

## REVIEW ARTICLE

# The prevention and treatment of jet lag

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*Travel across multiple time zones is a common feature of modern life. After transmeridian flights, the internal clocks are desynchronized from the external environment and it can take several days to re-adjust to the new external time cues. The time taken is related to the direction of the flight and to the number of time zones crossed as well as to individual variability. The result of this desynchronization between the human circadian system and the new environmental timing is described as "jet lag". Although the term "jet lag" refers to disturbances in a variety of symptoms, jet-lagged travellers mostly complain of loss of sleep and of its consequences (e.g., diurnal sleepiness, depressed mood, decreased efficiency, premature awakening, etc.). The direct reason for sleep disturbances after a multiple time-zone flight is that sleep is very sensitive to changes in its temporal setting. The present report reviews current data concerning the symptoms of jet lag, the approaches proposed for the alleviation of jet lag and the effectiveness of these strategies.*

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Without help, circadian rhythms adapt slowly to abrupt changes of time cues, such as are found after rapid travel across a large number of time zones. During the resynchronization process, internal rhythms are out of phase with the external environment, leading to complaints of, for example, poor sleep, alertness and performance. Not all travellers experience subjective jet lag, however, for those that do, the condition can be debilitating. Westwards adaptation is on average slightly faster than eastwards and this is attributed to the natural tendency of the internal clock to delay in most people. On average the clock shifts approximately 1 h or slightly more per day such that it will take about a day for each hour of time zone change for adaptation to be complete. The rate of adaptation varies greatly from one individual to another and it is also possible for the internal clock to adapt in the "wrong" direction, for example by delaying 16 h instead of advancing 8 h.

The most frequently reported symptoms include disturbed sleep, impaired daytime alertness and performance, gastrointestinal problems, loss of appetite, inappropriate timing of defecation and excessive desire to urinate during the night. All of the above may be ascribed in large part to temporary desynchronization of circadian rhythms.

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Meals eaten out of phase with the internal clock may give rise to inappropriate pancreatic and metabolic responses some of which may be long-term risk factors for heart disease [1]. The circadian clock influences the organization of the menstrual cycle and menstrual problems have been reported in air hostesses [2]. Thus, although jet lag appears to be a transient problem it may have long-term consequences for frequent travellers. Subjective perception of global "jet lag" is more closely related to sleep disturbance than to any other function. Evidently sleep disturbance is easier to perceive than, for example, out of phase hormones.

## Sleep disturbance

Transient insomnia associated with jet lag has attracted considerable attention in recent years. Although the term "jet lag" refers to disturbances in a variety of symptoms, jet-lagged travellers mostly complain of loss of sleep and of its consequences (e.g., diurnal sleepiness, depressed mood, decreased efficiency, premature awaking, etc.). The direct reason for sleep disturbances after a multiple time-zone flight is that sleep is very sensitive to changes in its temporal setting. Sleep structure results from an interaction between the output of the endogenous circadian pacemaker and the homeostatic factors such as the time spent awake or the amount of prior sleep [3–7].

The endogenous circadian pacemaker is a major determinant of sleep timing, sleep structure, and the consolidation of sleep and wakefulness. Usually we go to sleep late in the evening soon after the circadian core body temperature (CBT) rhythm begins to decline and on the rising phase of the melatonin rhythm, and we wake up in the morning just after the CBT rhythm begins to rise and on the falling phase of the melatonin rhythm. Sleep duration is longest when sleep episodes are initiated shortly after the maximum of CBT [8]. Sleep episodes initiated on the later part of the rising limb of the CBT rhythm are disrupted and of short duration. Rapid eye movement (REM) sleep reaches its maximum shortly after the time of the temperature trough. The deep stage of non-REM (NREM) sleep—that is, stages 3–4 or slow wave sleep (SWS) during the major sleep episode—appears to be little affected by the circadian pacemaker [9–15]. Sleep spindle activity in NREM sleep is markedly affected by endogenous circadian phase [10].

The prior history of sleep and wakefulness is another determinant of sleep structure. Thus, SWS and computer-detected slow-wave activity (SWA) in the electroencephalogram (EEG) decrease in the course of sleep, independent of circadian phase [10, 11], and an extension of wakefulness results in an enhancement of SWS and SWA in subsequent sleep [3, 16]. Even REM sleep, which is generally thought to be primarily under circadian control, is affected by the prior history of sleep and wakefulness. After total sleep deprivation, a REM rebound has been observed in the second recovery night [17]. Likewise, the latency to REM sleep can be reduced by reducing the pressure for NREM sleep [18].

Just as sleep structure is partly controlled by the endogenous circadian pacemaker, sleep propensity is also influenced by the internal timing system. The circadian rhythm of sleep propensity relates to the changes in sleep ability or sleep tendency within the 24-h day. There is a consistent circadian rhythmic pattern in our tendency to fall asleep, even during the daytime hours when individuals are living in accordance with their normal routine. Several methods have been developed to assess the 24-h cycle

in sleep tendency [19–21]. The “ultrashort sleep-waking schedule” (or the 7/13 paradigm) was developed by Lavie in 1986 [21], in order to trace the course of daily variations in sleep propensity. In this method, subjects are instructed to attempt to sleep for 7 min every 20 min during a 24-h period. The total amount of sleep obtained in each trial is used to construct the 24-h sleep propensity function (SPF) which describes the speed of falling asleep at different times across the 24-h day. Several 7/13 studies showed stable 24 h sleep patterns, both between and within subjects [22–24].

The SPF has three distinct features: (1) The nocturnal “sleep gate” refers to the steep rise in sleepiness which occurs in the late evening hours that marks the start of a period characterized by consistently high levels of sleep propensity. The timing of the “sleep gate” has been found to be stable within subjects, on the rising phase of melatonin rhythm and on the falling phase of the CBT [25]. (2) The “mid-afternoon sleepiness peak” refers to relatively high sleep propensity in the afternoon hours. (3) The “forbidden zone for sleep” is characterized by very low sleep propensity in the early evening hours. This period lasts typically 2–3 h, and is ended abruptly by the opening of the “sleep gate”. Because essentially no rest is provided by the 7/13 paradigm, this dramatic period of very low sleep propensity in the early evening hours, is clearly spontaneous and provides strong evidence for the controlling influence of the endogenous circadian pacemaker over our underlying levels of sleepiness.

By combining the knowledge about the circadian characteristics of sleep and sleepiness and the regulatory processes that subserves sleep homeostasis, the effects of a flight across multiple time-zones can be predicted. This prediction will be made by examining the change in the relative position of sleep at the appropriate local time.

After an eastward flight, sleep is scheduled in advance of the “home” bedtime, and therefore, located before the onset of melatonin secretion, on the rising phase of CBT and hence before the opening of the “sleep gate”. Conversely, after a westward flight, sleep is scheduled in a delayed position with regard to the “home” bedtime, and therefore, located after the onset of melatonin secretion, and after the time of the temperature trough and hence after the opening of the “sleep gate”.

One factor to be considered for flights in either direction is the amount of prior sleep loss or time awake. This factor is particularly important for understanding the quality and structure of sleep during the first post-flight night, because of the loss of sleep often induced by preparing for international flights, and by the inability of most people to sleep on the aircraft. An increase in sleep loss or time awake would be expected to reduce initial sleep latency and enhance the amount of SWS.

There have been several studies of sleep using EEG recordings after transmeridian flights, testing this general concept (e.g. [26–29] and see references within [30]). Studies which examined post-flight sleep after eastward flights [26, 27, 29] found difficulty in falling asleep which was often accompanied by increased wakefulness in the early part of the night as bedtime corresponded with the “forbidden zone for sleep” in the “home” time zone. In some cases where the flight involved overnight travel without sleep these changes did not appear on the first night in the new time zone. Problems with sleep efficiency continued for several days after the flight, with reductions in the amount and percentage of REM sleep as the timing of sleep initiation was on the later part of the rising limb of the CBT rhythm, but with no change in REM latency. SWS was reduced in some cases. Studies which examined post-flight sleep after westward flights [26–28] found less severity of sleep disturbance and usually for a shorter period, lasting possibly 2–3 days after the flight. On the first post-flight night sleep latency

was short and sleep was found to be of good quality with increased SWS in the early part of the night. The rapid sleep onset may be related to the lateness of going to sleep, as bedtime corresponds with early morning in the "home" time zone as well as to the slight prior sleep deprivation. The increase in SWA is also likely to be due to the delay to the first sleep period. Reduction in sleep efficiency was found toward the end of the night at the time corresponding to daytime in the "home" time zone. On subsequent nights, when the pressure for SWS is less, there was an increase in REM sleep as bedtime corresponds with early morning in the "home" time zone, at the time of the temperature trough and when REM sleep reaches its maximum. The increase in REM sleep was particularly high during the first half of sleep.

## **Prevention and treatment**

There is as yet no strategy which will reliably and consistently eliminate jet lag, although several approaches have met with some success. If it were possible to shift instantly and reliably the circadian clock by whatever means, all problems due to the endogenous clock would theoretically be countered. Thus, a search has been initiated for a treatment which does just this. One of the major problems in this area is the uncontrollable nature of field studies on jet lag and the fact that so far it has not been possible to simulate time-zone change in the laboratory taking into account all the factors which may arise in the field.

## ***Sleep***

A primary consideration is to ensure adequate sleep. A quiet, dark bedroom is clearly desirable and sleep should be taken as far as possible during the future night time in the destination time zone. Timed naps can in theory markedly increase alertness [31]. However, napping is frequently not possible either before or during a flight. Some authors (e.g. [30]) recommend not to nap in the destination time zone, and to time meals and sleep etc. to be in synchrony with the new environment. This advice may be hard to follow after a sleepless long haul economy flight in a crowded plane and it is obvious that passengers in first, club and business class will have more opportunity to sleep during flight.

The use of short-acting hypnotics has its place in the alleviation of sleep disturbance during and after time-zone change. This subject has been extensively reviewed recently and will not be considered further here [30, 32].

## ***Chronobiological approaches***

### ***Light***

The light-dark cycle is the principle time cue for resetting human circadian rhythms. Correctly timed exposure to white light (artificial or natural) of suitable intensity and duration will both phase advance and phase delay the circadian clock according to a phase response curve [33, 34]. Light of 3000–10 000 lux applied shortly after the minimum of core body temperature (or the maximum of plasma melatonin) will advance the internal clock, light scheduled shortly before core temperature minimum

will phase delay. Phase response curves (PCRs) describing these interactions enable theoretical predictions to be made concerning the timing of light treatment to adapt to time zone change and it is possible to obtain computer programs or hard copy instructions for self administration of light in the destination time zone [35].

It is rather impractical to receive bright light treatment in the middle of the night (i.e., just before or after the core temperature minimum) prior to departure, although in principle this would be possible during flight. The recent report of phase shifts induced by popliteal light (given with a "biliblanket" behind the knee) requires confirmation, but if effective this approach would enable light treatment at any time including during sleep [36]. In addition to its phase shifting ability, bright light has immediate alerting and temperature raising properties [37]. It acutely suppresses plasma melatonin production [38] and this may to some extent be related to the alerting and temperature raising effects.

### *Avoidance of light*

Of equal if not greater importance than timed light exposure is avoidance of light. Natural bright light exposure is difficult to control and perceived at the "wrong" time can delay adaptation of the internal clock or even precipitate resynchronization in the wrong, or slowest, direction. There is good evidence that exposure to natural light when returning home in the early morning after a night shift opposes the delay required to sleep well during the day [39]. Travelling eastwards over more than 4–5 time zones, and arriving in the early morning subjects will experience light opposed to their adaptation. Again, instructions for timed avoidance of light in the destination time zone are available [35].

### *Effectiveness of light treatment*

The number of field studies using light for jet lag is small and the results not always consistent. In general, with appropriate timing of light exposure a modest acceleration in the rate of adaptation of circadian rhythms to the new sleep–wake schedule is observed. Bright light given under more controlled laboratory conditions following transmeridian flights appeared to speed up reentrainment [40]. A recent review by Samel and Wegman [41] has summarized all the available data. Their conclusions are that there is some evidence that correctly timed bright light may have been effective in accelerating reentrainment, however, many questions remain.

In addition to effects on alertness, temperature, melatonin and circadian phase shifting, there is a small amount of evidence that bright light can acutely modify some hormonal and metabolic responses after forced phase shift. Meals taken out of phase during subjective night can lead to raised insulin, glucose and plasma triglyceride levels [1]. Such increases may be risk factors for heart disease (for references see [1]). Raised plasma triglyceride levels after a night time meal can be attenuated by 8 h bright light treatment (ca 1000 lux broad spectrum white light) before, during and after the meal (Ribeiro *et al.* unpublished observations).

### *Melatonin*

The "darkness" hormone melatonin is normally released at night and the duration of secretion reflects the length of the night. It appears to serve similar functions in all life forms so far studied, these being to act as a time signal for the organization of daily and annual rhythms [42]. The relative importance of melatonin as a circadian and/or seasonal time cue varies between and possibly within species. In adult mammals

it is not essential for circadian organization (except that it appears to play an important role in neonatal circadian organisation): it acts as a daylength signal for the timing of seasonal rhythms. In humans it appears to reinforce behaviour associated with darkness, for example it has soporific and temperature lowering effects. Daytime sleep-inducing effects of melatonin on the EEG appeared rapidly, even after administration of dosages that did not increase the plasma level of melatonin much beyond its normal nighttime physiological levels [43–49]. Spectral analysis of the EEG sleep recordings showed that melatonin significantly increased activity in the theta band (4–7 Hz) and in the sigma band (spindles: 12–14 Hz). On the other hand, there was a significant decrease of the power in the delta bands (1–3 Hz). The enhancement effects of melatonin on the EEG power density in the sigma range, and its suppression effects in the low-frequency range, are consistent with the effects of hypnotics that are GABA-benzodiazepine receptor agonists [46–51].

Melatonin is available in the UK from a licensed manufacturer on prescription. The availability varies in different countries. Only licensed preparations have guaranteed content and purity.

Since melatonin was originally proposed as a human chronobiotic [52] its phase shifting [53–56] and resynchronising properties [57–62] have been investigated together with its acute effects on sleep, temperature and performance (reviewed in [56, 61, 62]). There is good evidence for both phase advancing and phase delaying effects in humans which have been formalized as a PRC: three PRCs to melatonin have been published and substantially resemble each other [55, 56, 63]. Melatonin given approximately 8–13 h before core temperature minimum will phase advance, and given approximately 1–4 h after core temperature minimum will phase delay. However, its effects on the circadian system appear to be both more complicated and much weaker than those of light. For example to date it appears unable consistently to entrain free running circadian rhythms of core temperature [56]. Its ability to phase advance its own endogenous rhythm and the core temperature rhythm is dose dependent in the range 0.05–5 mg fast release, as is its ability to lower core temperature and alertness during the hours following acute ingestion [64]. A number of studies have investigated its effectiveness in hastening adaptation to time-zone change in both laboratory simulations and in field conditions.

### *Effectiveness of melatonin treatment*

At the time of writing at least three studies using melatonin have addressed its possible ability to hasten adaptation to simulated phase shift [58, 59, 60] and at least nine placebo-controlled field studies [57, 65–73] have reported the use of melatonin to alleviate perceived jet lag (primarily sleep disturbance). The first study [57, 65] over eight time zones eastwards used a time sequence of administration (5 mg melatonin daily) designed to initiate an eastward phase shift prior to departure by early evening administration (1800 h) for 3 days prior to flight and to reinforce the advance by bedtime (2300 h) administration in the new local time zone for 4 days. The results indicated that both subjective jet lag ratings and objective (actigraphic sleep parameters, endogenous melatonin and cortisol) parameters adapted more rapidly in the melatonin treated group ( $n=8$ ) compared with the placebo group ( $n=9$ ). Subjective jet lag was significantly correlated with sleep quality. In two of the simulated phase shift studies [58, 59] melatonin clearly increased the rate of circadian adaptation. The study of Samel *et al.* [58] showed more rapid resynchronization of a number of marker rhythms

and suggested that melatonin, correctly timed, could specify the direction of re-entrainment. They did not, however, find beneficial effects on sleep. Deacon and Arendt [59] found improved sleep and behavioural variables well before circadian resynchronization and in spite of the fact that some of their subjects delayed to reentrain and others advanced. Adaptation of 6-sulphatoxymelatonin was significantly more rapid by analysis of variance whereas because of the different directions of re-entrainment there were no differences in acrophase values. Dawson and colleagues [60] found improved sleep but no differences in rate of adaptation with melatonin, however, they used three split doses of melatonin which appeared to cover both the phase delay and phase advance portions of the PRC.

Field studies have largely used subjective measures to evaluate response. Most have reported some improvement in subjective symptoms. Doses from 0.5–10 mg fast release have been employed, usually over a period of 3–5 days after the flight at bedtime in the new time zone. It remains questionable whether or not pre-flight administration to initiate a phase advance or delay is desirable and which dose is the most appropriate. The very large variation in individual pharmacokinetics of melatonin may play an important role in the response and this has never been properly investigated.

The largest controlled study reported to date used a total of 320 subjects treated post flight at bedtime for 4 days after an eastward flight (6–8 time zones). Melatonin (5 mg fast release) was strikingly efficient at improving sleep latency, sleep quality, daytime sleepiness and fatigue, compared with placebo. A lower dose (0.5 mg) of fast-release preparation was less effective, as was a slow release preparation [71].

These positive reports are contrasted by two other studies. One [72] reported problems with pre-flight (3 days) melatonin administration to long-haul aircrew but improvement in subjective measures with only post-flight treatment. In another large controlled study using 5 mg or 0.5 mg, taken at bedtime and 0.5 mg on a shifting schedule to phase advance (New York to Oslo), melatonin was completely ineffective at alleviating subjective symptoms of jet lag [73]. All the previous studies used subjects either demonstrably or theoretically synchronized to the local environment pre-treatment whereas with the latter two studies circadian status (and hence the appropriate timing for melatonin) was unknown.

In both controlled and uncontrolled field studies on the travelling public over the last 12 years [61, 62] we have observed an overall 50% reduction in subjective assessment (visual analogue scale) of jet-lag symptoms ( $n=474$ ) using 5 mg fast release melatonin compared with placebo ( $n=126$ ). We currently use a single phase advancing pre-flight early evening treatment eastwards followed by treatment at bedtime for 4 days after arrival (with a predicted preflight induced advance of 1–2 h this is estimated to be a phase advancing time for most time zone transitions). Westwards we advise subjects to take melatonin for 4 days at bedtime (2300 h or later: a phase delay time over more than six time zones) in the new time zone. This timing enables the exploitation of both sleep inducing and phase shifting effects. The subjective improvement increases with the number of time zones crossed. Short stopovers may require specific instructions, or indeed advice not to use melatonin at all when circadian phase is unpredictable.

As with light treatment, many questions remain. Very few studies have employed objective measures of response: polysomnographic assessment of sleep in field studies is essential. The extent to which timing is critical remains unanswered. However, the fact that unsuccessful studies are associated with unknown circadian time of treatment, suggests that timing is indeed important. Dose, formulation and timing require to be defined in a suitably large population. There is virtually no information on long-term

safety. However, using a licensed preparation and normal healthy volunteer subjects (over 18 years old, not pregnant, not intending to be pregnant, not lactating, with no personal or family history of psychiatric disorder, taking no medication—except minor analgesics and oral contraceptives, with informed consent and the permission of their physician) the only significant side effect in our field studies of jet lag ( $n > 500$ ) has been sleepiness. It is worth noting that a recent report from the Mayo Clinic [74] describes the presence of potentially dangerous contaminants in certain melatonin preparations available over the counter in the USA.

## Miscellaneous

In addition to the approaches described above, a number of other strategies have been proposed for the alleviation of jet lag. These include a specific diet to follow, the use of vitamin B12, aromatherapy, etc. To the authors knowledge, there is no good scientific evidence for the effectiveness of any of these strategies. Suppression of melatonin secretion may have a role in hastening adaptation to phase shift according to some preliminary evidence [67].

## Practice Points

1. Where possible choose daytime flights to minimize loss of sleep and fatigue.
2. Travel business or first class (!).
3. Avoid large meals out of phase [1], caffeine and alcohol [30, 76, 77] during flight, drink lots of water as an aircraft cabin is a dehydrating environment.
4. Avoid taking critical decisions, important meetings etc. for the first day after arrival.
5. Avoid or seek bright light according to e.g. reference [35].
6. Consider short acting hypnotics during the flight (to sleep during the destination night time) and for the first few days after arrival.
7. Consider, with the advice of your physician, the use of correctly timed melatonin if a licensed, quality controlled preparation, and instructions as to use are available. Use the lowest effective dose. Be aware that there is very little short-term and no long-term safety data available.
8. There is no evidence that melatonin is useful in subjects who are not synchronized to the local environment prior to travel, e.g., in long haul flight crew or after a very short stay in a new time zone.

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## Research Agenda

1. It is essential that the different strategies proposed for alleviating jet lag are evaluated objectively, including the use of polysomnography and evaluation of circadian status, in controlled field studies. Such studies will need to be performed over different numbers of time zones and in different directions, using the most common flight departure and arrival times in a sufficiently large number of subjects.

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