Adv Ther (2010) 27(11):796-813.
DOI 10.1007/s12325-010-0065-y

REVIEW

Jet Lag, Circadian Rhythm Sleep Disturbances, and Depression: the Role of Melatonin and its Analogs

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Received: June 21, 2010 / Published online: September 6, 2010

ABSTRACT

Traveling through several time zones results in a constellation of symptoms known as jet lag. These include reduced alertness, daytime fatigue, loss of appetite, reduced cognitive skills, and disruption of the sleep/wake cycle. In susceptible air travel passengers, jet lag may exacerbate affective illness and result in psychiatric morbidity. Dysregulation of circadian rhythms and melatonin secretion represent the common underlying factor in jet lag and other circadian disorders. Recent studies have established the effectiveness of strategically timed administration of melatonin and appropriate timed exposure to environmental schedules including light in counteracting the dysregulation (chronobiotic actions). With the introduction of melatonergic agonists such as ramelteon and tasimelteon, which have both a stronger affinity for MT_1 and MT_2 melatonin receptors and a longer half-life, new therapeutic options now exist for treating the sleep disturbances associated with jet lag. The melatonin analogs are unique inasmuch as they can also enhance daytime alertness. The recently introduced melatonergic antidepressant agomelatine, which has established its supremacy over other antidepressants in having a significant chronobiologic activity, represents a good choice for treating depressive symptoms that are associated with jet lag.

Keywords: agomelatine; chronobiotic; fatigue; insomnia; jet lag; melatonin; mood disorders; ramelteon; tasimelteon

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INTRODUCTION

The cyclical nature of geophysical variations in the solar day as well as seasonal changes of the environmental day/night cycle impact the circadian cycles of all living organisms. Adaptation to these changes has evolved to include regulation by an endogenous mechanism known as the "biological clock," able to be synchronized by environmental signals or *Zeitgebers* ("time-givers"). In humans, the circadian periodicity, which is regulated by the suprachiasmatic nucleus (SCN) of the hypothalamus, the body's main "biological clock," is about 24.2 hours.[1] This periodicity is synchronized to exactly 24.0 hours by the external light/dark (LD) cycle acting through retinal-hypothalamic links.[2,3] Desynchronization of these circadian rhythms occurs under various conditions of environmental insult, giving rise to different kinds of circadian rhythm sleep disorders (CRSD).[4,5] Major CRSD include delayed sleep-phase syndrome, advanced sleep-phase syndrome, non-24-hour sleep/wake rhythm disorder, free-running sleep disorder, jet lag, and shift-work disorder.[6] These circadian rhythm disorders have a major impact on the health, social life, and work performance (often negative) of individuals.[7,8]

Jet lag comprises a constellation of symptoms that occurs as a result of disruptions of entrainment associated with time-zone transitions.[8,9] These symptoms consist of daytime fatigue, impaired alertness, insomnia, loss of appetite, poor psychomotor co-ordination, reduced cognitive skills, and depressed mood. The severity of jet lag symptoms depends on the number of time zones crossed, as well as the direction of travel. Eastbound travel tends to cause difficulties in falling asleep, whereas westbound travel interferes with sleep maintenance.[10]

The disruptive effects of jet lag have been documented at the molecular level of clock genes present in the SCN and peripheral tissues.[11] Eastbound travel causes phase advances in the body's circadian rhythms, while westbound flight induces phase delays in circadian rhythms. As a consequence, jet travelers are forced to synchronize their bodily rhythms; this resynchronization occurs at a speed of approximately 1.5 hours a day after westward flights, and approximately 1 hour a day after eastward flights, irrespective of whether their travel occurs during daytime or night.[8,12,13] Regardless of the direction of air travel there is also travel fatigue due to factors such as the cramped seats, altered feeding schedule, alcohol consumption, poor air quality, and inability to sleep.[8,14,15] These factors further aggravate the symptoms of jet lag.

Circadian Rhythm Disturbances in Jet Lag

In mammals, the circadian timing system is composed of many individual, tissue-specific cellular clocks.[16] At a molecular level, these circadian clocks are based on clock genes, some of which encode proteins able to feedback and inhibit their own transcription. The cellular oscillators consist of interlocked transcriptional and posttranslational feedback loops that involve a small number of core clock genes (about 12 genes identified to date).[16]

To generate coherent physiological and behavioral responses, the phases of this multitude of cellular clocks are orchestrated by a master circadian pacemaker residing in SCN.[17] The central clock is a key regulator of many bodily functions that follow a circadian rhythm, such as sleep and wakefulness, thermoregulation, glucose homeostasis and fat metabolism. The SCN communicates day-night cycle phase information to the rest of the

body through neuronal and humoral signals, including the autonomic nervous system and the neuroendocrine system.[18] Through them the peripheral circadian cellular clocks synchronize to the same phase. At the same time, the clocks of the periphery are able to respond to other environmental cues such as food intake, and alter their phase according to these cues.[16]

Synchronization of circadian rhythms, particularly the sleep/wake rhythm, to environmental LD cycles is essential for maintaining one's normal physical and mental health.[11] After time-zone transitions, bodily rhythms shift out of phase with local environment. The resulting internal desynchronization is largely responsible for the general malaise, sleep disturbances, loss of mental efficiency, irritability, anxiety, and fatigue that are encountered during the first week after a transmeridian flight. Inasmuch as the endogenous circadian system is slow to adapt to new time cues, a host of physiological and behavioral problems persist until the correct phase relationship is re-established between bodily rhythms and external *Zeitgebers*.[8,12,13]

Under normal conditions, the various circadian rhythms in the body are synchronized between themselves and with the external LD cycle.[19] When normal human beings are deprived of *Zeitgebers* some circadian rhythms, eg, the activity/rest cycle may lengthen to nearly 45 hours whereas the period of temperature, rapid eye movement sleep, and cortisol cycles remains close to 25 hours. This results in "internal desynchronization," that occurs in some people traveling across time zones.[10] Adaptation to time-zone transitions is particularly difficult in the elderly. This is because temporal organization of physiological processes is often deficient at an old age, and consequently this group is especially at risk for extended internal desynchronization following rapid time-zone transitions.[19,20] Indeed, in mice, entrainment to advancing schedules is not only more difficult but even increases mortality in aged animals.[21]

A comparison was made of effects of jet lag on several physiological and psychological variables in aircraft pilots flying the routes from Madrid to Mexico City (seven time zones) or from Madrid to Tokyo (eight time zones).[22,23] Activity/rest and heart rate rhythms, which are hypothesized to be linked to weak or exogenous oscillators became rapidly synchronized while temperature or 6-sulfatoxymelatonin excretion rhythms, which are regulated by the biological clock,[24] showed more rigid responses after the phase-shift. In young (<50 years) and old pilots (>50 years), the activity/rest rhythm rapidly adjusted to the new time schedule, whereas the acrophase of the temperature rhythm tended to remain close to the initial schedule. Among the group of older pilots the temperature rhythms showed no evidence of entrainment on reaching Tokyo, nor following the return flight to Madrid.[23] Changes in urinary 6-sulfatoxymelatonin and cortisol excretion were consistent with temperature regulation.[22]

Sleep Disturbances in Jet Lag

Both subjective and objective sleep recording studies have shown that poor sleep is a predictable consequence of rapid time-zone transitions. Sleep fragmentation, premature awakenings, difficulty in sleep initiation, and decrements in performance are the commonest features of jet lag.[7-9,12,13] Takahashi et al. evaluated the effects of transmeridian travel on various sleep parameters such as total sleep time, sleep onset latency, and sleep offset in a group of academicians who traveled from Japan to the USA and Canada, and back.[25] A significant decrease in total sleep time was noted on the second posttravel day following

eastward travel. After the decrease however, the total sleep time increased and then decreased again before returning to pretravel baseline. No significant variation in total sleep time was noted among westward travelers. The findings are consistent with those of earlier reports showing that the times of sleep onset and offset at the point of destination were affected by direction of travel. Eastward flight produced earlier times of sleep onset (0.5 hours) and sleep offset (1.5 hours) after trips, and the effect lasted for 2 days. Conversely, westward flights delayed the times of sleep onset and offset approximately by 1 hour until the fifth posttravel day. No effect on the quality or the length of sleep was noted.[15,26] The reduction in daytime activity seen following international air travel is linked to a restriction of the length of nocturnal sleep prior to arrival at the new destination.[27] Several studies have reported similar effects of simulated and real jet lag on sleep/wake problems.[28-31]

Management of Work Schedules for Pilots and Elite Athletes

Improperly designed work schedules, which do not take into consideration our present understanding of jet lag effects, can significantly impact the health of industry workers such as airline pilots. These health effects include a chronic dysregulation condition with consequent increases in psychophysiological disorders, a higher incidence of stress-related emotional changes, and diminished life expectancy. The potential tolerance of employees with regard to age and personality obtained by chronobiological assessment should be taken into account when designing work schedules, including stopover duration and rest periods between flights.[32-36] The optimal work strategy for this population is a compromise between these extreme alternatives: a long rest period at stopovers until full re-entrainment is achieved, or a short stop spent in relative isolation, maintaining the employees' retiring time to which he is accustomed at home so that re-entrainment to the new location is prevented. With an expected re-entrainment schedule equating to 1 hour/day westward or 1.5 hours/day eastward, the desired layover period can be kept at between 24 hours to 2 days to allow enough rest without greatly affecting home circadian rhythmicity.[37]

When considering athletic performance it has been shown that elite athletes traveling to the west or east over six to eight time zones demonstrate reduced grip strength and poor performance in training sessions, and that these effects last for up to several days after the flight.[37] Decreases in daily profiles of grip strength were also reported for a group of Olympic athletes and sedentary subjects who traveled eastward over 10 time zones.[38] In addition to poor athletic performance, sleep loss and mood disturbances must also be considered when dealing with rapid travel over several time zones.

PHARMACOLOGICAL MANAGEMENT OF JET LAG

Use of Melatonin and its Analogs

Several studies have investigated the effectiveness of a number of pharmacological interventions for minimizing jet lag symptoms. Drugs such as modafinil, dextroamphetamine sulfate, and caffeine have been evaluated for their ability to combat the fatigue and reduced alertness associated with jet lag. Of these, both slow-release and fast-release caffeine have been found effective.[30,39,40] As noted below, several studies have also shown that exogenously administered melatonin can alleviate jet lag symptoms, both by causing sleep propensity and by regulating timing of the sleep/wake cycle.

Melatonin is produced in most organisms, from algae to primates, and participates in various physiological processes. In addition to its effects on sleep and circadian regulatory actions, melatonin has a number of important health maintenance effects, including antioxidant, immunomodulatory, and oncostatic activities.[41] Melatonin has also been found beneficial in modulating pain perception[42] and in protecting against septic shock.[43]

In mammals including humans, the phase and amplitude of melatonin secretion are considered to be an "arm" of the biological clock,[44] by acting as a chronobiotic, eg, by affecting the phase and amplitude of circadian oscillation.[45] Due to its predictable regulation by environmental *Zeitgebers*, melatonin secretion is considered to be a marker or chemical code of the night. Up to a limit, the longer the length of darkness the longer the duration of melatonin secretion. In mammals that are seasonally responsive, the seasonal changes in the hours of light and dark produce parallel patterns of changes in melatonin secretion, and those alterations in melatonin cause the seasonal body changes.[46-49]

The timing of melatonin secretion is closely associated with the timing of sleep propensity and coincides with decreases in core body temperature. Physiologic doses of melatonin, ie, those resulting in circulating melatonin levels within normal nocturnal level (<200 pg/mL), have been shown to promote sleep onset in young healthy adults.[50] A wide range of melatonin doses (0.1-10 mg) were administered to young healthy adults, melatonin efficacy being similar between physiologic or pharmacologic doses of melatonin. Induction of high-circulating melatonin did not cause uncontrollable sleep initiation or general anesthesia.[51] Melatonin has the capacity to alter the timing of circadian rhythms and functions, thereby synchronizing them with prevailing LD cycles. Melatonin is now used successfully for treating various CRSD and conditions such as shift-work disorder.[12,52,53]

The chronobiological effects of melatonin are exerted through membrane G-protein-coupled MT_1 and MT_2 melatonin receptors present in the SCN,[54,55] while sleep-related actions may also involve additional brain regions in which MT_1 and MT_2 receptors have been described.[47] Melatonin acutely inhibits neuronal firing in SCN by acting on MT_1 melatonin receptors,[56] an effect that has been proposed as the mechanism by which melatonin regulates the sleep/wake cycle.[57] Melatonin's phase-shifting effects are mediated through MT_2 melatonin receptors present in SCN.[58] These two melatonin receptors modulate gamma-aminobutyric acid ($GABA_A$) receptors in the SCN differentially;[59] these GABA receptors, reportedly, both phase shift and synchronize SCN clock cells.[60]

Melatonin in Jet Lag

In the earlier discussion of jet lag symptoms, it was noted that transmeridian travel affects the sleep, circadian rhythms, and daytime activity of travelers, effects that often take several days to resynchronize to local environmental conditions. The time required for adaptation is generally determined by the size of the phase shift and *Zeitgeber* strength. This approximates to an adaptive shift of 1-1.5 hours per day, with eastbound flight causing a greater prolongation of symptoms when compared with westbound flights.[61,62]

Melatonin administration has been shown to shift circadian rhythms in humans.[63-65] This effect is a key factor in melatonin's actions in reducing jet lag symptoms, the therapeutic value of which has now been demonstrated in numerous studies.[30,66-73] Field studies on melatonin effectiveness to reduce jet lag symptoms are summarized in Table 1.

Table 1. Field studies of melatonin and jet lag in eastward and westward air travel.

Time zones	Dose (mg)	Number of days preflight	Time preflight	Time on flight day	Time at destination	Number of days	Results	Comments	Reference
Eastbound flights									
8	5	2	18:00h	18:00h	22:00-24:00h	4	VAS jet lag improved		10
9	5	1	17:00h		22:00-24:00h	4	Jet lag improved		74
12	5	3	10:00-12:00h	10:00-12:00h	22:00-24:00h	3	VAS jet lag improved		75
6, 9 &11	5	None	None	None	23:00h	3	Accelerated cortisol adaptation, nonsignificant VAS improvement		76
	8	None	None	17:00-18:00h	22:00-23:00h	3	VAS & sleepiness improved		68
8	10	3	30 min prebed	15:30-18:00h	30 min prebed	4	Bed/rise times advanced, slept longer	Posttravel avoided light	77
6 to 8	5 or 0.5 FR; 2 SR	None	None	None	Prebed	4	FR melatonin improved sleep quality, gave sleep shorter latency		78
6	5 or 0.5	None	None	Bedtime shifting schedule	Prebed	4	No effect	Shifted bedtime 1 h earlier daily; timing of melatonin poor	70
10	5	None	None	09:00-10:00h	22:00-23:00h	4	No difference from placebo	Irregular activity after arrival; inappropriate timing of melatonin	72
6 to 9	5 vs. zolpidem 10 vs. both	None	None	17:00-21:00h	Prebed	4	Either melatonin or zolpidem reduced jet lag and improved sleep	Zolpidem more effective but with side effects; the combination had adverse reactions	79
7	5 SR Caffeine 300	1	17:00h	16:00h	23:00h 08:00h	3 5	Resynchronization of hormone faster in both	Caffeine affected sleep quality	80
5	2mg SR vs. zopiclone 5	None	None	None	22:00h	1	Melatonin and zopiclone improved sleep measures equally		81
7	5 SR Caffeine 300		17:00h	16:00h	23:00h 08:00h	3 5	Improved recovery of sleep. Less daytime sleepiness	Caffeine affected sleep quality	30
13	3	None	None	10:00h	Prebed	7	Sleep and wakefulness resynchronized in 2.27 days	20-30 min daily blocks of exercise outdoors at destination. No placebo control	82

(continued on next page)

Table 1. Field studies of melatonin and jet lag in eastward and westward air travel. (*Continued*)

Time zones	Dose (mg)	Number of days preflight	Time preflight	Time on flight day	Time at destination	Number of days	Results	Comments	Reference
Westbound flights									
12	5	None	10:00-12:00h		22:00-24:00h	3	VAS jet lag improved, re-established sleep quicker	More severe jet lag than after eastbound flight	75
6, 9 & 11	5	None	None	None	23:00h	5	Nonsignificant improvement as compared to placebo		76
12	5	2 None	07:00-08:00h None	05:00h 05:00h	22:00-24:00h 22:00-24:00h	5 5	Worse than placebo trend to improve	Preflight rhythms disordered	67
12	3	None	None	11:00h	23:00h	6	Sleep and wakefulness resynchronized in 2.13 days	2-3 h daily blocks of exercise outdoors at destination. No placebo control	65
11	3	None	None	13:00h	Prebed	8	Sleep and wakefulness resynchronized in 2.54 days	20-30 min daily blocks of exercise outdoors at destination. No placebo control	82

FR=fast release; SR=slow release; VAS=visual analog scale.

In the first placebo-controlled clinical trial of this phenomenon, melatonin (5 mg dose) was administered in the early evening (18:00 hours) for 3 days prior to flight and for 4 days postflight at 23:00 hours to passengers traveling east over eight time zones.[66] Melatonin's superiority over the placebo substance was shown by subjective measures of jet lag (self-recorded sleep parameters, mood ratings), as well as by objective measures such as melatonin and cortisol rhythms, which adapted more rapidly in the melatonin-treated group than in the placebo-controlled group. The same investigators replicated this study in a larger sample consisting of 52 passengers who flew eastbound across eight time zones (from the UK to Australia). Melatonin in 5 mg doses was given 2 days prior to departure and for 4 days following the participants' arrival at the destination point. Significant reductions in jet lag symptoms were reported following melatonin ingestion.[83] Melatonin administration was also found to be of benefit to air-crew members whose jet lag symptoms were significantly reduced following the therapeutic regimen.[67] A meta-analysis of 10 studies using melatonin to alleviate jet lag symptoms found that melatonin taken at bedtime (22:00 hours) at the destination of the flight effectively decreased the symptoms of jet lag.[84] The dose of melatonin varied from 0.5 mg to 5.0 mg/day.

The effectiveness of melatonin administration for reducing jet lag symptoms was investigated in a study of a group of elite sports competitors who traveled from Buenos Aires to Tokyo (crossing 12 time zones) to participate in the final games of an international soccer competition.[65] The day before leaving Buenos Aires all participants were given 3 mg of melatonin at a time equating to their expected bedtime at Tokyo. This schedule of melatonin administration was adhered to continuously throughout the entire period of study. Participants were also asked to complete daily sleep log diaries. Upon arrival in Tokyo the subjects performed daily physical exercise out of doors during specific times (08:30 to 11:30 hours) in the morning, and from 15:00

to 18:00 hours in the afternoon. The purpose of this scheduling was to cover the phase-delay and phase-advance effects of light symmetrically, since this is known to influence the phase-response curve.[85] It was hypothesized that this strategically timed restriction of light exposure during the hypothetical minimum of body temperature would produce a contradictory signal for the clock (phase advance with first light exposure and phase delay with second), thus helping to eliminate endogenous phase effects. Exposure to sunlight and physical exercise was avoided at other times of the day. Individual actigrams derived from sleep log data revealed that subjects became synchronized within 24-48 hours, well in advance of what would have been expected in the absence of such a treatment schedule.[65] The findings of the study confirmed the value of a combined intervention approach: the investigators concluded that the timed administration of melatonin, restrictions in light exposure, and physical exercise, when used in a carefully integrated manner, could compensate for the normally expected blunting of endogenous melatonin secretion, and could thus be recommended for overcoming jet lag symptoms in long-haul flights.

Similar benefits of combined modality therapy were also found among nonathletes. In a study of the effects of melatonin plus other interventions on jet lag, sedentary volunteers (75 subjects crossing 13 time zones on an eastbound flight from Sydney to Buenos Aires, and 49 subjects on a westbound flight from Buenos Aires to Sydney, both by a transpolar route) were selected for investigation.[82] Passengers on the eastbound flight received 3 mg of melatonin daily 30 minutes before their expected bedtime at Sydney, beginning on the day of the flight and continuing throughout the period of their trip. All subjects were advised to perform their normal routine and to walk outdoors for at least 30 minutes at two restricted times of the day. Passengers on the westbound flight took 3 mg melatonin on the day of their flight to Buenos Aires at the expected sleeping time at Buenos Aires and continued it for 8 days in Buenos Aires. On reaching Buenos Aires, all volunteers were advised to perform their normal routines and to walk outdoors for at least 30 minutes at the same two restricted periods of the day as in Sydney. Subjects were also advised to maintain sleep diaries throughout the period of study. The sleep log diaries included the evaluation of sleep quality, morning freshness, and daily alertness on a visual analog scale.[82] The mean resynchronization rate was 2.27±1.1 days during the eastbound flight and 2.54±1.3 days for the westbound flight. These findings compared favorably to the expected minimal resynchronization rate after 13 hours of flight without any treatment, thus supporting the conclusion that jet lag symptoms can be significantly reduced by the carefully timed application of melatonin, light exposure, and physical activity.

In another study, the combined use of slow-release caffeine and melatonin improved several jet lag symptoms during an eastbound flight.[30] For travel of 11-13 hours, whether eastbound or westbound, available data from limited field studies indicate that a combination of melatonin, exposure to outdoor light, and exercise have a potent ameliorative effect on jet lag symptoms.[47]

Light exposure and avoidance of it in certain periods also determine adaptation to time-zone change[86] and in this regard the spectral quality of light plays an important role. Light sensitive retinal ganglion cells that contain melanopsin are maximally sensitive to short wavelength light (blue 460-480 nm).[87] Short wavelength light has greater phase shifting (melatonin suppressing) effects than white light, and hence

it was suggested that devices enriched with short wavelengths would be more effective for phase shifting and thus could be used in overcoming the effects of jet lag.[12] Exposure to natural sunlight together with timed administration of melatonin have been recommended by the American Academy of Sleep Medicine to hasten adaptation after changing time zone.[88]

There is very little information on the relative merits of different melatonin preparations for use on the alleviation of jet lag. A recent study evaluated the efficacy of three melatonin preparations, 3 mg regular fast release, 3 mg sustained release, and 3 mg surge-sustained release (a mixture of 1 mg fast release plus 2 mg sustained release).[64] Circadian phase advances or delays were assessed in two separate experiments using plasma melatonin levels as a parameter. Thirteen normal healthy male subjects aged 26 to 53 years were chosen for experiment 1 (circadian phase advance) and nine normal healthy male subjects aged 26 to 54 years were included in experiment 2 (circadian phase delay). In both studies, a fast-release melatonin preparation induced the expected phase changes. No differences in phase advance efficacy were observed among the three melatonin release preparations, while in the phase-delay study, phase shifts for the sustained release preparations could not be determined due to persistent high melatonin levels during sampling times. Based on this study it can be concluded that a fast-release melatonin preparation is effective for reducing circadian misalignment for both eastward and westward travel.[64]

Analysis of available evidence indicates that oral administration of melatonin is the best pharmacological treatment currently available for reducing the symptoms of jet lag. Hence, it can be concluded that strategically timed administration of melatonin is helpful for

Table 2. Recommended treatment for eastbound flight of up to 9 hours.

Day pretravel	Rise 1 hour earlier, go outdoors to be exposed to bright outdoor light, or use a bright light box if one is available. Take nonsoporific dose of melatonin 0.75 mg tablet* 2 hours prior to bedtime Ensure that you have adequate sleep before travel
Day of flight	Take melatonin 0.75 mg at 18:00h or 3 mg if boarding a plane and you plan to sleep
At destination	Wake in morning and be active outdoors for 30 min Take melatonin 0.75 mg 2 hours prior to bedtime until adapted

*Melatonin in doses higher than 1 mg are both mildly sleep-inducing and will phase shift the circadian clock, while doses under 1 mg are not soporific.[50]
These recommendations are speculative, based on references 8, 9, 13, 15, 26, 47, and 86.

Table 3. Recommended treatment for eastward or westward flight of 10 to 14 hours.

Day pretravel	Stay up 2.5 hours later with exposure to bright outdoor light or bright light box for 2 hours prior to bedtime Take nonsoporific dose of melatonin 0.75 mg on rising Ensure that you have adequate sleep before travel
Day of flight	Take melatonin 0.75 mg on rising
At destination	30 min exercise outdoors in bright light or using bright light box, between 08:00h and 11:00h and also between 13:00h and 17:00h Take melatonin 3 mg 2 hours before bedtime until adapted

These recommendations are speculative, based on references 8, 9, 13, 15, 15, 25, 26, 47, and 65.

Table 4. Recommended treatment for westbound flight of up to 9 hours.

Day pretravel	Stay up 2.5 hours later, with exposure to bright outdoor light or bright light box for 2 hours Take nonsoporific dose of melatonin 75 mg on rising Ensure you have adequate sleep before travel
Day of flight	Take melatonin 0.75 mg on rising
At destination	Stay up until desired bedtime, with exposure to bright outdoor light or bright light box Take melatonin 0.75 mg on rising Avoid morning bright light using sunglasses until adapted

These recommendations are speculative, based on references 8, 9, 13, 15, 26, 47, and 86.

readjusting the body clock during rapid time-zone transitions and can help millions of air travelers who suffer from jet lag symptoms (Tables 2-4). However, in view of the fact that the most important factor in adapting to time-zone change is to preserve sleep, melatonin agonists could be of advantage as compared with melatonin in alleviating the symptoms of jet lag, since they are more potent than melatonin for both initiating and maintaining sleep while also having effective chronobiotic properties.

Potential Use of Melatonin Agonists in Jet Lag

Ramelteon, a MT_1/MT_2 melatonin receptor agonist, has been shown in randomized, double-blind, placebo-controlled trials to be effective for treating insomnia.[89-91] It also has been shown to accelerate re-entrainment of circadian rhythms after an 8-hour phase advance of the LD cycle in rodents.[92] Compared with melatonin, ramelteon has an affinity for MT_1 and MT_2 melatonin receptors which is 3-16 times greater, and additionally has a longer half-life.[93] In addition to its efficacy for treating insomnia, its safety for treating chronic insomnia has been shown in various studies.[94-97]

Ramelteon has been shown to be effective as a phase-shifting agent in humans. In the first study of its effectiveness for treating CRSD, ramelteon was administered at doses of 1, 2, 4, and 8 mg to 75 affected adult subjects (18-45 years) for 6 days.[98] Ramelteon's significant promotion of phase-advance shifts in the target subjects demonstrated its efficacy for treating CRSD.

Ramelteon's effectiveness for treating jet lag symptoms was investigated in a recent placebo-controlled study of 110 healthy adults who had a history of jet lag sleep disturbances and who had flown eastward across five time zones from Hawaii to the east coast of the US.[99] Ramelteon (1-8 mg) was administered 5 minutes before bedtime for four nights following arrival at destination. Sleep parameters were measured using polysomnography and actigraphy on nights 2, 3, and 4, while next-day residual effects were assessed using psychomotor and memory function tests. Compared with placebo, there was a significant decrease in mean latency to persistent sleep on nights 2-4 with 1 mg ramelteon. Although a trend towards reduction in mean latency to persistent sleep was noted with 4 mg and 8 mg doses, the differences compared with placebo did not attain significance. When nights were considered individually, a significant reduction in latency to persistent sleep was detected on night 4 with 8 mg ramelteon.[99] Illustrating the importance of light as the strongest synchronizing agent for the circadian clock, two subsets of participants were evaluated including one kept in constant dim light (for the purpose of calculations of phase by evaluation of dim light melatonin offset time) and the other allowed to experience a natural light setting. The participants kept in dim light experienced significant reductions in mean latency to persistent sleep with ramelteon 1 mg

(nights 2 and 3) and 4 mg (night 3) and smaller, nonsignificant reductions with ramelteon 8 mg, whereas participants taking ramelteon in the natural light setting demonstrated no significant differences in latency to persistent sleep.[99] Hence, the chronobiotic effect of ramelteon was strongly affected by light circadian cues.[99] Indeed, although light therapy has been used as a treatment for jet lag with some success, its effectiveness is dependent upon appropriate timing and, if administered at a wrong time of the day, may hinder circadian adaptation by causing an inappropriate phase shift.[100] Future studies on large samples with more than 8-hour phase shifts of jet travel are needed to prove the efficacy of ramelteon in different doses in improving sleep quality and daytime performance and alertness in healthy adults.

Tasimelteon, another synthetic melatonin MT_1/MT_2 agonist, has also been recently studied for its effectiveness in reducing jet lag symptoms. Vanda Pharmaceutical has completed phase 2 and 3 studies on tasimelteon, and a randomized controlled trial for transient insomnia after sleep time shift was recently published.[101] Tasimelteon was effective in reducing sleep onset latency and in resetting the circadian melatonin rhythm, which indicated its potential suitability as treatment for jet lag, shift work, and other circadian rhythm sleep disorders.[101] The drug is well tolerated, does not induce impairment of next-day functioning or dependence, and seems to be safe in short-term treatment.

Jet Lag, Depression, and the Possible Role of Agomelatine

As noted above, jet lag symptoms are not exclusively physical. Jet airline passengers who have traveled both eastward and westward also frequently report that they have experienced depressive symptoms.[102-104]

Over a 6-year period Katz and coworkers studied 152 long-distance travelers who had been hospitalized in the Jerusalem Mental Health Center, Kfar Shaul Hospital for psychiatric complaints.[104] The patients were divided into groups based upon the number of time zones crossed. The direction of flight was mainly eastbound. Possible links between jet lag and major depressive disorder or psychotic disorder were evaluated based upon the following criteria: (a) absence of major mental problems before the flight, or good remission of existing disorders 1 year or more before the commencement of flight; and (b) the appearance of major affective syndromes or psychotic syndromes during first 7 days after landing. Although the number of first major affective episodes or psychotic syndromes associated with jet lag was found to be similar among groups, the number of relapses occurring conjointly with jet lag was found to be significantly greater in people crossing seven or more time zones.[104] The directionality of travel may also be a factor. In earlier studies, depression was noted in passengers with westbound flights and mania with eastbound flights.[102,103,105]

The hypothesis that various subtypes of affective disorders might be the result of rhythm failures (ie, that they were linked to "free-running rhythms") was first proposed by Halberg et al.[106] It has been suggested that internal phase angle disturbances, desynchronizations among various endogenous rhythms, ie, when these rhythms go in and out of phase with each other, may lie at the heart of depressive disorders.[107,108] The correction of the phase angle disturbances between sleep/wake cycles and circadian rhythms could thus remove the symptoms of depressive illness triggered by any factor including time-zone transitions.

In addition to the circadian rhythm disturbances, sleep disturbances also constitute the major feature encountered during rapid

time-zone transitions.[25,47] Evidence from epidemiological and electroencephalographic studies additionally implicate sleep disturbances as key factors in the pathogenesis of depressive illness.[109] The other evidence consistent with the circadian disruption hypothesis of depression comes from the observation that more than 80% of depressed patients have complaints of sleep disturbances[110-112] and demonstrate a variety of polysomnographic abnormalities.[113] Further, antidepressant therapies that also improve sleep efficiency are especially effective in reducing depressive symptomatology. Moreover, detailed analyses have shown that currently used antidepressants such as selective serotonin reuptake inhibitors exert adverse effects on sleep, and that the antidepressant effect may be counteracted by their effects on sleep.[114,115] These findings suggest that, for maximum effectiveness, an ideal antidepressant should simultaneously improve sleep efficiency and reduce depressive symptomatology.

Recently, the melatonergic antidepressant agomelatine has been introduced. Agomelatine is a novel antidepressant that acts simultaneously as a MT_1/MT_2 receptor agonist and as a 5-hydroxytryptamine ($5HT_{2c}$) receptor antagonist.[116,117] This dual mechanism of action is unique and is the basis for its antidepressant efficacy and ability to mitigate sleep/wakefulness rhythm disturbances. The effectiveness of agomelatine in improving sleep quality and reducing depressive symptoms has now been demonstrated in a number of clinical trials.[118-121]

It has been proposed that the dysregulation of melatonin secretion underlies various circadian-rhythm sleep disorders and depression.[122] A number of clinical studies have reported that melatonin secretion is disturbed in depressives.[123-131] These results would suggest that melatonin administration might be a useful strategy for mood disorders.

However, treatment of depressive disorders with exogenous melatonin alone has not been successful. Nevertheless the introduction of the combined action antidepressant agomelatine, which, as noted above, affects both melatonergic and serotonergic receptors, offers a new therapeutic option for treating mood disorders. Agomelatine has been shown to be effective in treating sleep-related problems such as difficulty in falling asleep, staying asleep, disturbed nocturnal sleep, and early morning awakening—symptoms that feature prominently in patients with depressive disorders.[132] The chronobiotic action of agomelatine was clinically evaluated in a study conducted in healthy older men. Administration of agomelatine (50 mg) or placebo to eight healthy older adults for a period of 15 days revealed that agomelatine caused phase advances of an average of 2 hours in the temperature profile as well as in the temporal organization of cortisol secretion.[133] These findings suggest that agomelatine is useful as a chronobiotic agent. Further evidence for agomelatine's usefulness as a treatment for chronobiological disorders has emerged from its application in the treatment of seasonal affective disorder.[134]

CONCLUSION

Jet lag symptoms include daytime fatigue, circadian rhythm sleep disturbances, impaired alertness, and many other minor conditions such as gastrointestinal disturbances, hormonal imbalances, and menstrual irregularities. In addition to these well-documented effects of jet lag, transmeridian air travel also exacerbates pre-existing affective disorders, and can produce severe symptoms in at-risk individuals, ie, those with a history of major depressive disorders.

Although only a few studies have specifically explored the potential linkage between jet lag

and major psychiatric disturbance, the frequency of its reported occurrence strongly suggests that this association merits further investigation. Accumulating evidence shows that jet lag can be managed by a combined treatment program which includes good sleep hygiene, adherence to work/rest schedules that do not disrupt circadian rhythms, the strategically timed use of the well-known chronobiotic, melatonin, and limited and carefully timed exposure to environmental light. The melatonergic agonists ramelteon and tasimelteon, which have strong affinity for MT_1 and MT_2 melatonin receptors, and, compared with melatonin, have a longer duration of action, can be more effective than melatonin alone in reducing the symptoms of jet lag.

The research evidence shows that a close linkage exists between jet lag and a number of physical and mental complaints in affected individuals. Disrupted sleep and transient disturbances to mood, the core symptoms of jet lag, underscore the relevance and value of a dual-action program of therapy.

Taken together, the research evidence showing the close linkage between jet lag and a number of symptoms such as disturbed sleep and transient disturbances in mood, point to the importance of applying a program of combined therapies for treating the constellation of complaints which are often reported by air travelers. In particular, when clinicians need to treat patients who have recently crossed a number of time zones, and who additionally have symptoms of dysphoria or depression, an antidepressant having both chronobiotic and sleep-promoting properties appears to be justified as a first-line choice for therapy. In this regard the newly introduced melatonergic antidepressant agomelatine may well be the best choice for jet lag-associated depressive disorders.

ACKNOWLEDGMENTS

The authors declare that there were no conflicts of interest.

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