How to Travel the World Without Jet Lag

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KEYWORDS

• Jet lag • Phase response curves • Melatonin
• Bright light • Sleep • Circadian rhythms

Several reviews on jet lag written by the authors[1,2] and others[3,4] have recently been published. The focus of this article is on describing in detail how melatonin, bright light, and sleep schedules can be used in conjunction with currently available flight times to reduce or eliminate jet lag. Our aim is to educate circadian rhythm researchers and sleep clinicians about the principles involved so that they can make similar jet travel schedules customized for individuals traveling in any direction across multiple time zones.

SYMPTOMS, HEALTH, AND SAFETY CONSEQUENCES OF JET LAG

Jet travel across multiple time zones produces jet lag, which includes difficulty initiating or maintaining nighttime sleep, daytime sleepiness, decreased alertness, loss of concentration, impaired performance, fatigue, irritability, disorientation, depressed mood, and gastrointestinal disturbances.[5–8] Jet lag is not just the bane of tourists; it can impair the judgment of business people and politicians, compromise the performance of athletes,[5,6] and pose a threat to public safety as it affects diplomats and the military.[9,10] In 2007, over 31 million US residents flew overseas, with about 12 million traveling to Europe and 7 million to Asia.[11] This census does not include military or government flights. Persons traveling for business and conventions took an average of 4.5 trips in the year.[11]

Frequent jet travel has long-term health risks. Cognitive deficits,[12] temporal lobe atrophy as determined by MRI scans,[13] and disturbances in the menstrual cycle[14] can all occur with frequent jet travel. Following transmeridian travel, it is likely that meals will be eaten at inappropriate circadian phases, and repeated occurrence of this could increase the risk of cardiovascular disease and type II diabetes.[15] There is an increased risk of cancer in flight attendants who frequently fly across many time zones.[16–18] Work in mice has shown that chronic jet lag accelerates the development of malignant tumors and reduces survival times.[19] Old mice subjected to weekly 6-hour phase shifts in the light-dark (LD) cycle died sooner when the LD cycle was advanced (equivalent to trips east across six time zones) than when it was delayed (trips west), and both groups died sooner than controls who were not shifted.[20] The effects of jet lag, both short and long term, are a public health issue that need to be addressed, and there is a need to prevent or at least minimize jet lag.

DURATION OF JET LAG AND WHY THERE IS MORE JET LAG AFTER FLYING EAST

Jet lag is caused by a temporary misalignment between the endogenous circadian clock,

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specifically the dorsomedial region of the suprachiasmatic nucleus,[21] which controls the body's circadian rhythms and the destination time zone and sleep/wake schedule. The symptoms of jet lag dissipate as the circadian clock is gradually reset (gradually phase shifts) to realign (re-entrain) to the time cues (zeitgebers) of the new time zone, primarily the LD cycle. Flying east requires a phase advance of the circadian clock, whereas flying west requires a phase delay. For example, when it is early in the day in the United States, it may already be approaching nighttime in Europe. Common language for persons living in the United States is to say that Europe is ahead of us, and that when you arrive there, you must set your wristwatch ahead by moving the hands later; however, your circadian clock has to be reset earlier, and the technical term is a *phase advance*. For example, if you flew east seven time zones (eg, Chicago to Paris) and expect to go to sleep at midnight in Paris, you are really trying to go to sleep at 5:00 PM according to the time of your circadian clock, which is still on Chicago time. You are trying to go to sleep earlier, to advance the time of your sleep, and your internal circadian clock has to phase advance to realign with your advanced sleep schedule and the new local time.

It takes longer to reset or re-entrain the circadian clock following eastward than westward flight,[22,23] which can be explained, at least in part, by the fact that the average free-running period (tau) of the human circadian clock is slightly longer than 24 hours.[24–26] Thus, most humans already have a natural tendency to drift slighter later each day, and it is much more difficult to phase advance the human circadian clock than to phase delay it,[27–29] even in older people.[30] Early estimates from real jet travelers are that the circadian clock phase delays 92 minutes per day after westward flights and phase advances 57 minutes per day after eastward flights.[22] Laboratory studies with an abrupt shift of the sleep/wake schedule, which mimic what happens after jet travel, show that the circadian clock can phase shift faster when people are exposed to bright light at the appropriate time. For example, in a study in which the sleep schedule was shifted 12 hours,[31] which is the largest possible shift, circadian rhythms shifted 9.6 hours over the first 4 days when they phase delayed (2.4 h/d or 144 min/d) and 6.2 hours when they phase advanced (1.6 h/d or 93 min/d, see Fig. 1 in the article by Eastman and Martin[28]). Previously we have developed jet travel plans assuming phase advances of 1.5 hours per day and phase delays of 2 hours per day, given appropriately timed bright light after landing.[32] These numbers are estimates, and, as explained herein, the exact magnitude of the phase shift will vary depending on the individual and the timing and intensity of bright light they receive at their destination. More research in real jet travelers is required to know the magnitude of the phase shifts that can be produced using schedules of bright light exposure and avoidance after landing.

The jet travel plans described later in this article do not include the large abrupt shifts of the sleep schedule typical after crossing many time zones, because this is what causes circadian misalignment. In the example with the 12-hour abrupt shift mentioned previously,[28] the circadian clock was still misaligned with the sleep schedule 8 days after the shift when the clock phase advanced and was just approaching complete re-entrainment 4 days after the shift when the clock phase delayed. Thus, for many days, jet lag symptoms would have been felt. This example also illustrates directional asymmetry, that is, the circadian clock phase delays faster than it phase advances. In the jet travel plans presented later, we use bright light to shift the circadian clock but we also gradually shift the sleep schedule to keep it aligned with the shifting circadian clock, avoiding circadian misalignment and jet lag. Before presenting these plans, we show what happens with an abrupt shift of the sleep schedule, which is what most people subject themselves to after flying across many time zones.

Fig. 1 shows what might happen to the circadian clock of a traveler, called Henry, marked by the time of his temperature minimum (Tmin) shown by the triangles. At home in San Francisco, Henry typically sleeps from 11:30 PM to 7:00 AM and remains on this sleep schedule in China, producing an abrupt 9-hour delay of his sleep schedule and an abrupt 9-hour advance after returning home. Under usual circumstances, the Tmin occurs about 3 to 4.5 hours before wake time with an 8-hour sleep episode.[33] While home, Henry usually only allows himself 7.5 hours of sleep. He cuts his sleep short by waking up earlier than would be natural (although he probably sleeps later on the weekends); therefore, we estimate his Tmin to be 3 hours before wake time at 4:00 AM. After the trip west from San Francisco to Beijing, his circadian clock phase delays 1.5 hours per day, and complete re-entrainment, with the Tmin in the same phase relationship to sleep (3 hours before waking), occurs 5 days after landing. In contrast, after the return flight east, his circadian clock may phase advance by 1 hour per day (shown by the filled triangles), and it takes much longer for complete re-entrainment to occur (9 days). However, it is possible that on his return flight his circadian clock will phase delay rather

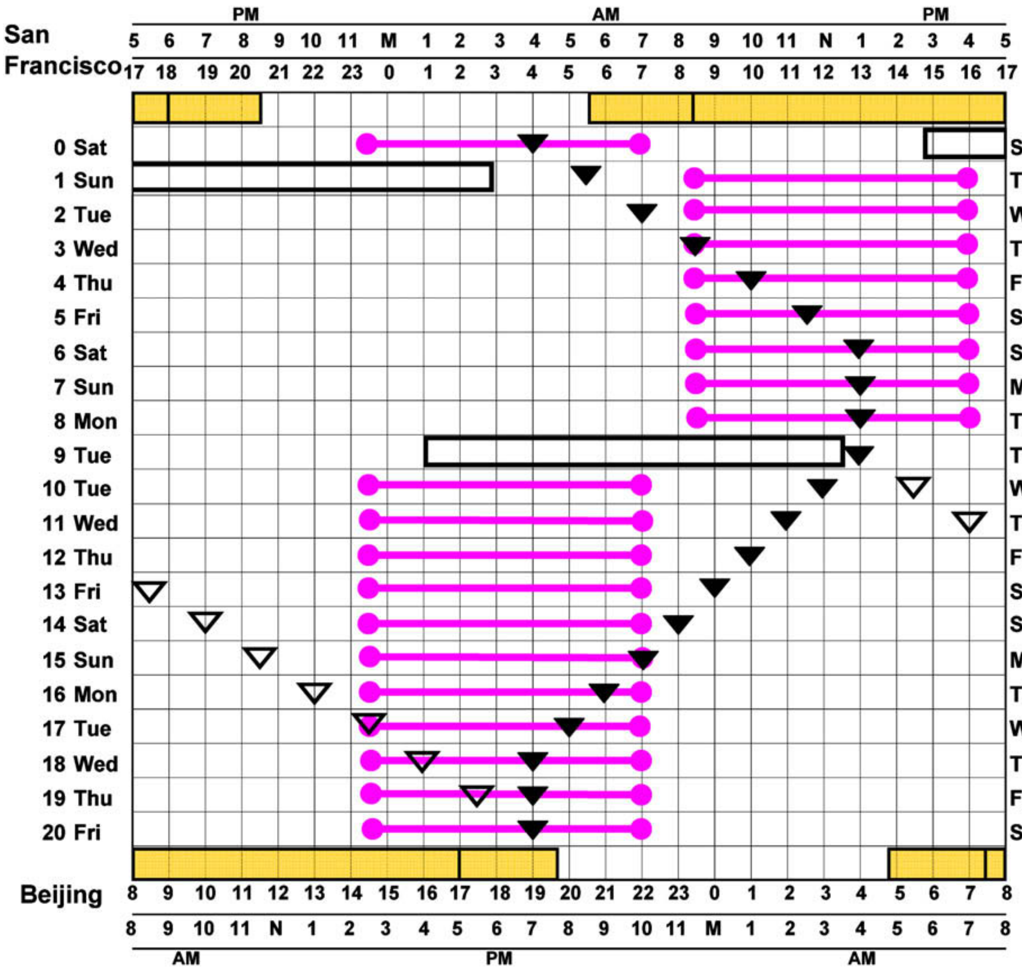

Fig. 1. Diagram showing a round trip flight from San Francisco to Beijing, China, across nine time zones. The rectangle on days 0 to 1 shows the time of the flight from San Francisco to Beijing (westward flight), and the rectangle on day 9 shows the return flight (eastward). The time lines on the top show the time in San Francisco (in daylight savings time), and the time lines on the bottom show the equivalent time in Beijing. The yellow horizontal bars show the maximum duration of the photoperiod (at the summer solstice), and the vertical lines within the bars show the minimum duration of the photoperiod (at the winter solstice). In-bed times (dark) are represented by the two circles connected by a line. This schedule shows what might happen to a traveler, called Henry, who usually sleeps from 11:30 PM to 7:00 AM and maintains that schedule while in Beijing. The triangle represents the temperature minimum (Tmin), a marker for the phase of the circadian clock, the sleepiest circadian time, and a rough marker for the crossover point from phase delays to phase advances in the light PRC. The Tmin phase delays by 1.5 hours per day after landing in Beijing until the original phase position of 4:00 AM is reached on day 6. After the return flight east (a phase advance of zeitgebers), two possibilities for re-entrainment are shown: (1) a phase delay of 1.5 hours per day (antidromic re-entrainment shown by the open triangles), and (2) a phase advance of 1 hour per day (orthodromic re-entrainment shown by the filled triangles). These daily phase shifts are the classic averages for phase shifts after flights as described by Aschoff and coworkers[22] but will be altered by the actual pattern of light and dark to which Henry is exposed. Because the Tmin quickly reaches the time for sleep after the trip west, Henry should have few days of jet lag. In contrast, after the return trip east, it takes a long time for the Tmin to reach sleep regardless of the direction of re-entrainment. The day of the week listed on the left and right sides changes at midnight, which is 9 hours later in the bottom time lines when compared with the top. On the days of the flights, it appears that Henry "gains" or "loses" a day (see the days of the week on the left and on the right), because he crosses the International Date Line twice. In reality, there are still 24 hours in a day. For the purposes of our descriptions, day numbers refer to the rows shown and do not change at midnight.

than phase advance (shown by the open triangles), and in this case complete re-entrainment will take 10 days. When the circadian clock phase shifts in the opposite direction to the shift in the LD cycle and sleep/wake schedule, this shift is considered re-entrainment in the "wrong" direction (antidromic re-entrainment).

Antidromic re-entrainment is common following eastward travel, especially when eight or more time zones are crossed.[23,34–37] For example, in one study[37] subjects flew eleven time zones east, and the circadian rhythm of endogenous melatonin was assessed before and after the flight. Seven of the eight subjects re-entrained by phase delaying instead of phase advancing. In another study with similar methodology,[35] six subjects flew eight time zones east but only four of them phase advanced. The melatonin rhythm of one subject phase delayed instead of phase advancing. Even more dramatic is that the melatonin rhythm of the sixth subject did not shift at all, even after 5 days in the new time zone (Los Angeles). Indeed, a previous study from the authors' laboratory has shown that phase advancing and phase delaying forces can conflict, resulting in essentially no phase shift.[27]

Jet lag symptoms are the worst when the Tmin occurs during the waking period, because the traveler will be sleepy in the hours surrounding the Tmin and will also have difficulty sleeping at times that are far from the Tmin. Even if adequate sleep is obtained (eg, because one uses hypnotics, because there is a lot of previous sleep deprivation, or because the individual is "phase tolerant"[38] and able to sleep at the wrong circadian phase), daytime activities will be impaired, especially near the Tmin. With age we become less phase tolerant,[39–41] and it follows that we will suffer more from the circadian misalignment of jet lag. Jet lag is not just due to loss of sleep on the day of travel. Such a sleep debt can be substantially "made up" the next night, but jet lag lingers due to circadian misalignment and the relatively slow moving circadian clock.

Henry (see **Fig. 1**) should start to feel good by day 3 after flying west to Beijing because his Tmin, which marks the sleepiest circadian time, will occur at the beginning of sleep, and it feels good to go to bed when you are very sleepy. This phase relationship is found in people living in temporal isolation who free-run with all of their rhythms synchronized (see Fig. 7 in the article by Eastman[42] and Fig. 17 in the article by Wever[24]). After the return trip east, if Henry's circadian clock phase advances (filled triangles), he should start to feel good by day 16, waking up slightly after the Tmin. We have previously stated that the goal for circadian adaptation to jet lag and to night shift work is to at least get the Tmin within the sleep episode.[28,43] However, when the Tmin is phase advancing into the sleep episode, it may be better to phase advance it 1 or 2 hours into sleep, because waking up at the sleepiest time is unpleasant. Eastman and Martin[28] have previously estimated that good sleep can be obtained for 6 hours before and 6 hours after the Tmin based on the results of several studies[44] and this interval may widen with increasing sleep debt. Henry should have the most difficulty maintaining sleep on day 2, and later on will have difficulty sleeping especially on days 11 to 14.

LIGHT AND MELATONIN PHASE RESPONSE CURVES

The most effective treatments for jet lag rely on shifting the circadian clock to the new time zone as fast as possible. To understand these schemes, one must understand phase response curves (PRCs). **Fig. 2** shows that bright light can help produce phase advances when applied late in the sleep episode and in the morning after the Tmin and can help produce phase delays when applied early in the sleep episode before the Tmin. Most human light PRCs show the crossover point from phase advances to phase delays around the time of the Tmin or a little later.[28,45–47] **Fig. 2** also shows that melatonin pills produce the greatest phase advances when taken in the afternoon and the greatest phase delays when taken in the morning. In the United States, melatonin pills are classified as a dietary supplement and are not approved by the Food and Drug Administration (FDA) for treating jet lag. Nevertheless, a wide body of research, including the melatonin PRC in **Fig. 2**, indicates that melatonin pills do effectively shift the circadian clock and are thus a useful tool for reducing jet lag. It is often said that the light and melatonin PRCs are 180 degrees out of phase, but **Fig. 2** shows this to be a bit of an oversimplification.

The light PRC can explain why Henry's circadian clock might phase delay rather than phase advance after the return flight east from China (ie, antidromic re-entrainment). In the first few days back home, days 10 to 12 in **Fig. 1**, if he spends more time outside before his Tmin than after, this light could push his circadian clock to phase delay (see Fig. 2 in the article by Eastman and Martin[28]) even though the zeitgebers and his sleep schedule advanced. We can also imagine that if he was exposed to enough phase advancing light on some days and phase delaying light on others, the net effect could be no phase shift at all. The authors have seen this occur in a laboratory study,[27] and it was observed in the traveler mentioned earlier who flew eight time zones east.[35] Travelers often develop superstitions about which procedures may help them overcome jet lag. It is probable that the time of landing combined with the light exposure during the first few days after landing explains most of the improvement commonly attributed to other factors such as diet or the amount of sleep obtained during the flight. Of course, sleep deprivation due to the flight will have its consequences, but, as mentioned earlier, one night of sleep deprivation can be mostly made up in a day, whereas jet lag can last much longer.

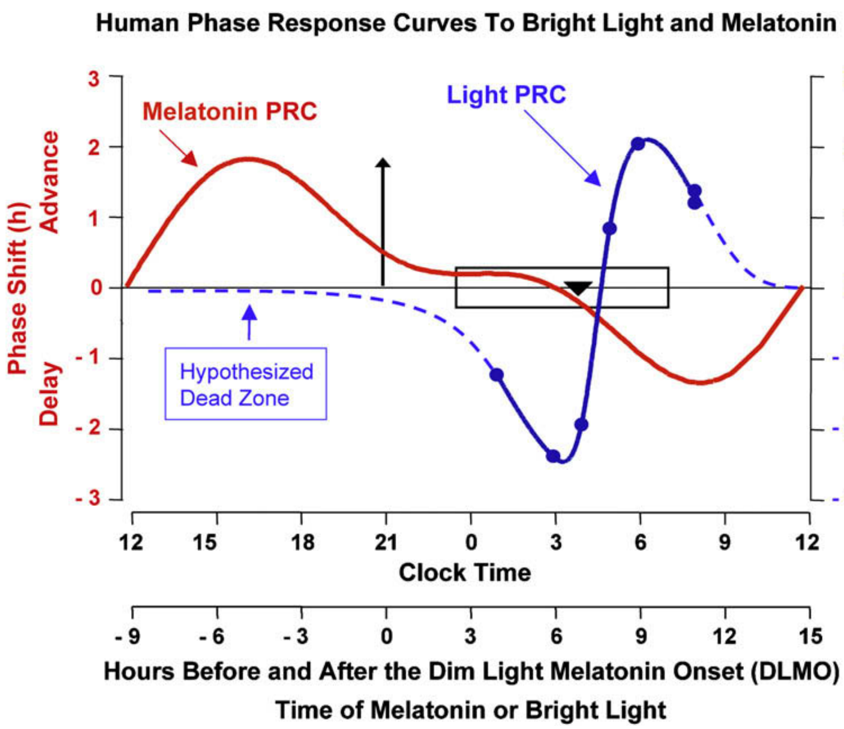

Fig. 2. PRCs generated from subjects free-running through an ultradian LD cycle (LD, 2.5:1.5) for three 24-hour days. Melatonin pills (3.0 mg) or bright light pulses (2 hours of ~3500 lux) were given each day, with different subjects receiving the zeitgeber at different times of day. Phase shifts were derived from circadian phase assessments conducted before and after the 3 days of free-running. The x-axis shows the time the pill was given or the time the bright light pulse began relative to each subject's DLMO, represented by zero on the bottom time line and the upward arrow. For convenience, we added a clock time axis for a subject with a DLMO of 21:00, a rectangle showing a typical entrained sleep time (starting 2.5 hours after the DLMO and lasting for 7.5 hours), and a triangle 7 hours after the DLMO showing the typical time of the temperature minimum (Tmin). The melatonin PRC is a curve fit to 27 points (27 subjects); the data points can be seen in the article by Burgess and coworkers.[83] The bright light PRC should be considered preliminary because there were only 7 points (7 subjects). The dashed sections correspond to times with no data points. This preliminary light PRC can also be seen in the article by Revell and Eastman.[1] The 2.5-hour interval from the DLMO to sleep onset was based on averages from our laboratory studies.[84,85]

Fig. 2 shows roughly equivalent magnitudes of phase advances for two specific doses of melatonin and bright light. The melatonin dose of 3.0 mg is typically sold over the counter as a sleeping aid and produces pharmacologic levels of melatonin. The light level of 3500 lux is more intense than what is usually obtained indoors and is produced by bright light boxes. Outdoor sunlight is even more intense, ranging from about 10,000 to 100,000 lux. The roughly equivalent maximum phase advances in these two PRCs may be a surprise to many circadian rhythm researchers who consider bright light to be more powerful at phase shifting the clock. Part of this preconception comes from a comparison between previous light PRCs in which the sleep/dark episode was shifted many hours in a laboratory[48] and the melatonin PRC in which sleep was at home and was not shifted; therefore, the magnitude of the phase shift was constrained by entrainment to the 24-hour day.[49] In the authors' PRCs shown in Fig. 2, the subjects were free-running and free to phase shift without constraint. To more accurately compare PRCs for light and melatonin, they need to be generated using the same protocol. Thus far, only the authors' PRCs in Fig. 2 are available for such a comparison; however, even the comparison in Fig. 2 is preliminary because the light PRC has so few points. The fact that there are roughly equivalent phase advances and a slightly larger phase delay with light given these two particular doses should be considered preliminary.

Fig. 2 shows that the light and melatonin PRCs have times of reduced sensitivity when the zeitgeber has very little phase shifting effect. These periods are often called "dead zones" and are a common feature of PRCs.[50] The dead zone in the light PRC in our figure is hypothetical because we do not yet have data in that region, but some other human light PRCs appear to have minimal phase shifts there in the middle of the day.[47] In contrast, the human bright light PRC does not have much of a dead zone when generated in protocols containing a sleep/dark episode that is shifted.[48,51] In these protocols, not only is bright light applied in the middle of the day, but the slight shift of sleep/dark permits dim light to impinge upon the sensitive portions of the PRC. This dim light could be responsible for the small phase shifts. In any case, humans are like other animals in that the timing of the circadian clock is not strongly affected by bright light in the middle of the day.

The dead zone in the 3-mg melatonin PRC shows that melatonin taken 1 or 2 hours before usual sleep onset and in the first half of the usual sleep episode will not greatly phase shift the clock. One explanation for this is that the dead zone begins when endogenous melatonin is first secreted from the pineal gland, marked by the dim light melatonin onset (DLMO), and ends several hours later on the falling limb of the melatonin profile after the pineal gland has shut off or greatly reduced its production of melatonin, a time often referred to as the SynOff.[52] Thus, exogenous melatonin has more of a phase shifting effect when there is less endogenous melatonin in the circulation, just like bright light has more of a phase shifting effect at night when bright light is ordinarily not present.

Fig. 3 shows that melatonin PRCs to different doses of melatonin have different shapes, just as light PRCs to different durations of light have different shapes.[53] The maximum of the phase advance portion of the 3-mg PRC is a few hours earlier than for the 0.5-mg PRC. Our working estimates for the best times to take these doses to help produce the largest phase advance are as follows: take the 3-mg dose 5 hours before the DLMO (7.5 hours before usual sleep onset or 12 hours before the Tmin), and take the 0.5-mg dose 2 hours before the DLMO (4.5 hours before sleep onset or 9 hours before the Tmin). Our recommended times for the 0.5-mg dose are based on a PRC to which there is no curve fit;[49] therefore, our estimates of the optimal time to take the 0.5-mg dose vary slightly depending on what curve fitting procedures are used (see Fig. 1 in the article by Revell and Eastman[1]). A further caveat to directly comparing these two melatonin PRCs is that they were generated from different protocols. We are currently generating a 0.5-mg PRC using the same method used to generate the 3.0-mg PRC, with subjects free-running through an ultradian LD cycle, so that we will have a better comparison of the PRC shapes with these different doses of melatonin in the near future. The working estimates mentioned previously for giving these doses for maximum phase advances are more precise when using the numbers relative to the DLMO than those relative to sleep onset or the Tmin. Both of the melatonin PRCs were generated using the DLMO as a phase marker, whereas the times for sleep onset and the Tmin were derived from the DLMO based on averages from our studies and others.[54–56] Of course, we often do not know the time of an individual's DLMO unless we invest the time and money to measure it. Most often, the advice on when to take melatonin is referenced to the individual's typical sleep onset time. Despite these limitations, if the timing of the

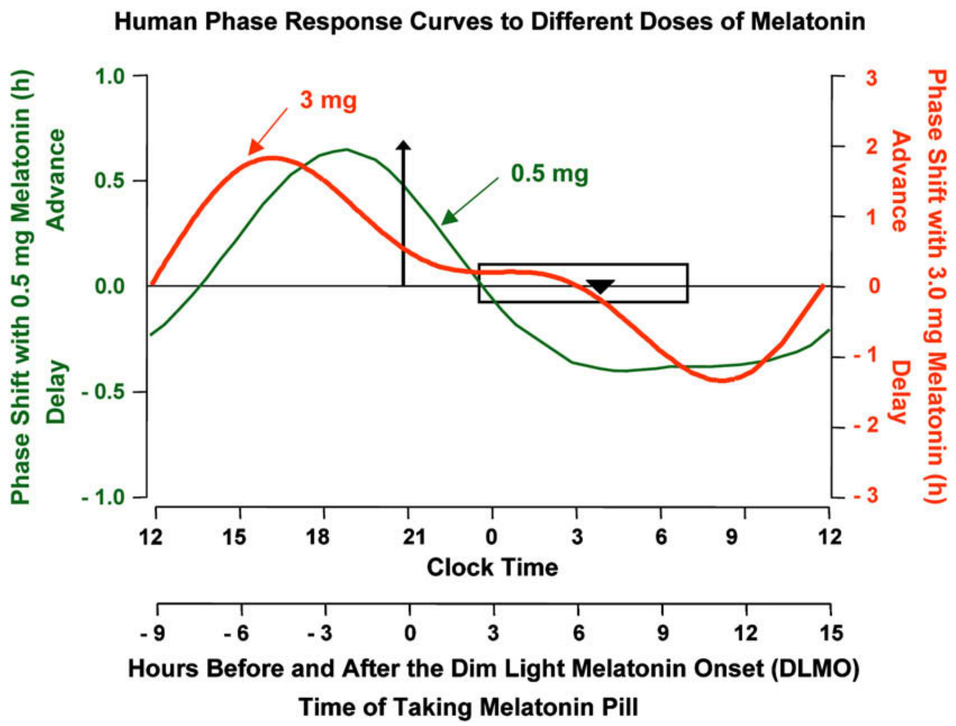

Fig. 3. The melatonin PRC to 3.0 mg from **Fig. 2** and a melatonin PRC to 0.5 mg. The curve for 0.5 mg was fit to the data reported by Lewy and coworkers.[49] Note the different y-axes for the different doses. This difference is probably not due to the difference in dose but rather to the difference in protocols (ie, free-running subjects for 3.0 mg and entrained subjects for 0.5 mg). These PRCs show that the 3.0-mg dose needs to be taken earlier than the 0.5-mg dose to produce the maximum phase advance.

dose ends up being about 2 hours earlier or later than the ideal (relative to the DLMO), it will still fall within a high amplitude part of the advance portions of these melatonin PRCs and will help to phase advance the circadian clock (see **Fig. 3**).

Obviously there is a need to generate PRCs to different doses of melatonin besides 0.5 and 3 mg. Other doses are available over the counter and on the Internet in the United States. However, we have chosen to start with these two doses because the 0.5-mg dose is a low dose intended only for phase shifting the circadian clock and for which sleepiness is an unwanted side effect, and the 3.0-mg dose is a large pharmacologic dose marketed primarily for its soporific effects. Despite melatonin often being marketed as a sleep aid, it is not universally associated with sleep or increased sleepiness because, in nocturnal animals, melatonin is associated with waking activity. Instead, the release of melatonin appears to signal darkness.

HOW TO MINIMIZE OR AVOID JET LAG

Given the knowledge of when to apply bright light or give melatonin pills to get the largest phase shifts, how can we help Henry minimize or avoid jet lag? **Fig. 4** shows one possibility. Henry uses a bright light box in the 2 hours before sleep the two nights before the flight to China. Commercially available light boxes are usually advertised for the treatment of winter depression or seasonal affective disorder, but these boxes are also useful for helping to phase shift the circadian clock, and therefore minimize or avoid jet lag. In addition to using the light box, Henry goes to bed 2.5 hours later on day −1, which helps place the bright light exposure closer to the Tmin and into a higher amplitude part of the phase delay portion of the light PRC (see **Fig. 2**). He delays bedtime by 2 hours for the next two nights to keep up with the phase delaying circadian clock and its PRC, which is also phase delaying, so that the bright light will continue to coincide with the delay portion of the light PRC. The bright light on day −1 helps push the Tmin 2 hours later from 4:00 to 6:00 AM, and the bright light on day 0 helps phase delay the Tmin another 2 hours to 8:00 AM. Bright light is avoided after waking (indicated by the Ds) because it could coincide with the phase advance portion of the light PRC. During this time Henry would do well to wear dark sunglasses if he needed to go outside. For the same reason, it is necessary to sleep in a dark bedroom or, if that is not possible, to use an eye mask while in bed. An early study in which the sleep schedule was delayed 2 hours per day and bright light from light boxes (about 2000–4000 lux) was used in the 2 hours before bed showed that the Tmin of most subjects entrained to the 26-hour day (ie, they phase delayed by 2 h/d);[57] therefore, a phase delay of 2 hours per day is a reasonable estimate when a light box is used. After landing, the light exposure that Henry receives (days 1–3) is unpredictable and dependent on his activities, the weather, and the temperature in Beijing; therefore, we show his Tmin phase delaying by only 1 hour per day. Because a study of subjects kept in room light (70 lux) showed that the circadian clock phase delayed by about 1 hour per day with a sleep schedule delay of 2 hours per day,[58] we believe that a rate of 1 hour per day is a reasonable estimate for how Henry's circadian clock will phase delay after landing. If Henry happens to be exposed to enough bright light before bed, his circadian clock might phase delay even faster. The phase delays stop when complete re-entrainment is reached.

To phase advance his circadian clock back to San Francisco time, Henry uses bright light in the morning and melatonin in the afternoon (days 8–15). He also advances his sleep schedule by 1 hour per day. In a recent study, we showed that a 1 hour per day advance of the sleep schedule combined with intermittent bright light from light boxes (~5000 lux) for the first 3.5 hours after waking and melatonin in the afternoon phase advanced the circadian clock by about 1 hour per day. Furthermore, this regimen did not produce jet lag type symptoms.[59] We found no difference in the magnitude of phase advance when a 0.5-mg dose was taken (on average 2.4 hours before the DLMO) and when a 3.0-mg dose was taken (on average 4.8 hours before the DLMO). These circadian times of administration coincide with the highest amplitude parts of the advance portions of the respective PRCs, close to our working estimates for optimal times of 2 hours and 5 hours before the DLMO. Although there was no significant difference in phase shift between the two doses, there was a slight difference in the sleepiness they produced. The 3.0-mg dose made our subjects slightly, although not significantly, more sleepy, whereas sleepiness after the 0.5-mg dose was almost identical to after placebo (see Fig. 6 in the article by Revell and coworkers[59]). To be safe and to avoid the mild soporific effects of melatonin, we have Henry use the 0.5-mg dose. On day 8, he takes it 4.5 hours before bedtime and 1 hour earlier each day. He could use a light box in the morning to help phase advance his circadian clock, but, because it is daylight in San Francisco, we recommend he go outside as much as possible because natural light

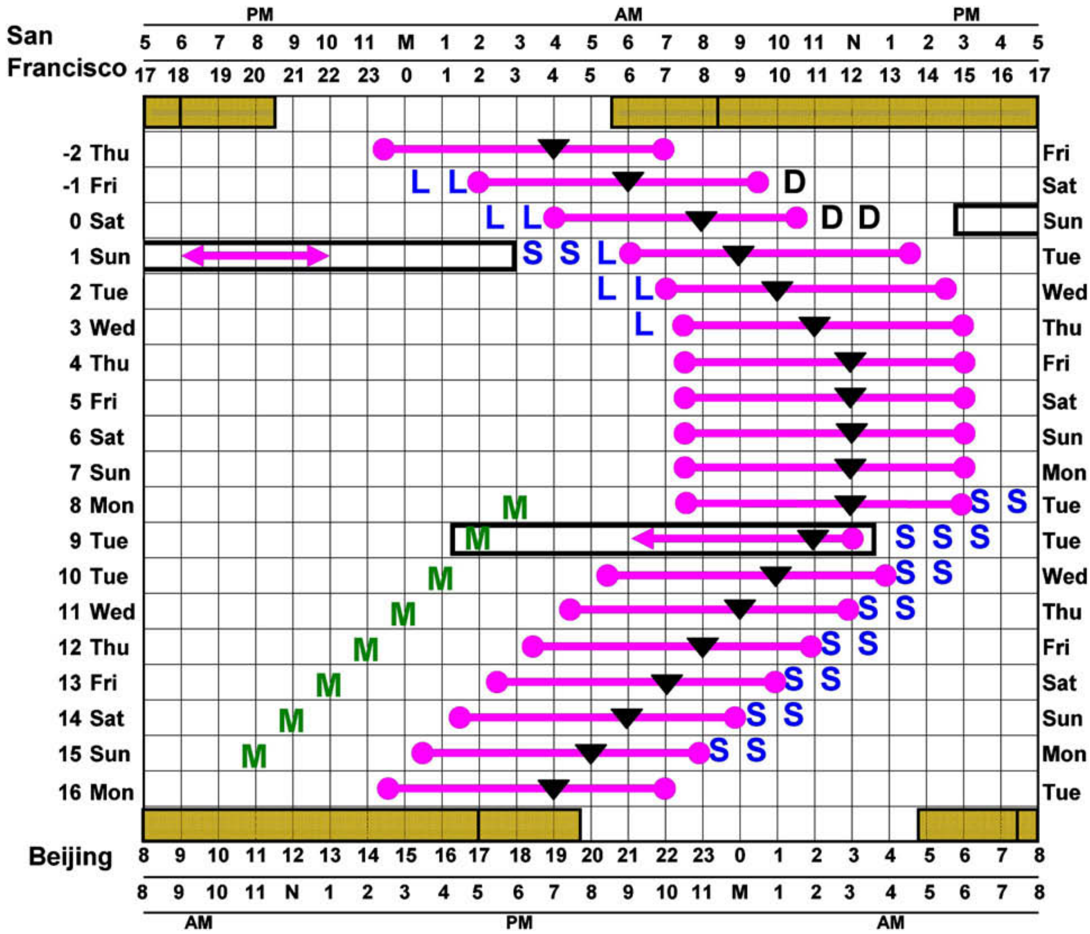

Fig. 4. The same flight schedule shown in Fig. 1 but, in this case, Henry gradually changes the time of his sleep episodes (dark), controls light exposure, and takes melatonin to phase shift his circadian clock and avoid circadian misalignment and jet lag. Bright light can be obtained by going outside (S indicates sunlight exposure) or from a light box (L), but S is always preferable to L. Intermittent bright light exposure should be sufficient during the times indicated. A light box is needed for days −1 and 0; Henry can seek brightly lit places for the Ls during the next few days in Beijing. The Ms on days 8 to 15 indicate 0.5 mg of melatonin, timed to coincide with the maximum phase advance portion of the 0.5-mg melatonin PRC. This low dose should not make Henry sleepy. The Ds indicate the times to stay indoors and avoid bright light or, if it is necessary to go out, to wear very dark sunglasses. Note that Henry stays on a slightly earlier sleep schedule while in Beijing compared with when home. The 10:30 PM to 6:30 AM sleep schedule makes it quicker and easier to phase advance back to San Francisco time after the return flight home. The sleep line within the rectangle on day 1 shows that it is OK to sleep on the plane, and the best time for a nap (siesta time in the middle of the day) is indicated. It is good to nap whenever the sleep episodes are gradually delaying. The sleep line within the return flight rectangle on day 9 starts with an arrow indicating it is OK to go to sleep earlier, which is true whenever a schedule has gradually advancing sleep episodes.

is almost always more intense than the light from light boxes and should have a greater phase shifting effect. We also recommend that he gradually change the time of his meals to keep them aligned with his circadian clock. Henry's circadian clock represented by the Tmin and his sleep schedule remain aligned; therefore, he should be free of the physiologic symptoms of jet lag, the suppression of endogenous melatonin by light, and, we believe, from the health hazards of circadian misalignment.

There are individual differences in the magnitude of phase shifts produced by bright light even in strictly controlled laboratory studies. What would happen to Henry if his circadian clock did not phase delay as much as 2 hours per day from days −2 to 0? There are two consequences: (1) it might take a few more days for complete re-entrainment, and (2) he might have trouble sleeping as late as planned (sleep maintenance insomnia) while the Tmin was very early within the sleep episode. Especially for early birds, who probably have shorter taus[60] and thus more trouble phase delaying, we recommend starting the light box treatment even before the sleep schedule is shifted, in this case on day −2, and/or delaying sleep by only 1 or 1.5 hours per day rather than 2 hours per day. The initial delay of bedtime on day −1 of 2.5 hours might be difficult for early birds, although it should be no trouble for night owls. If the traveler does not know whether he or she is an early bird or a night owl, most likely he or she is not either extreme. For most people, if scheduling permits, it would be even better to start the delaying schedule and light treatment a few days earlier than shown and to use a slow delay of the sleep schedule (ie, 1 h/d).

What would happen if Henry's clock did not phase advance as much as shown in **Fig. 4** (1 h/d) after the return flight east? His Tmin would gradually move later within the sleep episodes, and he might have difficulty falling asleep (sleep onset insomnia) and would feel sleepy upon waking. He would experience what extreme night owls or people with a delayed sleep phase live with every day when they try to conform to the 9 to 5 or 8 to 6 early bird world. This slight circadian misalignment is undesirable but is certainly not as bad as the massive circadian misalignment most travelers are subjected to when they abruptly shift the time of their sleep by several hours. We conducted a study in which the sleep schedule was advanced by 2 hours per day and intermittent bright light from light boxes was used upon waking in the morning in the hope of producing larger phase advances;[61] however, the circadian clock only phase advanced slightly more than when the sleep schedule was advanced by 1 hour per day, and the difference was not statistically significant. We deduced that circadian misalignment, with the Tmin occurring slightly after wake up time, occurred on average after the second advanced sleep episode; therefore, we do not recommend advancing the sleep schedule more than 1 hour per day. Furthermore, when scheduling permits, and especially for night owls who probably have longer taus, we recommend advancing by even less than 1 hour per day (eg, 0.5 h/d). Night owls might need more bright light in the morning to use a sleep schedule advance of 1 hour per day. Alternatively, they could choose to follow a delaying schedule for flying east.

We recognize that Henry might not be able to maintain the sleep schedule shown in **Fig. 4** upon his return to San Francisco or in the 2 days before the flight to China depending on his work and family commitments. However, given the increasing prevalence of flex time and working from home (telecommuting), he may be able to arrange it, especially with some advance notice. When people first hear about such sleep schedules and light treatments they sometimes develop the misconception that it will take too much time; however, after careful explanation, they understand that it only requires a rearrangement of time. For some people the scheduling and planning required to rearrange meetings and activities can seem overwhelming. Our Henry is in charge of his own work schedule and has no objection to following the prescribed sleep schedule. If he chooses to use a light box in the morning on days 10 to 15 rather than go outside to get his bright light exposure, he can do many activities while sitting there, such as reading, writing, working on a computer, watching television, eating, or talking on the phone. The intermittent nature of the light treatment means that, with a little bit of planning, he can get up to shower, dress, or prepare breakfast without interfering with the treatment. He could also get some of his bright light exposure from natural outdoor light while commuting to work. Another alternative would be to have a second light box at work to start the bright light exposure at home and do the rest at work. This approach would work well for people with desk jobs. We envision a future in which companies keep light boxes on hand for this purpose. After all, it is in their best interests to have a highly functioning employee rather than one who is sleepy and jet lagged.

A large variety of commercial light boxes are marketed for jet lag and seasonal affective disorder. We recommend boxes with the largest illuminated area because they are easier to sit in front of without having the head move out of range and are usually less intense and less aversive. One advantage of the very small light boxes is that they could be taken to work or on the plane and used overseas (providing the box is battery powered or able to process any variations in voltage that may occur). Light boxes that are enriched with blue wavelengths or that produce only blue light are currently in vogue because the circadian system is most sensitive to blue light;[62,63] however, we have shown that the older light boxes with cool white fluorescent lamps produce the same magnitude of phase shifts as those observed with blue-enriched fluorescent light in protocols with gradually advancing or gradually delaying sleep schedules.[64,65]

The melatonin PRCs (see **Fig. 3**) show that melatonin could be taken in the morning to help Henry when he needs to phase delay his circadian clock. We did not include it in the jet travel plan (see **Fig. 4**) because we have no experimental evidence that it would increase the phase delay produced by the bright light before bed. A 2 hour per day phase delay may be the maximum one can delay the circadian clock while using a gradually delaying sleep schedule. Furthermore, the 3.0-mg dose could make him sleepy, and we will not know the optimal time to give the 0.5-mg dose to produce delays until we generate our own 0.5 mg PRC.

Let us now consider a traveler, called Susan, who flies from Chicago to Paris and does nothing to phase shift her circadian clock before the flight. Fig. 5 shows what she can do to try to minimize jet lag, but this last minute approach has many problems. Obtaining outdoor light exposure and avoiding it at the appropriate times may be difficult due to weather or scheduled indoor or outdoor activities. If she happens to experience the wrong pattern of light exposure in the first few days in Paris (ie, a lot of bright light before her Tmin and none after), she could suffer from antidromic reentrainment (her circadian clock could phase delay), or her clock might not shift at all. Furthermore, even under the best circumstances, several days are wasted because of extreme circadian misalignment and jet lag. Susan will not be back to normal until 5 days after the flight, when she is waking up slightly after the Tmin.

Several publications, commercial computer sites, and programs and devices are available to tell the traveler when to seek and when to avoid outdoor light in the days after landing. For more discussion of several of these sources, the reader is referred to the article by Eastman and colleagues.[61] Although these schemes are based on the light PRC, they differ in ways which can result in completely opposite, and often incorrect, instructions for the traveler. For example, most expect the circadian clock to phase advance much faster than our 1 hour per day estimate. If the time scheduled for bright light exposure each day changes faster than the shifting of the circadian clock, the bright light could end up falling on the wrong side of the crossover point (other side of the Tmin) and hinder rather than help produce phase advances. With our preflight schedules, there is little danger of this because the bright light is applied far from the crossover point (Tmin), and knowing the exact time of the crossover point is not as crucial as it is when bright light exposure and avoidance are started after landing.

We recommend resetting the circadian clock at least partially toward the destination time zone before flying. Fig. 6 shows an example for Susan's trip to Paris. Four days before the flight she takes

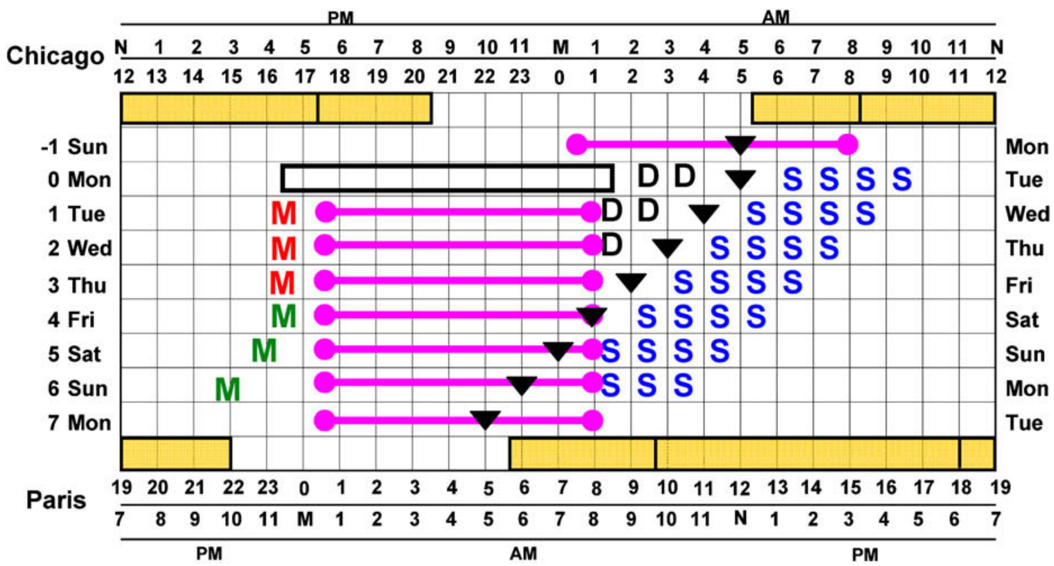

Fig. 5. Diagram showing a flight from Chicago to Paris, seven time zones east, with both time lines in daylight savings time. Other symbols are the same as in Figs. 1 and 4, with green Ms for 0.5 mg melatonin and red Ms for 3.0 mg melatonin. This schedule shows what might happen to a traveler, called Susan, who usually sleeps from 12:30 AM to 8:00 AM and does not do any preparation to avoid jet lag until after landing in Paris. On arrival, she is careful to get the ideal light exposure pattern to help phase advance her circadian clock to Paris time according to the light PRC; however, regardless of how much sleep she obtains at night, she will be sleepy during the day, especially in the hours around her Tmin (the triangles). Susan takes melatonin before bedtime on days 1 to 3, a large dose of 3.0 mg, to make her slightly sleepy and help her fall asleep so early (relative to home time). It will also help phase advance her clock according to the 3.0-mg melatonin PRC. On day 4 she switches to the smaller dose of melatonin, 0.5 mg, because her circadian clock has phase advanced so far that the 3.0-mg dose would no longer coincide with the times for maximum phase advances in the 3.0-mg PRC. She takes the 0.5-mg dose at the ideal times for maximum phase advances according to the 0.5-mg melatonin PRC. Susan's circadian clock phase advances by 1 hour per day. Her Tmin reaches the sleep episode by day 4, at which time her circadian misalignment and jet lag symptoms should start to subside. We do not think that this schedule is the best solution, because circadian misalignment is pronounced during the first few days after landing.

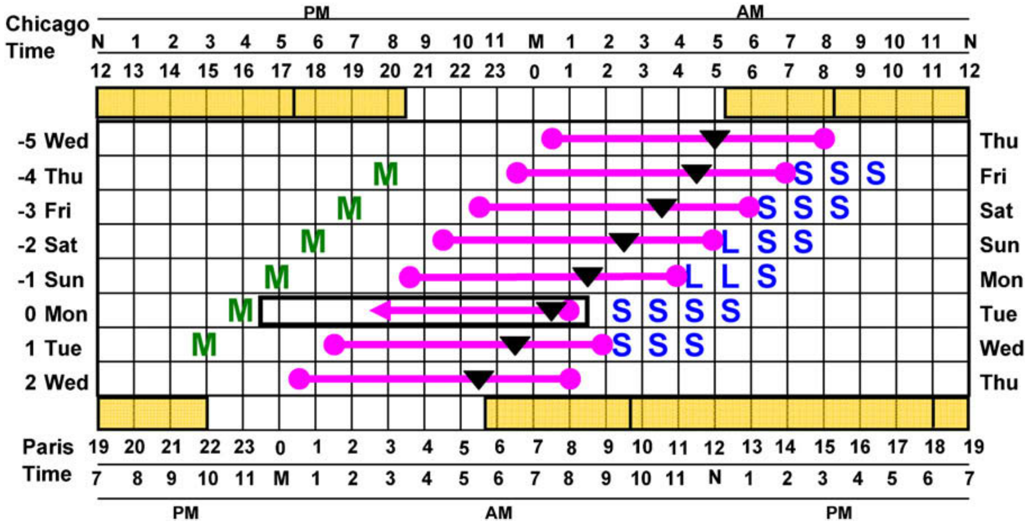

Fig. 6. Same flight schedule shown in Fig. 5 but, in this case, Susan uses melatonin and light exposure to phase advance her circadian clock toward the destination time zone before the flight and avoids circadian misalignment and jet lag. She advances her sleep schedule by 1 hour per day. She exposes herself to bright light in the morning either by going outside (S), which is best, or by using a light box (L) when it is before sunrise or otherwise impractical. She takes 0.5 mg of melatonin in the afternoon timed to produce the maximum phase advance according to the 0.5-mg melatonin PRC. This low dose should not make her sleepy. The arrow within the flight indicates that this is a good time to sleep and that going to sleep earlier is encouraged, as it is whenever the sleep schedule is gradually advanced.

0.5 mg of melatonin 4.5 hours before her usual sleep onset. That night she goes to bed 1 hour earlier than usual and wakes up 1 hour earlier than usual. She gets intermittent bright light in the morning, preferably by going outside. The whole schedule is advanced by 1 hour per day. Depending on the time of year, at some point she will be waking up before sunrise and will need to use a light box (Ss change to Ls). After landing (day 0), all of the bright outdoor light she receives will help phase advance her circadian clock because none will occur before her Tmin. This approach will prevent antidromic re-entrainment. Her circadian clock and her sleep schedule remain aligned throughout, and she should have little or no jet lag. It may be difficult for her to fall asleep early on the first night (day −4), but if she thinks that will be a problem she can minimize it by starting the melatonin and bright light even before shifting her sleep schedule (on day −5). If she can fly business or first class, she may be able to sleep on the plane; it will be the ideal circadian time for her to sleep, and she should arrive with little sleep deprivation. If she has to fly coach, she may arrive slightly sleep deprived; however, one night of sleep deprivation can largely be made up in a day, whereas jet lag can last much longer.

Obviously, a schedule like this (see Fig. 6) can be made for flying east across different numbers of time zones, not just seven, and contain more or less days of phase advancing before the flight. The more days of phase shifting before the flight, the less jet lag after landing and the quicker the remaining jet lag will dissipate. We have made personalized advancing schedules like these for ourselves, friends, and colleagues. They usually report little trouble falling asleep or waking up earlier following the sleep schedule before the flight, which makes sense because their circadian clocks are phase advancing. The most troubling inconvenience to them is missing out on evening social and family contacts because of the early bedtimes. The importance of a few nights of social contacts has to be balanced with that of optimal performance and alertness for several days after landing. A key point is that even just 1 or 2 days of a preflight shift will help reduce the subsequent jet lag.

As mentioned previously, it is easier for most people to phase delay than to phase advance; therefore, especially for night owls, if scheduling permits, it would be better to delay the sleep schedule before flying east rather than to advance it. Intermittent bright light should be used in the 2 hours before bed (see the first few days in Fig. 4). The decision of whether to try to phase advance the circadian clock or phase delay it before flying east depends on the number of time zones crossed, the sleep schedule desired at the destination, whether the individual is an extreme along the morningness-eveningness continuum, and the scheduling constraints of the individual. Even general guidelines, such as phase advance the circadian clock for crossing up to seven time zones east and phase delay the clock for crossing eight or more time zones east[1,32,66] may not always apply to all travelers. For example, one of the authors and her husband, who are night owls, always delay their sleep schedule by 2 hours per day before flying east, even across only six time zones. The advantage for a night owl is that the delaying schedule can be stopped a few days early, leaving the individual on an early schedule at the destination.

DRUGS ONLY MASK JET LAG AND ARE LIMITED IN THEIR EFFECTS

With no preparation before jet travel and random light exposure on arrival, the nighttime insomnia and daytime sleepiness often associated with jet lag can be treated with drugs and naps as a last resort. In this scenario, one treats the symptoms only, and the cause, the underlying circadian misalignment, will continue until the circadian clock finally re-entrains to the new time zone. Re-entrainment to the new time zone may take a week or more (see **Fig. 1**) or longer still if you are unfortunate enough to suffer from a clock that does not initially shift.[35] Pharmaceutical treatment of jet lag symptoms, such as with caffeine[67] and hypnotics[68–70] or large doses of melatonin at bedtime for its soporific effect[9,67,69,71,72] will not eliminate jet lag. Research indicates that although hypnotic medications can improve sleep quantity, sleepiness will still be felt around the Tmin when it occurs during waking hours.[73–75] Caffeine can be used during the day, but even moderate doses taken well before bedtime will impair sleep[76] (although this effect may be overridden by further uses of hypnotics). Furthermore, stimulants such as caffeine,[77] modafinil (Provigil),[78,79] and even bright light exposure[80] and prophylactic naps[77] can all improve alertness and performance but do not return them to normal levels while the underlying circadian misalignment persists. Modafinil is not yet FDA approved for treating jet lag related sleepiness. All drugs have some risks for abuse and dependence, some hypnotics may produce morning hang-over effects,[81] and short-acting benzodiazepines have been associated with transient global amnesia when taken for jet lag.[82]

SUMMARY

In this article we have explained the circadian principles behind how to phase shift the circadian clock with bright light and melatonin and have presented current light and melatonin PRCs that indicate the correct timing of these zeitgebers to produce the desired phase shifting effect. We have provided detailed examples of a few jet travel plans and hope that you are now equipped to devise your own. If you have difficulty doing this, you are invited to contact us for advice.

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