	7 d	F
3 11 NZ	hallucination, paranoia - recovered on stopping	2 d	M ?
4 10 US	confusion, insomnia, tachycardia, abnormal thinking. Recurred on rechallenge	1 d	F 38
5 07 US	ataxia, dizziness, headache. "recovered with sequelae"	4 d	F 81
6 29 US	headache, hypertonia, tremor - improved on stopping. [was also taking unspecified vitamins]	5 d	F 28
7 35 US	paraesthesia, tachycardia - improved on stopping	1 d	F 41
8 Ellis 96	headache, odd taste in mouth - reported during clinical trial of M for insomnia [2 patients?]	7 d	??
9* Sheldon 98	convulsant effects in 4 of 6 severely neurologically disabled children with seizures, treated with M for sleep disorders	14 d	7months; 7, 8 & 9 yr
10 40 US	convulsion - recurrence when medication was continued	?	M 40
BLOOD CLOTTING			
11* 08 US	eye haemorrhage, purpura, reduced prothrombin - suspected interaction with warfarin	8 d	M 84
12* 09 US	nosebleed, reduced prothrombin - suspected interaction with warfarin	5 d	F 51
13* 21 US	reduced prothrombin - suspected interaction with warfarin. Was taking M 10mg daily	?	M 48
14* 24 US	reduced prothrombin - suspected interaction with warfarin. Also taking digoxin, frusemide, diclofenac	?	F 72
15* 26 US	prothrombin affected [not clear how] - suspected interaction with warfarin.	?	??
16* 27 US	prothrombin affected [not clear how] - suspected interaction with warfarin.	?	M 61
CARDIOVASCULAR			
17 16 US	ventricular arrhythmia	?	?F
18 41 AUS	chest pain, dyspnoea, fatigue, atrial fibrillation, paresis - recovered, no sequelae	1 d	F 58
19 47 CAN	tachycardia	?	F ?
20 05 US	arrhythmia, tachycardia, dizziness, paraesthesia - also on nicotine, pyridoxine	8 d	F 46
21 06 US	angina, palpitation, hypotension - also on vitamins,	?	F 46

	oestrogen, testosterone		
22 13 US	chest pain, dyspnoea - also on thyroxine	?	M 45
23 37 US	fatigue, syncope	1 d	F 63
SKIN			
24/25* Bardazzi 98 IT	fixed drug eruption in 2 men: erythematous-vesicular plaques on the penis, appearing 6-8 hr after rechallenge, disappearing within 10 d	few d	M 35 & 42

REFERENCES

References to studies included in this review

87 Arendt {published data only}

**Arendt J, Aldhous M, English J, Marks V, Arendt JH, Marks M, Folkard S. Some effects of jet-lag and their alleviation by melatonin. *Ergonomics* 1987; 30:1379-1393.

Arendt J, Aldhous M, Marks V. Alleviation of jet lag by melatonin: preliminary results of controlled double blind trial. *Br Med J* 1986;292:1170.

88 Arendt {published data only}

*Arendt J, Aldhous M. Further evaluation of the treatment of jet lag by melatonin: a double blind crossover study. *Ann Rev Chronopharmacol* 1988;5:53-55.

Skene DJ, Aldhous M, Arendt J. Melatonin, jet lag and sleep-wake cycle.. In: Horne J, editor(s). *Sleep '88. Proceedings of the 9th European Congress of Sleep Research, Jerusalem 1988. Stuttgart/New York: Gustav Fischer, 1989: 39-41.*

89 Petrie {published data only}

Petrie K, Conaglen JV, Thompson, Chamberlain K. Effect of melatonin on jet lag after long haul flights. *BMJ* 1989;298:705-707.

91 Nickelsen {published data only}

Nickelsen T, Lang A, Bergau L. In: Arendt J, Pevet P, editor(s). *Advances in Pineal Research. Vol. 5, John Libbey & Co, 1991:303-6.*

92 Claustrat {published data only}

Claustrat B, Brun J, David M, Sassolas G, Chazot G. Melatonin and jet lag: confirmatory result using a simplified protocol. *Biological Psychiatry* 1992;32:705-711.

93 Petrie {published data only}

Petrie K, Dawson AG, Thompson L, Brook R. A double-blind trial of melatonin as a treatment for jet lag in international cabin crew. *Biological Psychiatry* 1993;33:526-530.

97 Spitzer {published data only}

Spitzer RL, Terman M, Malt U, Singer F, Terman JS, Williams JBW, Lewy AJ. Failure of melatonin to affect jet lag in a randomized double blind trial. *Society for Light Treatment and Biological Rhythms: SLTBR Abstracts* 1997;9:1.

*Spitzer RL, Terman M, Williams JBW, Terman JS, Malt UF, Singer F, Lewy AJ. Jet lag: clinical features, validation of a new syndrome-specific scale, and lack of response to melatonin in a randomized double-blind trial. *American Journal of Psychiatry* 1999;156:1392-1396.

98 Suhner a {published data only}

Suhner A, Schlagenhauf P, Johnson R, Tschopp A, Steffen R. Comparative study to determine the optimal melatonin dosage form for the alleviation of jet lag. *Chronobiology International* 1998b;15:655-666.

98 Suhner b {published data only}

Suhner A, Schlagenhauf P, Hoefler I, Johnson R, Tschopp A, Steffen R. Suhner A. Melatonin and jet-lag. *Dissertation ETH No. 12823. Zurich, Switzerland: Swiss Federal Institute of Technology, 1988:85-103.*

Suhner A, Schlagenhauf P, Hoefler I, Johnson R, Tschopp A, Steffen R. Efficacy and tolerability of melatonin and zolpidem for the alleviation of jet-lag. *Book of Abstracts, 6th Conference of the International Society of Travel Medicine, Montreal, Canada, June 6-10,1999. 1999:95, abs G03.*

References to studies excluded from this review

Arendt 95, 97a, 97b

Arendt J, Deacon S. Treatment of circadian rhythm disorders. *Chronobiology International* 1997;14:185-204.

Arendt J, Deacon S, English J, Hampton S, Morgan L. Melatonin and adjustment to phase shift. *J Sleep Res* 1995;4 (Suppl 2): 74-79.

Arendt J, Skene DJ, Middleton B, Lockley S, Deacon S. Efficacy of melatonin treatment in jet lag, shift work and blindness. *J Biol Rhythms* 1997;12:604-17.

Comperatore 96

Comperatore CA, Lieberman HR, Kirby AW, Adams B, Crowley JS. Melatonin efficacy in aviation missions requiring rapid deployment and night operations. *Aviation, Space and Environmental Medicine* 1996;67:520-524.

References to studies awaiting assessment

Edwards

Edwards BJ, Atkinson G, Waterhouse J, Reilly T, Godfrey R, Budgett R. Use of melatonin in recovery from jet-lag following an eastward flight across 10 time-zones. *Ergonomics* 2000;43(10):1501-1513.

Additional references

Armstrong 86

Armstrong SM, Cassone VM, Chesworth MJ, Redman JR, Short RV. Synchronizaion of mammalian circadian rhythms by melatonin. *J Neural Transm (Suppl)* 1986;21:375-94.

Bardazzi 98

Bardazzi F, Placucci F, Neri I, D'Antuono A, Patrizi A. Fixed drug eruption due to melatonin. *Acta Dermato-Venereologica* 1998;78(1):69-70.

Cochrane Handbook 99

Cochrane Collaboration. *Cochrane Reviewers' Handbook*. 4.0 Edition. Cochrane Collaboration, 1999.

Comperatore 90

Comperatore CA, Krueger GP. Scott I, ed. *Occupational Medicine: state of the art reviews*. Vol. 5, Philadelphia: Hanley& Belfus, 1990:323-342.

Dalton 00

Dalton EJ, Rotondi D, Levitan RD, Kennedy RH, Brown GM. Use of slow-release melatonin in treatment-resistant depression. *J Psychiatry & Neuroscience* 2000;25:48-52.

Ellis 96

Ellis CM, Lemmens G, Parkes JD. Melatonin and insomnia. *J Sleep Research* 1996;5:61-65.

Force 97

Force RW, Hansen L, Bedell M. Psychotic episode after melatonin. *Annals of Pharmacotherapy* 1997;31:1408.

Lewy 92

Lewy AJ, Ahmed S, Jackson JM, Sack RI. Melatonin shifts human circadian rhythms according to phase response curve.. *Chronobiology International* 1992;9(5):380-392.

Lewy 95

Lewy AJ, Sack RL, Blood ML, Bauer VK, Cutler NL, Thomas KH. Melatonin marks circadian phase position and resets the endogenous circadian pacemaker in humans. *Circadian clocks and their adjustment*. ;Ciba Foundation Symposium 183Chichester: Wiley, 1995:303-321.

Martindale 99

Martindale. *The complete drug reference*. 32nd Edition. London: Pharmaceutical Press, 1999.

Pennebaker 82

Pennebaker JW. *The psychology of physical symptoms*. New York: Springer Verlag, 1982.

SED 96

Dukes MNG, ed. *Meyler's Side Effects of Drugs*. 13th Edition. Amsterdam: Elsevier, 1996.

SEDA

Aronson JK, ed. *Side Effects of Drugs Annual*. Vol. 10-23, Amsterdam: Elsevier, 1986 to 1999.

Sheldon 98

Sheldon SH. Pro-convulsant effects of oral melatonin in neurologically disabled children. *Lancet* 1998;351:1254.

Waterhouse 97

Waterhouse J, Reilly T, Atkinson. Jet-lag. *Lancet* 1997;350:1611-16.

Winget 84

Winget CM, DeRoshia CW, Markley CL, Holley DC. A review of the human physiological changes associated with desynchronization of biological rhythms. *Aviat Space Environ Med* 1984;55:1085-96.

Zhdanova 00

Zhdanova IV. In: Culebras A, editor(s). Sleep Disorders and Neurological Disease. New York - Basel: Marcel Dekker, 2000:137-157.

* Indicates the major publication for the study

GRAPHS

To view a graph or table, click on the outcome title of the summary table below.

To view graphs using MetaView: select "Outline" on the menu bar, then scroll down to Links and then click on Metaview graphs.

01 Global jet-lag ratings

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Global jet-lag ratings	5	209	WMD [Fixed] [95% CI]	-37.351 [-39.793, -34.910]

COVER SHEET

Title	Melatonin for the prevention and treatment of jet lag
Reviewer(s)	Herxheimer A, Petrie KJ
Contribution of reviewer(s)	AH wrote the protocol, searched for relevant papers, assessed and reviewed them, wrote the text of the review KJP contributed to the protocol, searched for relevant papers, assessed and reviewed them, and contributed to the text of the review
Issue protocol first published	1999/2
Issue review first published	2000/1
Date of most recent amendment	27 August 2002
Date of most recent SUBSTANTIVE amendment	13 December 2001
Most recent changes	Information not supplied by reviewer
Date new studies sought but none found	Information not supplied by reviewer
Date new studies found but not yet included/excluded	23 April 2001
Date new studies found and included/excluded	Information not supplied by reviewer

Date reviewers' conclusions section amended **Information not supplied by reviewer**

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Cochrane Library number CD001520

Editorial group [Cochrane Depression, Anxiety and Neurosis Group](#)

Editorial group code HM-DEPRESSN

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- University of Auckland NEW ZEALAND
- UK Cochrane Centre UK

Index Terms

Medical Subject Headings (MeSH)

[Antioxidants](#) [therapeutic use]; [Jet Lag Syndrome](#) [drug therapy]; [Melatonin](#) [therapeutic use]; [Randomized Controlled Trials](#)

Mesh check words: [Human](#)

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GRAPHS

Review: Melatonin for the prevention and treatment of jet lag
 Comparison: 01 Global jet-lag ratings
 Outcome: 01 Global jet-lag ratings

