Jet lag: trends and coping strategies

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The number of travellers undertaking long-distance flights has continued to increase. Such flights are associated with travel fatigue and jet lag, the symptoms of which are considered here, along with their similarities, differences, and causes. Difficulties with jet lag because of sleep loss and decreased performance are emphasised. Since jet lag is caused mainly by inappropriate timing of the body clock in the new time zone, the pertinent properties of the body clock are outlined, with a description of how the body clock can be adjusted. The methods, both pharmacological and behavioural, that have been used to alleviate the negative results of time-zone transitions, are reviewed. The results form the rationale for advice to travellers flying in different directions and crossing several time zones. Finally, there is an account of the main problems that remain unresolved.

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Effect of long-haul flights

> "I do not suffer from jet lag, only with difficulties in sleeping"
>
> *(Comment from an Olympic athlete after flying from UK to Australia)*

Long-haul flights are associated with negative feelings after arrival that constitute travel fatigue.[2–4] Panel 1 shows the main symptoms and causes. The effects are due to time spent in an environment that is cramped and offers little opportunity for exercise, a restricted choice of food, dehydration due to dry cabin air,[7] and cabin hypoxia, which increases fatigue and changes the daily profiles of some variables.[8] Concern has been expressed about the possibility of an increased frequency of deep-vein thrombosis in these circumstances.[9] Travel between hemispheres produces disorientation because of changes in climate and natural lighting.

Many of these symptoms appear also during long road journeys. Travel fatigue disappears once travellers have settled down at their destination. Panel 2 summarises advice on how to cope with the difficulties associated with travel fatigue.[4,10]

When several (about three or more) time zones are crossed, jet lag is noticed. The subjective symptoms of jet lag (panel 1) are similar to travel fatigue, but there are important differences. First, the symptoms do not disappear after a good night's sleep—indeed, sleep difficulties are one of the main symptoms of jet lag—but take a number of days equal to about two-thirds of the number of time zones that have been crossed. Second, jet lag is noted after time-zone transitions in the laboratory, when effects caused by travelling and changes in culture and meals are absent.

Jet lag is due to the effects in the new time zone of an unadjusted body clock. This absence of rapid adjustment results in loss of sleep at night, and all the daily (circadian) rhythms that are controlled by the body clock are inappropriately phased. Jet lag abates as the body clock adjusts to the new time zone, a topic that has been much reviewed.[11–14]

The severity of jet lag increases with the number of time zones crossed, is worse for older travellers (although the reason for this finding is unclear),[15] and depends on the direction of the time-zone transition—flights to the east are associated with more jet lag than flights west.[16] Sleep and circadian rhythms are also disrupted in aircrew,[17–19] thus, experience of time-zone transitions does not act as a protection, although many aircrew members change their sleep behaviour to keep jet-lag difficulties to a minimum.

Role of the body clock

To understand and cope with jet lag, we should be aware of the basic properties of the body clock, and the roles of this structure in healthy people. The suprachiasmatic nuclei, paired groups of cells either side of the midline at the base of the hypothalamus, are the site of the body clock. These nuclei have melatonin type 2 receptors[20] and receive information about light from the eyes via the retinohypothalamic tract. There is also an input via the intergeniculate leaflet, which is believed to carry information about physical activity and general excitement.

Molecular studies show that the clock is formed by cyclic interactions between clock genes and clock proteins, and most genetic information for the clock is

Search strategy and selection criteria

Web of Science and PubMed were searched for articles published from January, 1997, to March, 2006. Search phrases included "jet lag", "time-zone transitions", and their synonyms. Furthermore, "zeitgebers", "light", "exercise", "melatonin", and "meals" were explored, with the limiter "humans". Key authors and authors commonly cited in bibliographies were used as further sources. More than 500 articles were obtained, but the restriction in the number of allowed references meant that only articles thought to be most important and methodologically sound were selected. If several articles had been produced by the same group of authors, only the most recent was included. The topic of jet lag was reviewed in this journal in 1997.[1] The material covered in that review has not been repeated, but updates about new publications and changing emphases are provided, as well as advice for travellers.

Panel 1: Common symptoms of travel fatigue and jet lag, and differences in their causes

Travel fatigue

Symptoms

- General fatigue.
- Disorientation and increased likelihood of headache.
- Travel weariness.

Causes

- Disruption of sleep and normal routine, difficulties associated with travel (checking in, baggage claim, customs clearance), and general dehydration.

Jet lag

Symptoms

- Poor sleep during the new night-time, including delayed sleep onset (after eastward flights), early awakening (after westward flights), and fractionated sleep (after flights in either direction).
- Poor performance during the new daytime at both physical and mental tasks.
- Negative subjective changes. These include increased fatigue, frequency of headaches and irritability, and decreased ability to concentrate.
- Gastrointestinal disturbances (indigestion, the frequency of defecation, and the consistency of the stools) and decreased interest in, and enjoyment of, meals.

Cause

- Slow adjustment of the body clock to the new time zone, so that daily rhythms and the internal drive for sleep and wakefulness are out of synchrony with the new environment.

Differences between travel fatigue and jet lag

- Travel fatigue is associated with any long journey; jet lag generally needs three or more time zones to be crossed rapidly. However, there is a noticeable difference in individuals' susceptibility to the effects of changing time; some even have difficulty in dealing with the 1 h change accompanying the switch to and from daylight saving time.
- Travel fatigue abates by the next day, the traveller having had a good night's sleep; jet lag after eastward flights lasts for several days roughly equal to two-thirds of the number of time zones crossed,[5] and about half the number of time zones crossed after westward flights. Again, there are obvious differences between individuals.[6]

conserved between species.[21] In rodents studied in bright rather than dim light, the cyclic processes and behaviour are disrupted by shifts of the external light-dark cycle, as would take place after a time-zone transition.[22] The behavioural changes are reminiscent of jet lag in travellers. Light has also been shown to alter clock-gene expression in people.[23]

In the absence of external rhythmic inputs and time cues, the body clock and daily rhythms continue, but with a period that is not exactly equal to 24 h (hence the term circadian). This period is regarded as intrinsic to the body clock. Estimates of this period have decreased over the years from initial estimates of about 25 h, because the effects of light have been progressively removed. Laboratory experiments,[24] with blind or sighted individuals exposed to low levels of light (150 lux or less), indicate an intrinsic period of about 24·5 h.

Whatever the exact period is for the body clock, for it to be of value its timing needs to be adjusted to the solar day. This adjustment is brought about by rhythmic cues in the environment, known as zeitgebers (time-givers). The effect of a zeitgeber on the body clock depends on its time of presentation; a zeitgeber can produce a phase advance, phase delay, or no phase shift. This relation between the time of presentation of the zeitgeber and the phase shift produced is called a phase-response curve. The main zeitgebers are the light-dark cycle and the rhythmic secretion of the pineal hormone melatonin (taking place during nocturnal sleep in healthy people); however, exercise

Panel 2: Advice for coping with travel fatigue

Before the journey

Plan the journey well in advance.
Arrange for any stopover to be comfortable.
Arrange documentation, inoculations, visas, etc.
Make arrangements at the destination.

During the journey

Take some roughage (eg, apples) to eat.
Drink plenty of water or fruit juice (rather than tea, coffee, or alcohol).

On reaching the destination

Relax and rehydrate with non-alcoholic drinks.
Take a shower.
Take a brief nap, if needed, but not enough to stop getting to sleep at night.

exerts a much weaker effect than do other zeitgebers. Figure 1 shows simplified phase shifts that can be produced in individuals by these zeitgebers. There is interindividual variation in the timing of the temperature minimum (Tmin) and dim-light melatonin onset, and the switches from phase advance to phase delay or no shift are less clear-cut than might be inferred from this figure.[26,28]

The body clock brings about daily rhythms in core temperature, plasma hormone concentrations, and the sleep-wake cycle—all of which, in their turn, exert widespread effects. Thus, the whole body becomes rhythmic. The body clock is not readily perturbed by external factors, which is useful when waking during the night or naps during the daytime are considered, since a change in timing of the body clock would be inappropriate then. However, this resistance to phase shifting is the cause of many of the difficulties associated with time-zone transitions.

The body clock promotes activity in the daytime and recovery and restitution during the night, which enables preparations to be made for the switches between the active and sleeping phases. The circadian rhythms of core temperature and melatonin secretion are closely associated with the rhythm of sleep propensity. Superimposed on these rhythms are effects attributable to the sleep homoeostat. When the amount of time awake, fatigue, and the need for sleep increases, alertness falls. These changes are reversed during sleep.

The ease of getting to sleep and staying asleep depends not only on previous wake time but also on associations with the circadian rhythm of core temperature.[29] Sleep is easiest to initiate when core temperature is falling rapidly or is at its lowest, and most difficult when body temperature is rising rapidly or is high. Waking is the opposite of sleep initiation because it happens when core temperature is rising or is high. As a result, wakefulness is maintained in the daytime[30] and, since the normal core temperature minimum occurs between 0300 h and 0700 h (figure 1), the conventional times of sleeping are synchronised with the rhythm of core temperature so that an unbroken night's sleep can be obtained. As a result, when the body clock is inappropriately phased, sleep is difficult to initiate and maintain.

There is a general parallelism between core temperature and mental performance, but deterioration because of time awake is also important, especially for tasks that need large amounts of central processing or short-term memory. Mental performance improves with rising core temperature throughout the early hours of the waking day; in the latter half of the day, tasks requiring little central processing or memory (eg, simple reaction time) continue to be done well until the evening, although mood changes and tasks needing more central processing and short-term memory (eg, decision-making) deteriorate because of fatigue before the evening fall in core temperature.[31] Several mathematical models[32] have assessed changes in mood and performance under different combinations of time of day and time awake, many of which include an additional deterioration in mental performance caused by sleep loss.

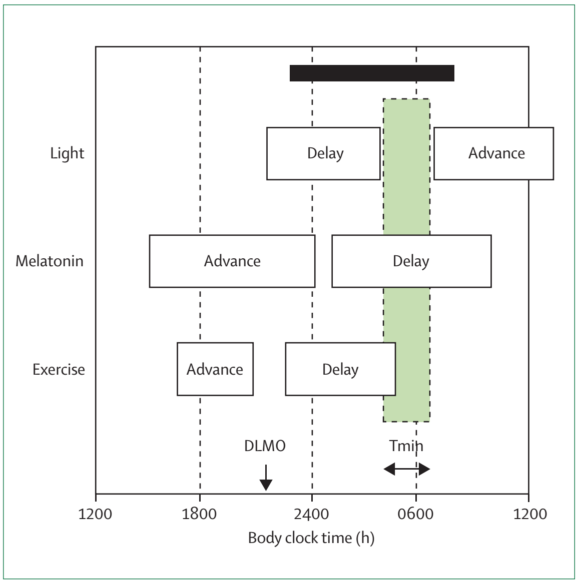

Figure 1: **Phase shifts (advances and delays) of the body clock produced by light, melatonin ingestion,[25,26] and exercise[27] at different times during the day**
Body clock markers, dim-light melatonin onset (DLMO), and the minimum of core temperature (Tmin), are shown, and the shaded area shows a range of Tmin that is usually seen. Horizontal black bar indicates normal sleep time.

There is evidence[4] that many aspects of physical activity display circadian rhythms that are closely in phase with that of core body temperature. These aspects include peak force of muscle contraction, anaerobic power output, performance in long-jump and high-jump, and an individual's motivation to undertake sustained effort. Furthermore, sports that simulate contests or that involve timing skills (eg, swimming, cycling, football, tennis, and badminton) show circadian variation.

However, the view that there are circadian rhythms in physical activity has been criticised.[33] One criticism relates to the frequency of measurement during the course of a day. Maximum physical exertion is far more difficult to measure repeatedly than is sleep propensity or mental performance, because of muscle and biochemical fatigue.[34] Another challenge is that the extent to which the body clock is responsible for any observed rhythms has often not been established, since such rhythms have a substantial exogenous component (due to sleep-wake cycle). Even so, several variables related to sports performance do show an endogenous component (due to the body clock).[35] Even though sleep loss seems to have little effect on muscle strength, top performance requires components—eg, mood, strategy,

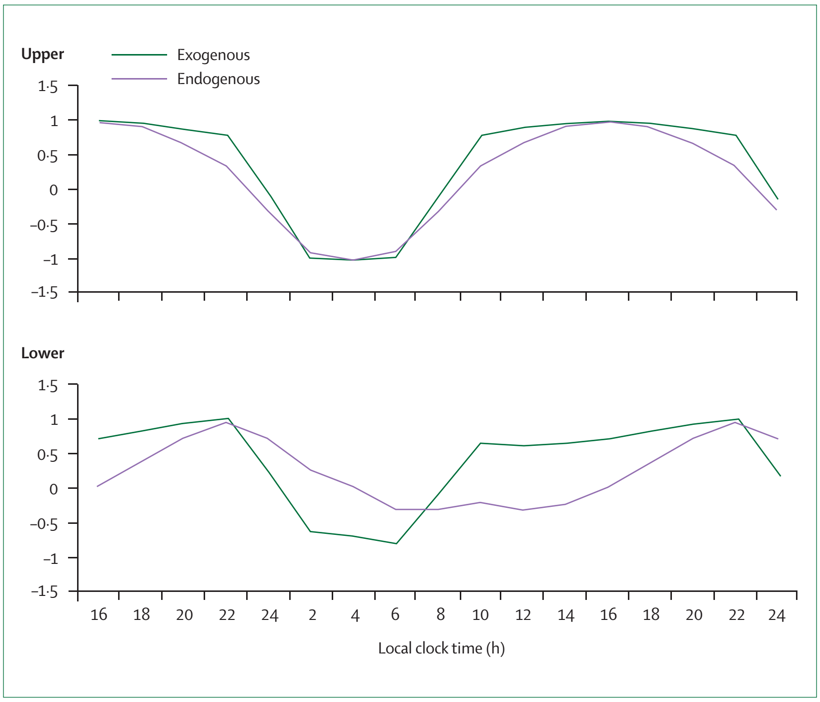

Figure 2: **Diagrammatic representation of circadian rhythms of variables with a large endogenous or exogenous component**

Upper=before time-zone transitions in control conditions, with subjects sleeping 2400 h–0800 h. Lower=after time-zone transition, simulating the immediate effects of an 8-h time-zone transition to the east. The exogenous component was described as +1 during waking and –1 during sleep times. The endogenous component was described as a cosine curve (mean of 0 and amplitude of 1) peaking at 1700 h during control time and not adjusting to post-shift time (ie, peaking at 0100 h by the new local time). Before the time-zone transition, the rhythms are similar in phase and amplitude. The exogenous rhythm (exogenous and endogenous components mixed in the ratio 4 to 1) seems to adjust in phase to the new local time and with little change in shape. By contrast, the endogenous rhythm (exogenous and endogenous components mixed in the ratio 1 to 2) changes in shape and its phase adjusts very little to new local time.

and the desire to train to a maximum—that are affected by sleep loss.[36]

The importance of the body clock itself, rather than the rhythms of core temperature and plasma melatonin, in the production of the rhythms in sleep and performance is unresolved; for individuals living healthily and who are adjusted to their environment, the body clock and circadian rhythms are synchronised to one another, which makes it very difficult to separate out their individual roles.

Time-zone transitions

A recorded rhythm can be regarded as a mixture of components because of effects of the body clock (the endogenous component) coupled with effects of the individual's environment and lifestyle (the exogenous component). These components are usually synchronised, but this synchronicity is lost in the days after a time-zone transition, since, unlike the exogenous component, the endogenous component has not adjusted. The effects of this loss of synchrony can be seen by comparison of hypothetical data showing two rhythms before and after a time-zone transition (figure 2). The rhythm with a substantial exogenous component seems to adapt its phase immediately. However, a rhythm with a larger endogenous than exogenous component, becomes distorted after the transition, showing poor phase adjustment and a decreased amplitude. Heart rate has a large exogenous component, rectal temperature has endogenous and exogenous components of about equal size, and the rhythm of melatonin secretion, when measured in dim light, has only a small exogenous component.

In general, therefore, overt circadian rhythms will adjust to time-zone transitions at different rates. Those with a larger exogenous component—eg, food intake[37] and physical activity—will seem to adjust more rapidly than will those with a larger endogenous component—eg, sleep, mood, and mental performance.

Poor sleep (assessed by actimetry, by polysomnography, and subjectively) is one of the main drawbacks associated with time-zone transitions.[38,39] After a westward flight, individuals feel tired during the new evening by local time and yet wake prematurely (because of rising core temperature and falling melatonin secretion produced by their unadjusted body clock). After an eastward flight, individuals do not feel tired at midnight by local time (daytime by their unadjusted body clock); however, they are ready for sleep as the new day dawns. Like jet lag, sleep disturbances are worse after eastward flights than after westward flights.[38] Mental performance, mood, and alertness all worsen, due not only to the endogenous component of these rhythms (ie, being awake when body temperature is low and attempting sleep when it is high) but also because of sleep loss.[31]

Several studies show that elite athletes have sleep loss and mood disturbance after long-haul flights.[4,39–41] Moreover, athletes travelling five time zones to the west showed shifts in performance profiles (including grip, back, and leg strengths) that were in phase with the unadjusted rhythm of intra-aural temperature.[42] A similar change of daily profiles in grip strength was seen in a group of Olympic athletes and sedentary people travelling ten time zones to the east.[43] Lemmer and co-workers[44] reported that elite athletes travelling to the west or east over six to eight time zones showed altered grip strength and poor performance in training sessions for several days after the flight.

With repeated long-haul flights, there is evidence for some long-term difficulties for aircrew. Irregularities of the menstrual cycle have been known for some time, and these fluctuations have been linked to altered patterns of melatonin secretion.[45] Deficits of cognitive performance[46] and increases in psychotic and major affective disorders[47] have also been described. Such effects have not been reported in healthy travellers whose experience of time-zone transitions is far less extensive than those who regularly travel long distances.

One implication of differences in flexibility of habits, age, or chronotype[48] (ie, whether their circadian rhythms and lifestyle are phased earlier or later than average) is that there might be differences in peoples' responses to time-zone transitions. In one study,[49] travellers with rigid sleeping habits had more symptoms of jet lag than did those with less rigid sleeping habits. Another study of elite athletes and their trainers[50] failed to show an effect of chronotype on the amount of jet lag; instead, the amount of jet lag depended on the individuals' travel schedule. Despite having slept substantially less during the flights, those whose schedule had a shorter interval between their last full sleep before the flight and their first one at their destination had less jet lag than those whose schedule resulted in this interval being longer. The contribution of different light exposures was not assessed.

People older than 60 years have less regular circadian rhythms, and lower amplitude, phase-advanced body temperature and melatonin rhythms than do younger controls.[15,30,51] These individuals also have greater difficulty in coping with jet lag, especially after eastward flights.[15,16] The phase-response curve to light is slightly different in older people.[52] However, agomelatine, a melatonin agonist, can promote phase advances in elderly men when given in the evening,[53] and exercise taken at bedtime induces phase delays similar to those seen in younger controls.[54]

Alleviation of jet lag

There is an obvious premium on promotion of body clock adjustment, which requires knowledge of the zeitgebers that adjust the body clock to its normal state. Furthermore, amelioration of the symptoms of jet lag—especially poor-sleep improvement and reduction of daytime fatigue—will be beneficial, even though this improvement need not include adjustment of the body clock.

The best way to alleviate jet lag is by adjustment of the body clock. The main zeitgebers in individuals are the light-dark cycle and the nocturnal secretion of melatonin. Sleep, physical activity, and food intake have also been implicated. The effects of light exposure and melatonin secretion act to synchronise the body clock with the sleep-wake and light-dark cycles.[24]

A phase-response curve to light (figure 1) has been established.[55,56] Exposure to gradually increasing light intensity[57] rather than a pulse of light exerts a modest effect, and continual pulses of light seem to be almost as effective as continuous light over the same period.[58–60] The amount of phase shifting depends on light intensity, and small shifts are produced by domestic lighting, which is important to those whose exposure to natural light is restricted.[55,61,62]

The detailed nature of the receptors, the wavelength of light they respond to most,[63,64] and their distribution in the retina,[65] remain uncertain. Some believe that the photosensitive pigment is derived from vitamin B2,[66] but this theory is disputed.[67,68] The claim[69] that light could be received by non-ocular receptors (situated at the back of the knee) has not been substantiated.[70–73]

Changes to the time of sleep shift the body clock in the opposite direction to that produced by light given at the same time.[74–77] The role of sleep itself (rather than lack of exposure to light) is difficult to assess since shutting the eyelids introduces a light-dark cycle. However, Danilenko and co-workers[78] reported small advances of the body clock when sleep was advanced by 20 minutes daily in individuals who remained in light intensities less than 0·2 lux. Even if sleep itself can act as a weak zeitgeber, the effects are small compared with those caused by light exposure associated with a normal lifestyle.

The chemistry and roles of melatonin have been much reviewed.[79–84] A phase-response curve to melatonin shows that exogenous melatonin delays the body clock after waking and advances it in the afternoon and evening (figure 1).[25,26,85,86] However, phase delays have proved difficult to show convincingly.[87] Since light inhibits the release of melatonin, these two zeitgebers act jointly—eg, light on morning awakening advances the body clock directly (through the light phase-response curve) and also because of suppression of melatonin secretion (which would cause a phase delay at this time). Exposure to bright light coupled with melatonin ingestion, with the times designed to promote phase shifts in the same direction, has produced additive effects.[88,89] However, if the two interventions are given at the same time (when some degree of antagonism is predicted; figure 1), the extent to which they oppose one another is disputed.[90,91]

The light intensity needed to suppress melatonin secretion is lower than that once thought, especially if the individual has recently been living in low light intensities,[92–94] and some argue[82] that such a result needs a reassessment of the melatonin phase-response curve. There is some evidence that melatonin secretion is suppressed more by light in the upper visual field,[95] and that shorter wavelengths (blue-green light) are more effective in causing this suppression and phase shifts of the rhythm than are longer wavelengths.[63,96,97]

Melatonin ingestion also has a soporific effect and lowers core temperature.[98–100] Pineal secretion normally begins in the evening and is associated with the increase in sleep propensity and decrease in core temperature at this time.[98,101] These outcomes might be a direct effect of melatonin on the suprachiasmatic nuclei or a vasodilatory action on the cutaneous vasculature via melatonin type 2 receptors, or both.[20,102] Vasodilatation will lower core temperature, but fatigue and the ability to fall asleep are associated more with the rise in distal cutaneous temperature than with the fall in core temperature.[103]

Details of a phase-response curve for exercise are unclear (figure 1). Phase shifts have been produced by periods of exercise,[27,58,104,105] but the phase changes were small and phase advances have proved difficult to obtain. Separation of the direct effects of exercise from effects caused by light exposure can be difficult,[106] which indicates the possible value of studies on blind individuals.[105] However, phase delays were seen[107] when the sleep-wake cycle was delayed and exercise was done at night in very dim light (<1 lux). The exercise needed in such studies would be unacceptably severe for most people.[104] However, exercise is generally thought to improve sleep, provided that it is not too close to bedtime.[108]

There is very little evidence that diet can shift the body clock. Krauchi and colleagues[109] have shown that a carbohydrate-rich meal changed heart rate, core temperature, and melatonin secretion when eaten in the evening but not in the morning. However, the researchers thought that these effects were not caused by adjustment of the suprachiasmatic nuclei.

Earlier studies[1,2] of the effects of real or simulated time-zone transitions assessed various mental and physical activity tasks, physiological variables, and hormones. These studies provided a general understanding of the drawbacks caused by time-zone transitions, but were difficult and time-consuming to undertake. A more convenient protocol for field studies has been to use subjective assessments of jet lag and its symptoms, which raises issues of what travellers mean by jet lag, and the link between jet lag and its symptoms (panel 1).

Spitzer and co-workers[110] produced a questionnaire that contained 14 common symptoms of jet lag. Participants were asked at the end of the day how much individual symptoms bothered them during the previous 24 h, from which a total jet-lag score was calculated. The five symptoms that correlated least with the total score—confusion, napping, high sleep latency, fractionated sleep, and early awakening—were removed. The symptoms that remained formed the Columbia jet lag scale. They were: fatigue, daytime sleepiness, impaired concentration, decreased alertness, memory difficulties, clumsiness, weakness, lethargy, and light-headedness. The value of this approach is that it uses a set of symptoms to define jet lag. Disadvantages are that the assessments were made only once, they were made at the end of the day, and there were no references to nocturnal sleep.

The Liverpool jet lag questionnaire (panel 3), produced independently of the Columbia jet lag scale, addresses these disadvantages. This questionnaire is also symptom-based, but differs in the exact symptoms that are considered, and in the ways the data are collected and analysed (participants are required to answer the questionnaire several times per day and each symptom is assessed separately). The questionnaire was first used

***Panel 3:* The Liverpool jet lag questionnaire[5]**

1. Jet lag:

How much jet lag do you have?

0 -- 10
(insignificant jet lag) (very bad jet lag)

2. Last night's sleep. When compared with normal:

a. How easily did you get to sleep?

–5 ----------------------------- 0 ------------------------------ +5
(less) (normal) (more)

b. What time did you get to sleep?

–5 ----------------------------- 0 ------------------------------ +5
(earlier) (normal) (later)

c. How well did you sleep?

–5 ----------------------------- 0 ------------------------------ +5
(more waking episodes) (normal) (fewer waking episodes)

d. What was your waking time?

–5 ----------------------------- 0 ------------------------------ +5
(earlier) (normal) (later)

e. How alert did you feel 30 min after rising?

–5 ----------------------------- 0 ------------------------------ +5
(less) (normal) (more)

3. Fatigue:

In general, compared to normal, how tired do you feel at the moment?

–5 ----------------------------- 0 ------------------------------ +5
(more) (normal) (less)

4. Meals. Compared with normal:

a. How hungry did you feel before your meal?

–5 ----------------------------- 0 ------------------------------ +5
(less) (normal) (more)

b. How palatable (appetising) was the meal?

–5 ------- --------------------- 0 ----------------------------- +5
(less) (normal) (more)

c. After your meal, how do you now feel?

–5 ------------------------------ 0 ---------------------------- +5
(still hungry) (satisfied) (bloated)

5. Mental performance and mood. Compared with normal:

a. How well have you been able to concentrate?

–5 ------------------------------ 0 ---------------------------- +5
(worse) (normal) (better)

b. How motivated do you feel?

–5 ------------------------------ 0 ---------------------------- +5
(less) (normal) (more)

c. How irritable do you feel?

–5 ------------------------------ 0 ---------------------------- +5
(less) (normal) (more)

6. Bowel activity today. Compared with normal:

a. How frequent have your bowel motions been?

–5 -------------------------------- 0 -------------------------- +5
(less) (normal) (more)

b. How has the consistency been?

–5 -------------------------------- 0 -------------------------- +5
(harder) (normal) (looser)

for people who had travelled eastwards across ten time zones during the first 6 days after their flight.[5] Mean daily scores for jet lag and its symptoms were highest on the first post-shift day and decreased thereafter. However, rates of recovery were not equal; although jet lag, fatigue, difficulty in getting to sleep, and early awakening had not recovered fully after 6 days, gastrointestinal difficulties had recovered after 2–3 days.

This differential rate of recovery implies that the links between jet lag and its symptoms are of different strength. Further analysis considered the association between jet lag and its symptoms at different times of the day.[111] Jet lag correlated strongly with fatigue assessed at the same time—ie, there was a strong temporal specificity to this relation. This specificity was reduced when correlations between jet lag and losses of concentration and motivation were considered. For responses to food intake and stool consistency, the association with jet lag not only was weaker but also did not vary with the time of day when jet lag was assessed. Jet lag showed a complex relation with sleep. First, soon after rising, jet lag showed strong positive correlations (for the particular sleep just ended) with the difficulty of getting to sleep and premature waking. Second, estimates of jet lag made in the middle of the day showed no associations between sleep and jet lag. Third, estimates made just before going to bed were positively correlated (for the sleep about to be taken) with getting to sleep and waking earlier, and with the ease of getting to sleep. These results (table 1) were confirmed after a simulated time-zone transition.[112] In many respects, the Liverpool and Columbia questionnaires give similar results. The absence of direct sleep assessments from the Columbia questionnaire accords with the view that, by the end of the day, any difficulties with the previous sleep do not contribute to an assessment of jet lag.

The differences in associations between jet lag and its symptoms are due to different strengths of the endogenous components. When the endogenous component (ie, sleep, fatigue, and some aspects of perceived mental performance) is strong, the link between jet lag and its components will be strong, and the timing of the assessments will be important. However, there will be only a weak link with food intake, which has a weak endogenous component[37] and is affected far more by culture, habit, and the food being perceived as palatable.[113] Since jet lag and some of its symptoms show abnormally phased circadian rhythms, the most appropriate time of assessment is dependent on whether the aim is to investigate improved sleep (requiring assessments soon after rising or just before retiring to bed) or improved alertness and mental ability (requiring assessments during the course of the waking day).

If the assessment aim is to promote adjustment of the body clock, then direct measurements of body-clock markers rather than inferences drawn from jet lag and its symptoms are strongly preferable. These markers can be difficult to measure, but the development of several mathematical methods that use the activity rhythm to correct the temperature record for the direct effects of the sleep-wake cycle[114] offers the possibility of assessments of the rate of adjustment of the body clock.

Management of jet lag

Several reviews have assessed methods to alleviate jet lag.[4,11,81,115] Treatments include drugs and behavioural measures, however, no cure to prevent jet lag has yet been discovered. Short-acting hypnotics have been used in field studies, often in a military context, and have generally been shown to improve sleep.[42,74,116–119] Improved alertness, physical performance, and decreased jet lag the day after treatment have also been seen in some studies. These improvements might result from improved sleep or better adjustment of the body clock. Results from attempts to look specifically at this point have been inconsistent.[74,116,117]

Drugs to promote alertness, including modafinil, dextroamphetamine sulfate, and caffeine, have been investigated.[119–121] Of these drugs, only caffeine can be considered for more general use. There is evidence that both fast-acting and slow-release forms of caffeine can temporarily alleviate fatigue.

Many reviews and reports[79–81,83,84,120,122–127] confirm the effectiveness of melatonin ingestion, generally 3–5 mg, being taken 2–3 h before bedtime. Herxheimer and

	Association*	Temporal specificity†
Increased fatigue	Strong	Narrow
Decreased motivation	Strong/moderate	Narrow/moderate
Decreased concentration	Strong/moderate	Narrow/moderate
Increased irritability	Moderate	Moderate
Decreased enjoyment of meals	Weak	Wide
Looseness of stools	Weak	Moderate
Difficulty of getting to sleep	Strong	Narrow (on rising)
Ease of getting to sleep	Moderate	Narrow (on retiring)
Getting to sleep earlier	Moderate	Narrow (on retiring)
Waking earlier	Strong	Narrow (on rising)
Waking earlier	Moderate	Narrow (on retiring)

*Strong=β-coefficient >0·30; moderate=β-coefficient 0·15 to 0·30; weak=β-coefficient <0·15. †Narrow=positive association only when variable is measured at the same time as jet lag; moderate=positive association when variable is measured at the same time, 4 h earlier or 4 h later than jet lag; wide=positive association when variable is measured at widely different times from jet lag. Based on data in references in 111 and 112.

Table 1: **The association between jet lag and its symptoms**

Petrie[128] presented a discussion and meta-analysis of the results available at the time. Most studies on the effect of melatonin have included subjective assessments of jet lag together with fatigue and aspects of sleep. Suhner and colleagues,[124] for example, showed that melatonin improved sleep (when assessed in the morning) and decreased daytime sleepiness and fatigue (when assessed in the evening). These results suggest that any sleep-promoting effects of ingested melatonin are not carried over to the next day, a conclusion that was drawn also when physical activity was measured the morning after taking 5 mg melatonin before bedtime.[129]

Another meta-analysis[130] concluded that melatonin was ineffective at decreasing sleep latency. The sleep difficulties studied were associated with shift work, secondary sleep disorders in a clinical setting, and after time-zone transitions. Other studies[43,110] have not shown an effect of melatonin. Spitzer and colleagues[110] assessed the jet lag score at the end of the day but, since this score did not include assessments of the previous sleep, any sleep-promoting effects would have been missed. Edwards and co-workers[43] assessed jet lag at several times during the day, although any positive effects measured in the morning (eg, improved sleep) could possibly have been swamped by less positive responses during the rest of the day.

Whether the success of melatonin is because it acts as a natural hypnotic (soporific) or promotes adjustment of the body clock via the phase-response curve that exists for melatonin is unknown.[25,86] The few studies that investigated phase-shifting of the body clock by melatonin have not provided convincing results.[131] This absence of effect might indicate the fact that ingestion in the evening (to promote sleep) will rarely be at the best time for production of appropriate phase shifts.[1] Further, in most studies, possible confounding effects of the light-dark cycle have not been avoided.[90,91]

Few side-effects have been reported, but the absence of long-term trials into the toxic effects and no licence are serious drawbacks to recommendation of melatonin for protracted use.[128,130,132–134] Young people and pregnant women have been advised against the use of this substance.[133] Other hypnotics should be unnecessary. The timing of melatonin ingestion related to its chronobiotic was discussed in the previous *Lancet* Review.[1] Promising results with melatonin analogues in people are beginning to be reported.[135]

The phase-response curve to light is well established (figure 1), and light exposure and avoidance in the new time zone are regarded as an effective way to adjust the body clock.[55,136] Table 2, which is based on the phase-response curve to light and on the assumption that the individual's Tmin was 0400 h, suggests recommended times for light exposure and avoidance on the first day after a time-zone transition. On subsequent days, the times of light exposure and avoidance should be changed as the body clock adjusts. The exact changes needed are not known in detail, but to advance the times of exposure or avoidance by about 1 h per day when advancing the body clock and to delay the times by about 2 h per day when delaying it are reasonable estimates.[1]

After flights to the west, the times when light should be avoided tend to be during the night. This consonance between the requirement of light avoidance based on the phase-response curve and the natural light-dark cycle is one reason why jet lag after flights to the west is generally felt to be less pronounced.[16] Several field studies have confirmed the phase-shifting effects of light during night work, but far fewer studies have investigated time-zone transitions.[137] No study links phase adjustment of the body clock to the decline in jet lag and its symptoms. A field study with light visors[138] produced only moderate shifts of the body clock, and whether this result shows inadequacies with respect to

	Bad local times (h) for exposure to light	Good local times (h) for exposure to light
Time zones to the west (h)		
3	0200–0800*	1800-0000†
4	0100–0700*	1700–2300†
5	0000–0600*	1600–2200†
6	2300–0500*	1500-2100†
7	2200–0400*	1400–2000†
8	2100–0300*	1300–1900†
9	2000–0200*	1200–1800†
10	1900–0100*	1100–1700†
11	1800–0000*	1000–1600†
12	1700–2300*	0900–1500†
13	1600–2200*	0800–1400†
14	1500–2100*	0700–1300†
Time zones to the east (h)		
3	0000–0600†	0800–1400*
4	0100–0700†	0900–1500*
5	0200–0800†	1000–1600*
6	0300–0900†	1100–1700*
7	0400–1000†	1200–1800*
8	0500–1100†	1300–1900*
9	0600–1200†	1400–2000*
10	Can be treated as 14 h to the west‡	
11	Can be treated as 13 h to the west‡	
12	Can be treated as 12 h to the west‡	

*Promotion of a phase advance of the body clock †Promotion of a phase delay of the body clock ‡Body clock adjusts to large delays more easily than to large advances. This table is based on a Tmin of 0400 h; other values for Tmin would need the times to be adjusted accordingly. For example, an individual with a Tmin at 0600 h should, after a journey across three time zones to the west (see row 1), avoid light at 0400–1000 h and seek it at 2000–0200 h.

Table 2: **Recommendations for the use of bright light to adjust body clock after time-zone transitions**

the physical properties of the light used is unclear. Shining light into individuals' eyes is not the same as them receiving light that has been reflected from the surroundings—more field studies are needed. Negative correlation has been reported between the extent to which advice on light exposure had been adhered to and the severity of jet lag.[139] This study was novel since the information (advice on light exposure, individuals' adherence to it, and the jet lag experienced) was obtained from questionnaires and self-reports through the Internet.

There is no information about how exercise alone affects jet lag, and very little about food intake. One study[140] showed positive results in soldiers who had used the Argonne diet (alternate days of fasting and feeding on a protein-rich breakfast and carbohydrate-rich evening meal for 4 days before a trans-meridian flight). Effects of jet lag were reduced slightly but, as acknowledged by the researchers, there were methodological weaknesses in the investigation. The impracticability and restrictive nature of the regimen would be restricting factors for most travellers. Chiropractic[141] has been shown to have no effect on reducing jet lag symptoms. Aromatherapy has been suggested as a possible remedy for sleep loss[142] but experimental data are scarce.

Laboratory investigations of the combined effects of light and melatonin in promotion of phase shifts have been done[26,89] and advice exists on times of melatonin ingestion combined with times of light exposure or avoidance for flights to the east or west across different numbers of time zones.[13] The possibility of combining light exposure with exercise has been investigated in animals and modelled mathematically,[143] but no field studies in people seem to have been undertaken. One field study[127] used a combination of melatonin, light, and exercise in athletes travelling across 12 time zones. Melatonin (3 mg) was ingested in the evening and the athletes were exposed to the natural light-dark cycle when they undertook training sessions in the morning and evening in the new time zone; otherwise they remained indoors. The sleep-wake cycle inverted 2–3 days after the flight and most sleep indices were unchanged from baseline values. These results are difficult to interpret in detail because there does not seem to have been a placebo group. Moreover, whether the factors promoted adjustment of the body clock or acted directly to increase daytime alertness (light and exercise) and nocturnal sleep (melatonin) is unknown.

Panel 4: Combating of travel fatigue and jet lag

If the journey crosses fewer than about three time zones, then jet lag is unlikely to be a major difficulty for most people.

If the stay is too short for adjustment of the body clock (for most people, fewer than about 3 days), remain on home time, and attempt to arrange sleep and engagements to coincide with this.

If the journey is across more than three time zones and the stay is more than 3 days, then, as well as taking steps to keep travel fatigue to a minimum, jet lag can be kept to a minimum.

After the flight, the advice relates to:

- promotion of adjustment of the body clock by light;
- promotion of sleep (and clock adjustment) by melatonin;
- maintenance of daytime alertness.

Advice for travellers

Panel 4 summarises advice for travellers. Attempts have been made to partly adjust the sleep-wake cycle to the new time zone in the days before eastward flights, by combination of advancing sleep time (1 h per day) with bright light on rising for the 3 days before the flight.[144] Advancement of more than this amount is likely to cause sleep disturbances and encroach too much on a conventional lifestyle. Discontinuous bright light in the morning was equally effective.[60] Melatonin could also be used to advance the body clock before eastward flights by ingestion in the evening in the days before departure.[12] Clock markers have shown that morning light advances the body clock, but an effect of evening melatonin has yet to be shown.

Sleep on flights should be avoided unless it is night by destination time. Although banking sleep when the individual feels most tired—probably at night by departure time—might seem advantageous, there is a risk that it will tend to anchor rhythms to the old time-zone. Taking melatonin or other short-acting hypnotics at a time when sleep would be appropriate by destination time has been shown to be useful in some studies.[128]

Phase advances in excess of 8 h are difficult to achieve since the natural period of the body clock is greater than 24 h and because of effects of the natural light-dark cycle. In these circumstances, adjustment by phase delay is fairly common,[125,126] and promotion of this adjustment is recommended. There is the added advantage that the time of poorest performance (initially at about 1400 h after a flight to the east across ten time zones) delays towards the evening rather than advancing through the early afternoon and morning.[50] Inter-individual variation means that, for some people, even phase advances as small as 7 h can cause difficulty, especially if the person's Tmin is later than average. In these cases also, phase adjustment by delay becomes common.

Table 2 shows the times when bright light should be avoided, but avoidance can be especially difficult after eastward flights, since the flight often lands early in the morning, soon after sunrise. Some have suggested that wearing dark glasses and reaching the dim indoor light of the traveller's destination as soon as possible is a solution,[4] but there is little pertinent evidence on the effectiveness of this method, and how dim the indoor lighting needs to be is unknown. Again, such considerations tip the balance in favour of phase-delaying rather than phase-advancing the body clock after eastward transitions across more than nine time zones (table 2).

Caffeine is a stimulant that is widely used to maintain daytime alertness; other stimulants are unnecessary, but modafinil is becoming more widely used and seems to be without side-effects.[145] Gentle exercise in bright light (sightseeing or a game of golf or tennis) is recommended as an alternative.

Although there is plenty of advice for travellers coping with jet lag, there are several areas where more work is needed. The effects of light treatment[138] and the chronobiotic action of melatonin, together with long-term toxicology trials of it and its analogues,[53,82,84,85,134,135] need to be investigated in field studies. The decrement in sports performance after time-zone transitions should be clarified further.[4,33] We also need more detailed understanding of molecular changes associated with time-zone transitions,[22,23] with a view to developing drugs to promote clock adjustment,[146] and further assessments of new sleep-promoting and alertness-promoting drugs.[143]

Conflict of interest statement

We declare that we have no conflict of interest.

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