Chapter 5

Jet Lag

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Additional information is available at the end of the chapter

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Abstract

This chapter describes the phenomenon of Jet Lag and the symptoms associated with it, which vary not only from person to person, but also according to how many times zones are crossed, and in which direction. Homeostatic and circadian influences on sleep and vigilance are explained on the basis of Borbély's two-process model. Jet Lag is reasonably well explained scientifically today: rapid changes of time zones disturb the functioning of the body clock, which remains stubbornly set on departure times for a while. This can make sleep shallow or non-existent for substantial parts of the night while vigilance is less than optimal during parts of the day. Two main lines of research are described: one endeavors to accelerate the adaptation process; the other helps to fight insomnia and sleepiness between arrival and adjustment to the new time zone. Besides practical things that can be done to reduce the burden of Jet Lag, the adjustment process can be speeded up using bright light and melatonin. Sleeping pills and neurostimulants may be added to compensate for insomnia and sleepiness.

Keywords: chronobiology, circadian, circadian clock, homeostatic, Jet Lag, sleep debt, sleep inertia, sleepiness, time zone, vigilance, light, melatonin

1. Introduction

Jet Lag is a phenomenon that annoys to varying degrees the millions of people who travel across time zones each year. Its causes are relatively easy to understand.

Jet Lag results from a mismatch between the actual time in the arrival zone, and the internal time, which is set by the internal body clock (see below), itself reflecting the preceding time zone.

Its main symptoms include sleepiness at odd times during the day, and insomnia at night. They vary according to several variables, from individual sensitivity to age, to flight direction (East or West), to number of meridians crossed, to length of stay and to seasons.

Jet Lag treatment remains difficult, as no simple remedy is available, yet. As long as the earth keeps spinning round and our genome is not modified, the bad news is that Jet Lag is here to stay. Probably, some day it will be possible to turn the body clock forward or back and reset it immediately to the new time zone, but such a procedure has yet to be discovered. The natural process of adjustment to new time zones is efficient but slow.

In this chapter, we review the scientific literature on Jet Lag origin, describe its symptoms in more detail, and see what can be done about it.

2. What is Jet Lag?

2.1. Definition

The American Academy for Sleep Medicine (AASM), in the second edition of its International Classification of Sleep Disorders [1] defined Jet Lag (circadian disorder, Jet Lag type), as a disorder "related to a temporal mismatch between the timing of the sleep-wake cycle generated by the endogenous circadian clock produced by a rapid change in time zones." In other words, it results from crossing time zones too rapidly for the circadian clock to keep pace.

2.2. Sleep propensity in humans: circadian and homeostatic

2.2.1. Circadian influences

In mammals, periods where sleep is favored alternate with periods where it is not. The timing, the duration and the frequency of these periods are regulated in part by the circadian body clock (see below). Timing, duration and frequency also vary across species.

Mice for instance sleep in between 40 and 120 bouts of a few minutes per day-night periods (polyphasic sleep). Human infants also show polyphasic sleep, as infants frequently wake up at night and sleep partly during the day. Most of the time, sleep episodes progressively converge to monophasic sleep with growing age, until one large sleep episode occurs at night. This monophasic organization of sleep is somewhat challenged in older life and there may be a return to forms of polyphasic sleep.

Sleep propensity in humans is maximal at the beginning of the night, moderate in the afternoon, and minimal during the morning and the evening. In parts of the world where working is difficult in the afternoon for climatic reasons, sleep has been observed to come in two phases (biphasic sleep). As our distant ancestors came from tropical areas where work is harder when the sun is high, this biphasic organization of sleep may well have been the first one to have appeared, which might explain a biphasic design.

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2.2.2. Homeostatic influences

The propensity to sleep is also a function of the time lapse since the last sleeping episode. The longer the time since the last sleeping episode, the stronger the pressure to enter sleep.

2.2.3. Result of two processes

Propensity to sleep is thus the result of two processes, one circadian and one homeostatic. The combination of these two processes has been first modelized by Borbély [2]. The relative weight of the two processes against each other has not been determined to the day, but I assume that they are roughly equivalent.

The intensity of both processes (circadian and homeostatic) is minimal in the morning after a normal episode of sleep, which favors awakening. As the homeostatic pressure has already decreased and the circadian influence allows for some sleep, a tendency to nap may be observed in the afternoon. The processes are at odds in the evening—the homeostasis favoring sleep but the circadian factor opposing it—which explains why it is difficult to enter sleep at that time of the day. The processes converge at the beginning of the night, hence favorizing sleep.

2.3. Body clock (inner clock, internal clock, circadian clock)

Like other mammals, human beings have a circadian clock, a paired group of nuclei in the base of the hypothalamus—the suprachiasmatic nuclei. They receive information from the retina about external light. These data allow for a daily-based correction and synchronization with the daily cycle of light and dark. The suprachiasmatic nuclei are considered together to represent the "master clock" of the brain, synchronizing a series of hormones (such as melatonin, cortisol and growth hormone), behaviors and other more specialized body clocks (core body temperature, rapid eye movement sleep, for instance).

The actions of the suprachiasmatic nuclei monitor the change from day to night. They have a useful stabilizing function on the body's biological rhythms, but they are slow to react to changes in lighting schedules, so that after time zones have been crossed rapidly, the endogenous signals for sleep and wakefulness do not match the local light-dark and social schedules.

How is the body clock indexed by external time? The major factor is the alternation of dark (night) and light (day) periods. The light signals are transmitted to the hypothalamus and support alignment of the inner body clock to the external time. There are also minor time clues (often called by their original German name, "Zeitgebers"). Minor Zeitgebers include social schedules, eating and drinking patterns, external temperature and physical activity.

Core body temperature is one of the best markers of the body clock. It is important as it has been linked with sleep and its rapid eye movement (REM) and non-rapid eye movement (NREM) components. "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. 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 occurs when core temperature is rising or is high. Sleep is favored when body temperature is low or rapidly descending, as at the end of a normal evening" [3].

Some of the biological cycles adjust in a few days, while others, such as the core body temperature, take more time [4].

2.4. When the body clock is not in phase with external time

2.4.1. Body clock resilience: shift work

One fundamental aspect of the circadian influence is its resilience over time. A good example is shift work. If someone with a regular work schedule abruptly shifts to a night work, that person will usually find it quite difficult to enter sleep in the morning.

This would not make sense if there was only a homeostatic force at play. Indeed, the homeostatic pressure will be maximal after a night with no sleep, since the last sleep episode ended 24 h earlier. The homeostasis hence pushes to enter sleep as soon as circumstances will allow for it.

Sleep will however be difficult to find because the body clock insists that it is time to wake up. As a consequence, sleep, if it happens, will be shallowed and fragmented. It is only after several days that the new schedule will be integrated.

And then it could be time to change the work timetable again. Continuous shift work is an unending, impossible to stabilize, and most likely unhealthy process that modern day society is unfortunately not ready to reduce.

2.4.2. Body clock resilience: Jet Lag

Jet Lag is roughly the equivalent of shift work when people are transported in a fast way (jet airplanes) across one or several meridians, that is, east- or westwards. No Jet Lag should be expected in purely north- or southwards trips. When meridians are traversed, the internal clock remains indexed, for a few days at least, to the old schedule. It is thus not adjusted yet to the new timetable.

2.4.3. Shift work, Jet Lag and Zeitgebers

There is one substantial advantage of Jet Lag over shift work. In shift work, everything around the worker reminds her that it is presently night and that other people sleep. Most shops are closed, the sky is dark, there are less sounds from the city. The time clues are working against her and do not help synchronize the biological clock. In Jet Lag, what seems strange is the daytime sleepiness and the insomnia at night, although it is basically the same phenomenon. That is because the Zeitgebers here continuously act in favor of adjustment: external light, eating and other social schedules help adjust as fast as possible.

2.4.4. Jet Lag and travel fatigue

Jet Lag must be distinguished from travel fatigue, that happens every time transport has been long and uncomfortable, be it in car, train, boat or jet. Travel fatigue vanishes after a good night sleep. Jet Lag does not.

2.4.5. Sleep debt

An important factor in the understanding of Jet Lag is the issue of sleep debt (cumulative sleep loss). Insomnia of an hour or two during the first night will add to 1 or 2 h on the second night, and so on. The result after 2–3 days is increased sleepiness, which will favor sleep at times where a fast adaptation would indicate to stay awake (long naps at inappropriate times for instance, staying asleep too long in the morning or going to bed too early). This will delay the adaptation process.

One hour of sleep debt has been compared to the absorption of at least 33cl of beer [5]. A cumulative debt of 4 h should thus be compared to the absorption of four-five times 33cl. Sleep debt has also been found to parallel alcohol intoxication [6]. It is easy to understand that driving a car, for instance, should be avoided. Similarly, other important activities will be negatively impacted.

2.4.6. Sleep inertia

And then there is sleep inertia. Coming out of sleep is not comparable to an electrical switch, it is a biological process that has its complex rules. If you have slept enough and have no circadian problem, then you should feel fully awake after about 15–30 min. But if you have a sleep debt, or are suffering from the effects of shift work or Jet Lag, or have just had too long a nap, your brain may be half asleep, sometimes for hours, unable to sleep but unable to work properly either.

3. Jet Lag symptoms

3.1. Descriptive data

Jet Lag symptoms are frequent. Rogers and Reilly [7] indicated that 74% of surveyed travelers reported some form of Jet Lag. Of these respondents, 50% reported above-average tiredness and fatigue and 28% indicated some disruption in normal sleeping patterns. And 5% reported difficulties in concentration, while 5% reported eating problems. Gisquet [8] reported 80% of sleep disorders among travelers: difficulty in falling asleep, insomnia, premature awakening and daytime sleepiness. Among very frequent travelers such as flight personnel and international business executives, the disorder may be recurrent or even chronic [9].

The most obvious Jet Lag symptoms for the majority of travelers are the inability to sleep during destination night and to remain alert during destination day. It also includes difficulty in concentrating, clumsiness, difficulty with memory, general weakness, dizziness and lethargy [10]. General malaise, dysphoric mood, headaches and gastrointestinal disorders (indigestion, loss of appetite, bowel irregularities) have also been described but cause less harm.

Symptoms logically vary according to the time of day where assessments are made. They will be lighter when day-time overlaps with a day-time at home (or when night-time overlaps with night-time at home). They will be worse when day-time is superimposed on night-time at home (sleepiness) or when night-time is superimposed on day-time at home (insomnia).

Morning-type people may find it more difficult to adjust westwards and evening-type people have more trouble traveling eastwards [11]. People with more rigid sleeping habits suffer more [12]. Short sleepers understandably adjust easier. Age over 60 results in greater difficulty in adjusting to Jet Lag [13]. Gender does not make a significant difference [14].

3.2. Number of time zones crossed

As could be expected, symptoms of Jet Lag are generally worse the more time zones are crossed. Although traveling over one to four time zones is not universally considered Jet Lag, I propose here to do so for the sake of consistency. If the normal sleep schedule is partly included in night-time at destination (more or less from ±1 to 7–8 h), there is at least some overlap with the usual sleeping hours: the problem will either be to have difficulties in keeping on sleeping (having flown westwards) or in falling asleep (eastwards) but some sleep will be found at least. When more than seven or eight time zones are crossed, then sleepiness will be experienced during the whole day and sleep will always be difficult to find at night. This spectrum of symptoms also explains why Jet Lag treatment standardization is difficult.

Flying west is usually considered easier in terms of Jet Lag. This is intuitive, as it is easier to stand some sleepiness late at night than trying to force oneself to sleep when there is no urge to do so. To almost fully adjust, and as a rule of thumb, it is generally considered that 1 day is needed for an hour eastwards, and 2 or 3 days for an hour westwards. Six hours eastwards (e.g., New York to Brussels) thus mean six days to adjust. Six hours westwards (Brussels to New York) mean 4 days. Above 8 h, time zone difference, it is not clear whether you will adjust by advancing or retarding the body clock and there may be individuals who do either one or the other [15].

3.3. Sometimes severe adverse effects

Jet Lag is usually medically benign and self-limited. It may though occasionally cause serious misjudgments in business and professional dealings. As mentioned above, it may ruin holidays, especially if they are of short duration. Athletes will not perform at their highest level if the timing of contests does not coincide with their circadian peak and training occurs at inappropriate times [16].

But Jet Lag can sometimes be a more serious health issue. Loss of sleep is usually translated into excessive daytime sleepiness, and sleepiness is clearly associated with reduced performance and cognitive reaction time [17, 18]. Pilots on long-haul east-west flights have, for instance, been shown to microsleep during the "cruise" phase of a flight and even during the critical transition from the cruise phase to the descent phase, the point at which the planned descent to final approach altitude is initiated [19].

Countermeasures, such as controlled short cockpit naps, crew alternation or alertness monitoring have been proposed [20]. It has been estimated that 21.9% of all road accidents are related to sleepiness in general [21]. Business people have been observed to function at only 80% of their perception after traveling [22]. Studies in shift workers, who also suffer repeated episodes of dyssynchrony, suggest even more severe consequences, including rates of cancer,

cardiovascular disease and female reproductive problems [23, 24]. The part played by Jet Lag in performance degradation and accidents has not been estimated precisely so far but might be substantial.

4. Remedies

4.1. General considerations

4.1.1. The chronobiologist and the military

There are two main pathways followed by scientists to counter Jet Lag. Most studies have been performed by chronobiologists and have as their main goal to speed up the adjustment of the body clock to the new schedule, in particular using timed exposure and avoidance of bright light, as well as the timed use of the hormone melatonin. At the present time, chronobiologists have often succeeded in accelerating and thereby reducing the adjustment process. Their recommendations still make for a slow and not fully satisfactory result, especially when many time zones are crossed.

The second school of research is more pragmatic. Here we start from the point of view that we want to be as fully operational as we can and as soon as possible. So the body clock is more or less left to itself and allowed to take its time without much interference. The aim is to counter insomnia and fatigue or sleepiness with substances that help sleeping and waking until the moment the adjustment is complete and the body clock has taken over. Obtaining enough sleep at more or less the right time, albeit somewhat artificial through the use of sleep inducers, is crucial to be in shape the next day, helping to adjust to Jet Lag, and is also far more comfortable than insomnia. On the other hand, fighting excessive daytime sleepiness has been studied in diseases that make people abnormally sleepy during the day, such as narcolepsy. This is not Jet Lag, although many symptoms are shared, but this information may be useful. However, the pragmatic approach has only been fully developed in the military, as they understandably need realistic answers to the issues of sleep, fatigue and vigilance, so that soldiers and pilots are at their best on the battlefield 365/24/7 if needed and do not risk their lives unduly because of lack of vigilance. The services need to control Jet Lag as fast as possible and have a long and valuable experience with drugs, from which civilians can probably benefit.

4.1.2. What do people usually do?

Taking sleeping pills during flights and for a few days when at destination is in fact what many travelers do today, as an off-label (i.e., unapproved) treatment. This helps at least to obtain a subjectively better sleep, hopefully to be more awake the next day. Most people also use caffeine, some use alcohol and some even use stimulants. But most travelers do not know which medications to use, at which dosage and when to take them, in large part because one Jet Lag is not another Jet Lag.

Several general remedies have been proposed: low or high carbohydrate "Argonne" diets, relaxation, fresh nutrients, baths, aromatherapy, Bach flowers, essential oils, Ayurveda, homeotherapy, avoiding the stress of packing, adjusting to seasonal differences, physical exercise, foot massage, and optimal flight schedules, to name a few). They may prove to be effective at some point and hence be considered part of the proposals against Jet Lag, but I consider today that the evidence is not there yet.

4.1.3. Breaking the issue down

In fact, situations vary considerably depending on whether three or ten time zones are crossed. They also depend on whether the travel is done eastwards or westwards. I like to divide Jet Lag into three clusters. Unless one moves across more time zones than the amount of hours usually taken to sleep, part of the destination night overlaps with the normal sleep schedule.

Going westwards means resisting sleepiness in the evening, falling asleep rather easily and waking up too early (Group A). Going eastwards means finding it hard to fall asleep and making for difficult waking (Group C). Travel between West+8 h and East-8 h zones make for a clearly worse problem since there is no overlap at all (Group B).

In more detail, there are 23 different cases (24 time zones minus one - the one where the travel begins). Each of these situations actually deserves a specific « treatment », from the very easy, corresponding to changing the clock for the sake of daylight saving in the spring or autumn, to the real challenges of flying to the antipodes.

4.2. No-nonsense measures

4.2.1. Fast psychological adjustment

It may be interesting to set the wristwatch at the future new schedule as soon as the plane takes off and follows the destination schedules (meals, etc.) right after landing. These new time clues may help the body clock to adjust faster (to what extent has not been measured scientifically). But it cannot harm.

4.2.2. Exercise

It is usually recommended to do some physical exercise to adjust to the new schedules. It could be especially recommended at those times of the day when sleepiness is present. However, it is not recommended to undertake physical exercise less than 2 h before bedtime especially in eastwards flights, where sleep should be difficult to find.

4.2.3. Naps

Sleeping partly during daytime is the rule for babies, infants and many children. As mentioned earlier, this is also the case for adults in many parts of the world: by shifting some of the main sleep load from nighttime to naptime (siestas), working hours are adjusted to more favorable weather conditions. The circadian clock seems less rigid in the afternoon than in

the morning or the evening and may allow for individual variations that become the usual circadian pattern in the long run.

Naps may produce surprisingly powerful waking effects. Sleeping just a few minutes during the daytime may considerably reduce the urge for sleep that was present immediately before and made concentration difficult. Napping more than 20–25 min, however, can paradoxically be less favorable and induce a slight degree of drowsiness (because of sleep inertia, as we have seen) sometimes for hours. Longer naps also pull some sleep pressure off from the coming night, and thus may delay the adaptation to local time.

If there is a good indication for a nap, its optimal duration should thus be somewhere between 15 and 25 min. This is probably linked to the sleep stages that occur during the nap. Very light sleep (stage 1 sleep) is probably not very useful for recovery. Stage 2 sleep includes loss of awareness of the external world and seems to be quite beneficial. Stage 3 (deeper sleep) is even more effective but may include the negative impact of sleep inertia. REM sleep should be an exception in naps, but can happen when the body clock is still set to the home time, as REM sleep also depends on the circadian clock. We should thus focus on finding some stage 2 sleep: it will happen spontaneously if one manages to lose awareness during the nap. To make what is commonly called a powernap, a timer or an alarm clock can be launched for 15–25 min.

When there is a strong sleep debt, or if the nap timing corresponds to sleep time at home, it may be difficult to wake up after the programmed 15–25 min. Naps are thus a double-edged sword and make for a difficult issue.

4.2.4. Launch window

In spaceflight, a launch window is a time period during which a particular vehicle (rocket, space shuttle, etc.) must be launched in order to reach its intended target. If the rocket is not launched within the "window," it has to wait for the next opportunity.

Using this as a metaphor, and as seen above, there are times where day-time at destination overlaps with day-time at home. Jet Lag symptoms should be minimal at these times. The launch window is large when few time zones are crossed. It will be shorter—and split into two parts—when the globe is crossed. Knowledge of the launch window(s) may be crucial to plan and do the important things that should be done at destination, be it museum visits, family or business meetings, or political negotiations. It will of course be easier to choose meeting times as a powerful CEO than if one is looking for a job.

4.2.5. Stay duration

I could not find comprehensive statistics on worldwide average stay duration abroad. It would be important because if a lot of time is available ahead (weeks, months), Jet Lag is very likely to be a minor issue. But since most people do not have extensible holidays or inexhaustible extra time, I suspect that the majority of travel across time zones will last a week or two, or even less (weekend shopping trips to New York or Milan for instance). Here, and especially if a considerable distance is traveled for a round trip, Jet Lag may bother seriously. The good news is that readjustment is faster after short stays once back home.

For very short stays (2–3 days), and if the launch window is comfortable enough (see above), one may just as well decide to keep home schedules. For a westwards trip, this means going to bed early, at the usual home times. That will make for an early wake-up that can be used for doing some homework or early visits. For an eastwards trip, this means going to bed late at night and stay asleep late in the morning.

4.2.6. Discipline and wake-up time

As human circadian clocks take several days to adjust, exercising discipline for about 1 week will help saving much time, as the body clock will adjust faster. This means going to bed when there is little need to and waking up even if it is uncomfortable.

If not, chances are that Jet Lag will last longer and the body clock will swing between home and destination times.

4.2.7. Preflight scheduling (anticipating phase shift)

Although it is neither practical nor easy, it is theoretically possible to adopt destination timetables prior to departure. This can be useful when crucial meetings are scheduled and Jet Lag should absolutely be avoided. It means going to bed earlier or later—and waking up accordingly of course. Perhaps, it is only valuable with very little time difference (1–2 h). More than that would be heroical most of the time.

4.2.8. Sleep in two parts

Sleeping in two half nights can be useful when the destination is at the antipodes and the stay duration is short [25]. It would be comparable with a long nap (corresponding partly to sleep at home times) and a short sleep at night. This is still largely theoretical at this date but would be just as physiological and healthy as long as the total number of hours is slept.

It is possible that people have slept in two chunks for ages, for instance when they got to sleep early in the winter, then woke up and did several activities, to go back to sleep again until morning [26].

4.3. Accelerating the phase adjustment

4.3.1. The natural way is fine but slow

The body clock adjusts spontaneously and seamlessly to destination time. The only problem is that the change is slow and holidays or business stays abroad may be too short for its full and timely implementation.

As has been mentioned earlier here, it takes about one day by time zone when flying eastwards and two-thirds of a day when flying westwards to adjust for sleep and vigilance. Flying from London to Shanghai (eight time zones difference) may hence demand 8 days until Jet Lag symptoms become almost undetectable—the reverse course from Shanghai to London would take between 5 and 6 days.

Hormones such as cortisol may take up to 3 weeks to fully adjust—but this is fortunately not translated into obvious clinical symptoms [27].

Adjusting the body clock is a natural and complex process, based on the reception of time-givers. The most important of them is exposure to light above a certain threshold of physical intensity (bright light being apparently far more effective than dim light, although the issue is not closed). As mentioned before, other time-givers also play a less important part: social activity, meals, psychological adjustment, physical activity, and so on.

4.3.2. How to interact with the body clock?

Bright light has a direct time-setting action on the body clock supra-chiasmatic nuclei. It also inhibits the production of melatonin [28]. Melatonin in turn helps to adjust the body clock to the external day/night 24-h cycle. There are receptors for melatonin in the body clock, which allows exogenous artificial melatonin to act on it.

Exposure to bright light on the one hand and melatonin on the other hand are two complementary ways that can be used to push the body clock and adjust faster to the destination time. Bright light should also be avoided in certain conditions to prevent the unwanted opposite effect. Bright light especially needs to be administered at precise timings for every different kind of Jet Lag difference.

4.3.3. Bright light

Bright light is the main time-giver to the body clock. Its effects (phase-response curve) on the body clock were modeled 30 years ago [29]. Exposure to bright light in the morning should have the effect of advancing circadian rhythms: it helps to sleep earlier (useful when flying eastwards). Exposure to bright light in the evening should do the opposite, retarding the circadian rhythms and helping to sleep later (useful when flying westwards).

The switch-point is between retarding and advancing actions in the midst of the night (of the body clock). This has to be seriously taken into consideration. If bright light is taken at the wrong time when at destination, it may have the opposite effect contrary to what is wanted.

It is the retina (eyes) that matters, not body exposure, which is irrelevant here. Importantly, and as a result of retina automatic adaptation, artificial (dim) light may give a subjective impression of being almost as powerful as external light. In fact, when measured with physical instruments, common artificial lighting is usually more than 10 times weaker than daylight. To the brain and for that matter, living under artificial light is almost like living in the dark. So, to benefit from really activating light (bright light), the choice is between exposure to external solar light (it works even when the weather is cloudy most of the time), and the use of artificial lighting, such as powerful halogens (500 W), specially designed light boxes or a light visor— appliances that are easily portable and are worn on the head like a baseball cap. To avoid light when it is counterproductive, sunglasses or even an eye mask could be used if the circumstances allow.

4.3.4. Melatonin

Melatonin is a hormone produced by the pineal gland, a small brain structure in the epithalamus of almost all vertebrates (slightly behind the hypothalamus). Its secretion in humans is normally high at night and close to zero during the day, as it is inhibited by light. Its secretion thus begins in the evening and lasts until dawn. It follows a circadian cycle (very close to the external 24-h light-dark cycle). Its production is synchronized by the body clock with the light-dark cycle. Its effects are contrary to those of exposure to light [30].

The primary function of melatonin seems to be regulation of the day-night cycles. It also has a sleep-inducing action, especially at larger doses. It also works as an antioxidant and shows moderate anti-inflammatory properties.

The melatonin produced by the body is called endogenous. The one prescribed as a medical compound (artificial) is exogenous. Although melatonin is a natural hormone, using it exogenously at the dosages suggested here is not natural, since it will amount to about 5–25 times the 100–150 micrograms normally produced.

When exogenous melatonin is taken in the evening (before the onset of its natural endogenous secretion), it advances the body clock to an earlier time, which is useful when traveling eastwards. To benefit from both the phase-resetting and the sleep-inducing effect, long-acting larger doses (2.5 mg) can be used about 2 h before going to bed. But taking melatonin at nighttime when traveling westwards does not make much sense, since it will overlap with the endogenous secretion and probably won't do any good. When it is taken in the morning (of the home schedule), after endogenous levels have fallen, it will reset the clock to a later time. It may thus be preferable to take a short-acting small dose (0.5 mg) later at night [9].

Prescription of melatonin a few days before departure, at a time that coincides with bedtime at destination, has been suggested on theoretical bases but it remains unclear whether anticipatory treatment provides a substantial advantage over treatment that is administered after arrival at destination.

Melatonin is the most extensively studied treatment for Jet Lag so far. It has shown effects superior to placebos. In a meta-analysis, the subjective benefit has been estimated at around 40% (eastwards) and 50% (westwards) [31].

No major or consistent adverse events have been reported in the clinical trials that have been performed. But larger studies are still needed to confirm the drug's effectiveness and safety. Driving is not recommended after absorption of long-acting (extended release) dosages for about 5 h.

Melatonin is also the precursor of a new class of drugs—chronobiotics. Agonists such as Ramelteon, seem to possess sleep-inducing as well as phase-adjusting properties and is marketed in the US for insomnia with difficulties initiating sleep. Tasimelteon, another melatonin agonist, improves sleep latency, sleep quality, sleep maintenance and provides a shift in circadian rhythms after an abrupt advance in sleep time [32]. Agomelatin is another melatonin agonist, which also has antidepressant properties.

4.3.5. Seasons

Although a bit neglected in the scientific literature, the issues of seasons and latitude (north-south) inescapably increase the level of complexity. Although daylight duration is very similar in the summer and the winter close to the equator, it varies considerably closer to the north or south poles. There, as seasons change without interfering much with sleep duration, and as most people do not sleep behind opaque curtains or blinds, we must postulate some kind of mechanism which adjusts the body clock progressively to longer or shorter durations of external bright light and varying durations of melatonin secretion. It is likely that the other time-givers, such as meals and social life, help to achieve this adaptation.

What I want to insist on here is how complex it may be to determine the best timing for the administration of melatonin and bright light. The greater the north-south difference, the less unpredictable the reaction will be, as this area needs more research.

4.4. Sleep inducers

4.4.1. Drugs of all kinds

There is nothing more restorative than plain, normal, drug-free sleep. But there is also little doubt that sleep induced by sleeping-pills is more restorative than insomnia.

Over the centuries, humans seem to have experimented with all kinds of compounds including opioids, alcohol, cannabis and many others to obtain sedation (reducing excitation and anxiety), alter consciousness or induce sleep (among other effects). In addition to these, many such compounds are now produced artificially from raw chemicals.

4.4.2. Alcohol

Alcohol-containing beverages (from beer to whisky) work on several parts of the brain and not necessarily in the same order in all of us. To some, alcohol is mostly felt as a sedative; but to others, it may be felt as a stimulant, or as a social disinhibitor, a trigger to violence, and so on. But whatever the particular effect it has during wake time, it is metabolized rather rapidly by the liver and, as such, may elicit a rebound (awakening) effect during the night, so that sleep may become lighter and more irregular after a few hours [33, 34]. In the case of Jet Lag, and especially if flying westwards and risk waking up at night, absorbing alcohol is not a very good idea. Going east across a few time zones should be less of a problem, since the body clock increases the propensity to sleep in the later parts of nights.

4.4.3. Benzodiazepines

Among all the pharmacological classes that may induce sleep, benzodiazepines and z-drugs are the most studied for their sleep-inducing properties. Z-drugs are compounds that lack the chemical benzodiazepine structure but act, albeit probably more specifically, at the same brain location. They are effective and their side effects are well known and benign when used carefully on a short-term basis.

Side effects for short-time use may include sleepiness, lack of concentration, reduced memory, attention and muscle weakness. These should be a minor nuisance to most but may be substantial to others, as they vary from person to person and depend on the dosage, as well as the patient's health, age, weight, gender, and so on.

Their action duration, best described by their half-life, varies considerably, from about an hour to more than 48 h. This is determined by pharmacokinetic properties, such as the rate of absorption, extent of the distribution and elimination time. Sometimes, metabolites prolong the action of the original substance.

Short-acting drugs are most useful when it will be difficult to induce sleep, as in flying westwards. Mid-range duration drugs will be more useful when the problem lies in waking up too early.

4.4.4. Melatonin and its derivates as sleep-inducing substances

Beside their usefulness as body clock resetters, melatonin and its agonists (e.g., Ramelteon) have demonstrated action as sleeping pills. They may prefer to benzodiazepines because of their more "natural" origin (though the proposed dosages are not natural, as seen above). Hey should be taken 2 h before bedtime for their sleep-inducing effect. However, patient appraisal shows large divergences about their effectiveness as sleeping-pills proper (see [35] for instance).

4.5. Neuro-stimulants

4.5.1. Sleepiness and stimulants

When the body clock presses for sleep when it is plain morning, middle of the day or early evening at your destination, it may be difficult and sometimes impossible to enjoy the stay or do what was planned. Sleepiness may be very difficult, often painful to resist and hamper the normal functioning.

The burden on human activities and the heavy load of casualties caused by fatigue, whether military, civil or personal, have been very convincingly described in Caldwell and Caldwell's Fatigue in Aviation [36]. This great book also discusses in detail the various ways used by the military to counteract fatigue, among them being the use of stimulants and sleeping-pills (see also [37]).

As mentioned in the previous chapter, the first thing is to make sure an adequate number of hours of sleep is obtained. If not, homeostatic pressure and sleep debt will add to the circadian issue, as we have seen above. So the first thing to do is to sleep enough (see preceding chapter).

The use of stimulants must be seen as a last resort, after everything else has been tried.

Stimulants (caffeine, modafinil) have been recommended in Jet Lag situations for short (2 or 3 day) stays, since melatonin and bright light do not have time to suppress adaptation time [25].

Unfortunately, both caffeine and modafinil have a rather long duration of action (5–8 h for caffeine, 5–10 h for modafinil). This does no harm when sleepiness due to Jet Lag manifests itself in the morning or the afternoon (Groups B and C). But this long action makes them trickier to use when sleepiness is felt in the evening (Group A) and sleep is needed a few hours later.

4.5.2. Caffeine

A mild stimulant from the xanthine family, it is arguably the most widely used psychoactive drug in the world. It is found in coffee of course, but also in tea, cocoa, (chocolate), soft drinks, energy drinks, in some medications and over-the-counter preparations.

Its absorption is irregular, varies from person to person, and is influenced by food intake. Peak effects are observed after 1 h, while residual effects can be perceived from 5 to 8 h afterwards [38, 39], and even more in case of pregnancy or when taking hormonal contraceptives.

Three hundred milligram of slow-release caffeine has been shown to increase alertness and reduce other Jet Lag symptoms after eastwards flights across seven time zones [40]. But long-acting tablets of caffeine are not easy to find nowadays.

A cup of filter or instant coffee contains 100–150 mg caffeine. An expresso contains 50–75 mg. Black tea (or iced tea) contains 15–70 mg. Green tea contains 25–50 mg. Decaffeinated coffee or tea contain less than 15 mg.

Caffeine mildly increases neural activity in several parts of the brain. It is also diuretic, stimulates striated muscles and acts on the cardiovascular system. It is used to reduce physical fatigue and to prevent or treat drowsiness. It produces increased wakefulness, faster and clearer flow of thought, increased focus, and better general body coordination. The amount of caffeine needed to produce these effects varies from person to person, depending on body size and degree of tolerance. Caffeine has the desired effect of delaying or preventing sleep, but does not affect all people in the same way. It also improves performance during sleep deprivation [41]. In shift workers, it leads to fewer mistakes caused by drowsiness [42].

Side effects include restlessness, irritability, nervousness, shakiness, headache, lightheadedness, sleeplessness, nausea, vomiting.

The problem with caffeine is that most of us already take caffeine on a daily basis (e.g., 90% of the adult population in the US). The average consumption of adults is 300 mg/day (some of us 500 mg/day), that is, pretty much the dosage suggested to combat sleepiness in Jet Lag, as we have seen above. Fighting Jet Lag using caffeine basically only works for people who do not use it regularly. One option would be to wean oneself off caffeine about a week before the travel.

4.5.3. Energy drinks

So-called « Energy drinks » may contain between 80 and 200 mg caffeine and about 2–3 g taurine. It is unclear whether taurine adds efficacy to caffeine and the opposite may even be

true [43]. All in all, one can have an energy drink that has about the same effect as 1–3 cups of coffee.

4.5.4. Modafinil

Modafinil was originally developed as a treatment against narcolepsy, a disease that has sleep attacks and severe sleepiness as one of its core symptoms. Modafinil has been shown to have a moderate but significant effect on reducing sleepiness and the number of car accidents in shift work [44]. Recently, it has been shown to improve driving in real conditions in patients with excessive daytime sleepiness [45].

Modafinil thus increases wakefulness, alertness, concentration and decreases fatigue and sleepiness. It could slightly reduce appetite. It is assumed not to prevent subsequent sleep.

Compared with caffeine, modafinil has demonstrated less cardiovascular stimulation, and less interference with scheduled sleep. But it was also shown to be less effective than caffeine on the Stanford vigilance test [46].

4.6. Tailoring remedies

As seen above, Jet Lag means very different things as a function of the time zone differences, the direction of the flight, the duration of the stay, the purpose of the stay, the seasons, the differences in longitude. One must also add the still largely unexplored individual differences in sensitivity to it.

Thus, there is no way presently to universally suppress Jet Lag and its consequences. The best way to adjust nowadays is to break the issue down and to look for tailored solutions, especially taking into account the difference in time zones and flight directions. For each one, specific adjustment strategies can be proposed, and they will be more efficient and less harmful than universal ones [47].

5. Conclusions

Jet Lag is a phenomenon that is best explained by a mismatch between the circadian body clock and actual destination time. After fast (airplane) transportation to destination, the body clock remains set to departure schedules for a number of days that depend mostly on the amount of time zones crossed.

The circadian clock slowly adjusts to new schedules, thanks to external time-givers, especially the alternation of outside night and dark periods but also social meetings and meals.

Several remedies have been tried to speed up or bypass this adaptation, from no-nonsense tricks to bright light and melatonin to sleeping pills and stimulants. But, all in all, these remedies still tackle the issue in an unsatisfactory way. The best manner to cope presently seems to tailor the solutions to individual travels and demands.

Conflict of interest

There is no conflict of interest.

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