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JET LAG SYNDROME: CURRENT INSIGHT AND REVIEW OF THE SCIENTIFIC LITERATURE

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ABSTRACT The jet lag syndrome is a phenomenon of modern social life that occurs due to a mismatch between the body's natural circadian rhythm and the external environment due to rapid travel across multiple time zones. Jet lag syndrome symptoms are primarily related to sleep disturbance, interfering with travellers' social life and vocational performance. The symptoms usually last for a few days but can be for a week depending upon the changes in time zones. During the jet lag, abrupt shifts in the environmental light-dark cycle temporarily desynchronize the suprachiasmatic nucleus (SCN) of the hypothalamus downstream oscillatory networks from each other, resulting in increased sleepiness and impaired daytime functioning. Eastward travel is associated with a longer duration of jet lag than westward travel. Polysomnographic data show that jet lag results in changes in sleep-wake timing and different aspects of sleep architecture. This circadian misalignment can lead to a cluster of symptoms, including significant metabolic, cardiovascular, psychiatric, and neurological impairments.[1] Light is the major entrainment factor for the circadian clock, and timed bright light exposure at the appropriate portion of the light-dark cycle is the principal non-pharmacological approach. Nutraceuticals and pharmacological therapies include melatonin, melatonin receptor analogues (agonists), non-benzodiazepine hypnotic agents, caffeine, diphenhydramine (e.g., Benadryl, McNeil; Aler-Dryl, Reese), and armodafinil. The awareness about the jet lag syndrome, planned sleep schedule before departure and phase resetting by exposure to light or medication can help travellers overcome this condition. New research suggests that modification of clock function via genetic manipulation may one day have clinical applications.[2] The current perspective of the COVID-19 pandemic resulted in many countries imposing a lockdown, reducing sunlight exposure and altering daily social schedules. Therefore, it essentially leads to changing 'time zones' without actually travelling across time zones, causing social jet lag.[3]

KEYWORDS : Jet lag, circadian clock, time-zone, melatonin, biological clock, social jet lag

DEFINITION

The jet lag syndrome is a type of circadian rhythm sleep disorder (CRSD)[4] results due to temporary misalignment between the internal "biological clock" or circadian rhythm and the local environmental clock in a person who travels in a high-speed aircraft and rapidly crosses multiple time zones.[5] It emerged as the general public travelled by plane to distant parts in the 1960s. The term 'jet lag' was first used in a Los Angeles Times article on Feb 13 1966.[6] Jet Lag derives from the simple fact that jets travel so fast they leave your body rhythms behind. The condition usually occurs in transmeridian passengers from west to east or east to west, where they have to go across the time zones. The syndrome is a temporary phenomenon and leads to different signs and symptoms of disturbed sleep and cognition function impairment of travellers on arrival.[7] It may last several days until the traveller fully adjusted to the new time zone. The recovery depends on the individual characteristics, the number of time zones crossed and the direction of travel. Without specific treatment, the circadian clock will adjust to the destination time by roughly one time zone per day for the eastward journey and 1.5 time zones per day for the westward trip.[8]

PATHOPHYSIOLOGY

The jet lag syndrome occurs due to transient disruption of the circadian system when a high-speed aircraft or a Jet flight crosses at least two time zones across the transmeridian.[9,10]

In humans, light-dark cycles or many physiological processes in 24 hours are regulated by a circadian rhythm. The Circadian rhythm is a biological clock of the human body. This clock period is 24.2 hours[11], which is slightly longer than the environmental clock cycle of 24 hours, and this requires a slight phase advance daily to maintain entrainment with the light-dark cycle. The primary circadian pacemaker in mammals is the suprachiasmatic nucleus (SCN) in the anterior hypothalamus. This nucleus exists as paired structures on each side of the third ventricle above the optic chiasm.[11-13] The SCN controls the rhythm of core body temperature and human melatonin secretion. It releases alerting signals in the daytime and promotes sleep during dark periods or at night. The minimum core body temperature (CBTmin) and the dim light melatonin onset (DLMO) are two critical markers of the position of an individual's circadian rhythm with reference to the external environment.[14] The CBTmin occurs about 2 hours before a spontaneous awakening from the nocturnal sleep (around 4.00–5.00 AM in most individuals).[15-17] A decrease in core body temperature during the night corresponds to increased plasma melatonin. The DLMO occurs about 2-3 hours before a typical bedtime.[15-20]

Jet lag syndrome is a circadian rhythm type sleep disorder resulting from a temporary desynchronization of internal circadian rhythms and external clock time due to rapid crossing of at least two time zones. The body's circadian clock synchronized with the original time zone instead of the time zone where we travelled. So our circadian system continuously signals for sleeping or waking according to the original time zone until our endogenous or circadian clock matches with an external clock at the destination. It usually takes a few days to complete the synchronization of both the clocks.[21]

According to the American Association of sleep medicine, the Jet lag syndrome should meet three diagnostic criteria as follows:[22]

1. Insomnia or excessive daytime sleepiness associated with reducing total sleep time coinciding with jet travel across at least two time zones.
2. Impaired daytime function, general fatigue, or somatic symptoms begin within two days of travel.
3. The sleep disturbance cannot be explained by another disorder.

The typical manifestations of the jet lag syndrome based on Waterhouse et al.[23] include feeling tired in the new local daytime and yet unable to sleep at night (eastward flight), awake in the night and difficult to get back to the sleep (westward flight), feeling less able to concentrate or motivate oneself, and decreased mental and physical performance, increased incidence of headaches and irritability and loss of appetite and general bowel irregularities.[24] Other symptoms include excessive urination, menstrual abnormalities, abnormal insulin, and other hormone regulation. The persons who travelled towards the east suffer from delayed sleep phase disorder, and westward travellers suffer from advanced sleep phase disorder. A jet lag should not be confused with travel fatigue, which is not dependent on the time zone. [25]

Few studies revealed that a person who repeatedly air-travel transmeridian time zones may have an increased risk of memory impairment [26], reproductive dysfunction in women [27-30], and possibly cancer.[31, 32] A study shows that despite a decreased physical performance with jet lag, jet-lagged athletes do not have an increased risk of injury. [33]

The duration and intensity of the jet lag symptoms depend on several factors, such as travel direction, the number of time zones crossed, ability to sleep while travelling, availability and intensity of local circadian time cues, and individual differences in phase tolerance.

The symptoms are worse after eastward than westward travel. Westward travel is usually easy to handle by the biological clock because the average duration of a circadian clock in humans is longer than 24 hours. In this way, there is a natural tendency for a late bedtime and waking. However, 20% to 25% of humans have a shorter than 24-hour clock[34], and they can easily handle an eastward journey. It observed that following a trip, eastbound individuals would likely have more difficulty initiating sleep from a few days to around a week. In westward travel, there may be more difficulty in maintaining sleep later into the night.[35]

The exact incidence of the jet lag disorder is unknown,[22] around one million peoples were in the air at any moment worldwide before the COVID-19 pandemic. Not all travellers crossing time zones suffer from jet lag to the same degree, and these differences probably result from individual variation. All age group travellers have a risk of jet lag syndrome, and data suggests that older individuals may experience fewer symptoms than younger individuals.[36] Aircrews are more vulnerable to jet lag symptoms and have a chronic type of jet lag disorder.

Management:

Jet lag is generally temporary and usually doesn't need treatment. Symptoms often improve within a few days, though they sometimes last longer. To manage a jet lag disorder, taking action before, during and after the flight is required. When three or fewer time zones are crossed, the symptoms of jet lag will persist for only a short time. The treatment strategy is better suited for fatigue associated with travel, which does not involve any significant shifts in the clock itself.[25]

There are three components of jet lag management, including re-entrainment of the circadian clock with destination time clock by timed exposure of light or melatonin, scheduling of optimal duration and timing of sleep and using medication to relieve the symptoms of insomnia or daytime sleepiness. Light exposure after CBTmin induces phase advance and before CBTmin induces phase delay of the circadian rhythm.[37-39] The melatonin has the opposite effect of light in phase shifting. Hence bright light pushes, and melatonin pulls the circadian phase. Eastward travellers suffer from delayed sleep phase disorder, which requires adaptation by a phase advance, which is more complex than westward travel. At the same time, westward travellers are prone to have advanced sleep phase disorder that requires adaptation by a phase delay, which is more comfortable because of the intrinsic tendency for phase delay.[40]

In eastward travellers, one method is to phase advance 1 hour per day with bright light in the morning before travel begins,[41, 42] and light exposure after CBTmin at the new destination should be encouraged. Try to sleep 1-2 hours early and wake up early in the morning before the start of the trip. During a long flight, avoiding sleep loss and keeping sleeping hours according to the destination sleep period is also reasonable. Drink plenty of water, but consume alcohol and caffeine very judiciously.

Avoiding the evening light exposure on arrival at the destination can help prevent the phase delay.

Exogenous melatonin can also shift the circadian clock; therefore, melatonin 0.5-3.0 mg at local bedtime or before CBTmin might be helpful. However, melatonin in higher doses (3-5mg) has a direct hypnotic effect[43] and should be avoided if wakeful activities are required at the destination.

Arendt et al. conducted the first double-blind, placebo-controlled trial of melatonin in jet lag, and they observed that subjects receiving melatonin experienced significantly fewer severe symptoms based on subjective measures, including jet lag ratings, self-recorded sleep parameters, and mood ratings.[44] In clinical trials, melatonin receptor analogues (agonists), Ramelteon and Tasimelteon, have not been directly compared with exogenous melatonin therapy. Ramelteon (Rozerem, Takeda), a sedative-hypnotic, has been approved by the FDA for insomnia characterized by difficulty falling asleep. The selectivity of ramelteon for melatonin receptors contributes to sleep promotion and maintenance of the circadian rhythm underlying the normal sleep-wake cycle.[45]

No studies of diphenhydramine for use in jet lag syndrome have been conducted, even though this is the most common nonprescription antihistamine prescribed for insomnia. Side effects include daytime sleepiness, cognitive impairment, dizziness, blurred vision, and dry mouth and throat. Self-medication is a common problem that can result in adverse outcomes, especially in older adults.[46]

Hypnotics can help with sleep but do not necessarily help with alertness the next day.[47] Stimulants like caffeine before mid-day may help keep alert during local waking hours. In a systematic review of 13 randomized trials of persons with jet lag or shiftwork disorder, caffeine improved concept formation, reasoning, memory, orientation, attention, and perception compared to placebo.[48] Armodafinil, a central nervous system (CNS) stimulant, is designed to improve wakefulness in adults who experience excessive sleepiness because of obstructive sleep apnea, shiftwork disorder, and narcolepsy. A recent study found that 150 mg of armodafinil (an R-isomer of modafinil) helped to increase wakefulness after eastward travelling through six time zones.[49]

Westward travel is easy to handle because there is a phase

advance, requiring a phase delay to avoid jet lag. One should try to go to bed late at night and get up late in the morning, and evening bright light exposure for 1-3 hours before the start of the trip is helpful. During a flight, avoid sleep loss and sleep during the time corresponding to the destination's night, if possible. Drink adequate water and avoid alcoholic drinks; although alcohol shortens sleep latency, sleep continuity is disrupted.[50] On arrival, seeks evening bright light exposure and takes melatonin 0.5 mg during the second half of the night after CBTmin to phase delay. Hypnotic medications, especially Z-hypnotics (Zolpidem and Zaleplon), can use at bedtime to overcome insomnia.

Daytime short napping can also help overcome daytime tiredness or decreased alertness, provided it is less than 30 minutes and 8 hours before bedtime, to maintain the nighttime sleep quality.

While crossing more than eight time zones from your original time zone, the body might mistake early morning light for evening dusk and evening light for early morning light. Therefore one should avoid light exposure at the wrong portion of the phase response curve because this can fall on the wrong side of CBTmin. After eastward flights, avoid very early light (avoid inappropriate phase delay); on westward flights, avoid light at dusk (avoid inappropriate phase advance) for 2 to 3 days.[10] Some experts suggest that all flights that cross more than 8 to 10 time zones should be treated as Westward.[25] If avoiding bright light is impractical, wearing low-transmittance sunglasses may be a helpful alternative, as suggested by studies with simulated shift work.[51] Some artificial light goggles that can use in-flight give adequate photic stimuli to the retina in the dark period and help adapt the phase shifting.

New research suggests that modification of clock function via genetic manipulation may one day have clinical applications.[2]

CONCLUSION

The jet lag syndrome is a common problem in long-haul flight passengers when a mismatch of the biological clock with the destination time clock is expected as a normal physiological body response. Affected travellers have symptoms of disturbed sleep, sleepiness and insomnia. It is a significant occupational hazard for airline crew, leads to business losses, and psychologically affects travellers because of its health consequences. Extended flight travellers should avoid attention-seeking tasks or situations which require fast reflexes during the days following the trip. The jet-lag syndrome management should plan before departure and require clock or phase resetting by timed light exposure, melatonin exposure, or both. A wide array of prescription and over-the-counter (OTC) products have been the focus of study in managing jet lag. These modalities include light therapy, melatonin, melatonin receptor analogues, non-benzodiazepine hypnotics, caffeine, diphenhydramine, and CNS stimulants such as armodafinil. Depending on the individual patient's sleep-wake cycle and other factors, pharmacists can aid patients in selecting an appropriate treatment.

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