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Jet lag, circadian rhythm sleep disturbances and depression: the role of melatonin and its analogs

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Short version of title:

Melatonergic drugs in jet lag and depression

Abstract

Travelling 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 disruptions to sleep/wakefulness and other circadian rhythms. In susceptible air travel passengers, jet lag may exacerbate affective illness ans result in psychiatric morbidity. It is suggested that dysregulation of circadian rhythms and melatonin secretion represents the common underlying factor in jet lag and other circadian disorders. Hence the effective management of jet lag requires timely application of the well known chronobiotic melatonin. Recent studies have emphasized the importance of strategically timed administrations of melatonin and appropriate limited exposure to environmental schedules. However, with the introduction of the melatonergic agonists such as ramelteon and tasimelteon, which have both a strong affinity for MT_1 and MT_2 melatonin receptors and a longer half life, a new therapeutic option now exists for treating the sleep disturbances associated with jet lag. The melatonin analogs are unique inasmuch as they can also enhance daytime alertness. Since jet lag exacerbates affective disorders in susceptible air-travel passengers, and can thus produce psychiatric morbidity, there is a need for an effective antidepressant with chronobiotic properties. In this regard the recently introduced melatonergic antidepressant agomelatine, which has successfully established its supremacy over other antidepressants in having chronobiotic effects, represents a good choice for treating depressive symptoms that are associated with jet lag.

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

Introduction

The cyclical nature of geophysical variations in the solar day as well as seasonal changes of the environmental day/night cycle is manifested in all living organisms. Adaptation to these changes has evolved to include regulation by both an endogenous mechanism known as the "biological clock ", and an exogenous synchronizing component, the environmental *Zeitgeber*.[1] The circadian periodicity, which is regulated by the suprachiasmatic nucleus (SCN) of the hypothalamus, the body´s main "biological clock", is approximately 24.2h. This periodicity is synchronized to exactly 24.0 h 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] Major CRSD include delayed sleep phase syndrome, advanced sleep-phase syndrome,non-24 h sleep-wake rhythm disorder, free-running sleep disorder, jet lag and shift-work.[5] These circadian rhythm disorders have a major impact on the health, social life and work performance (often negative) of individuals.[6,7]

Jet lag comprises a constellation of symptoms that occurs as a result of disruptions of entrainment associated with time-zone transitions.[7,8] 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.[9]

The disruptive effects of jet lag have been documented at the molecular level of clock genes present in the SCN and peripheral tissues.[1] 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 h a day after westward flights and approximately 1 h a day after eastward flight irrespective of whether their travel occurs during daytime or night.[7,10,11] Regardless of the direction of air travel there is also travel fatigue due to factors such as the cramped seats, altered

feeding schedule, poor air quality and inability to sleep.[7,12,13] These factors further aggravate the symptoms of jet lag.

Circadian rhythm disturbances in jet lag

Synchronization of circadian rhythms, particularly the sleep/wake rhythm, to environmental LD cycles is essential for maintaining man's normal physical and mental health.[1] After time zone transitions, bodily rhythms shift out of phase with local environmental light *Zeitgeber*. 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*.[7,10,11] A complicating factor is that each of the body's multiple functions has its own unique circadian rhythm, and, further, these functions have separate time requirements for normalizing their phase relationships, not only with other internal rhythms, but also with the LD cycles of the environment. The complexity of this dynamic interaction means that the entire process can be impacted by even small physiological changes within the individual, and consequently there is considerable variability in the time period that each jet traveler requires for full circadian adjustment to local conditions. Adaptation to time zone transitions is particularly difficult in the elderly. In older people, temporal organization of physiological processes is deficient, and consequently this age group is especially at risk for extended internal desynchronization following rapid time zone transitions.[14]

A comparison has been made of effects of jet lag on several physiological and psychological variables in a two year collaborative field study of Spanish pilots flying the routes from Madrid to Mexico City (Mexico; 7 time zones) or from Madrid to Tokyo (8 time zones).[15] Pilots' activities, temperatures, and heart rates were recorded with telemetry. The pilots´ time estimates of short, intermediate and long intervals were recorded along with other psychological variables such as anxiety, fatigue, and performance. Urinary 6-sulphatoxymelatonin and cortisol excretion were also

measured.[16] Activity/rest and heart rate rhythms, which are hypothesized to be linked to weak or exogenous oscillators became rapidly synchronized while temperature or 6-sulphatoxymelatonin excretion rhythms, which are regulated by the biological clock,[17] showed more rigid responses after the phase-shift. In young (less than 50 yrs) and old pilots (more than 50 yrs), 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. This desynchronization was evident until the return flight (day 5) and persisted at least 1 day after arrival in Madrid. In the case of Madrid–Tokyo flights there was an abrupt phase advance of the activity/rest rhythm coincident with the light/dark *Zeitgeber* phase shift during the first day, whereas no apparent phase shift in the temperature rhythm was observed. On the second day in Tokyo a phase advance in the temperature rhythm occurred. The return flight to Madrid induced rapid re-entrainment of both rhythms. Among the group of older pilots however the temperature rhythms showed no evidence of entrainment on reaching Tokyo, nor following the return flight to Madrid.[15] Changes in urinary-6 sulphatoxymelatonin and cortisol excretion were consistent with temperature regulation.[16]

Sleep disturbances in jet lag

Both subjective and objective sleep recording studies have shown that poor sleep is a characteristic feature of rapid time zone transitions. Sleep fragmentation, premature awakenings, difficulty in initiation of sleep, and decrements in performance are the commonest features of jet lag.[6-8,10,11] 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 travelled from Japan to the USA and Canada and back.[18] A significant decrease in total sleep time was noted on the second post-travel day following eastward travel. After the decrease however the total sleep time increased and then decreased again before returning to pre-travel 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 h) and sleep offset (1.5 h)

after trips and the effect lasted for 2 days. Conversely westward flights delayed the times of sleep onset and offset approximately by 1 h until the 5th post travel day. No effect on the quality or the length of sleep was noted.[13,19,20] 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.[21] Several studies have reported on the effects of simulated and real jet lag on sleep-wake problems.[22-25]

Management of work schedules for pilots

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.[26-30] 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 accompanied with 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 h/day westward or 1.5 h/day eastward, the desired layout period can be kept to between 24 h to 2 days to allow enough rest without greatly affecting home circadian rhythmicity.[20,31]

Jetlag and athletic performance

It has been shown that elite athletes travelling 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.[32] Decreases in daily profiles of grip strength were also reported for a group of Olympic athletes and sedentary people who travelled eastward over ten time zones.[33] In addition to poor

athletic performance, sleep loss and mood disturbances also have also been reported following rapid travel over several time zones.[32,34]

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 sulphate, and caffeine have been evaluated for their ability to combat tried the fatigue and reduced alertness associated with jet lag. Of these both slow release and fast release caffeine have been found effective.[24,35,36] 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 oncogenic activities.[37] Melatonin has also been found beneficial in modulating pain perception[38] and in protecting against septic shock.[39]

In mammals including humans, the phase and amplitude of melatonin secretion are considered to act as an "arm" of the biological clock.[40] 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.[41-44]

The timing of melatonin secretion is closely associated with the timing of sleep propensity and coincides with decreases in core body temperature. 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.[10,45,46]

The chronobiological effects of melatonin are exerted through membrane G-protein-coupled MT_1 and MT_2 melatonin receptors present in the SCN.[47,48] while sleep related actions may also involve additional brain regions in which MT_1 and MT_2 receptors have been described.[42] Melatonin acutely inhibits neuronal firing in SCN by acting on MT_1 melatonin receptors.[49], an effect which has been proposed as the mechanism by which melatonin regulates the sleep-wake cycle.[50] Melatonin's phase shifting effects are mediated through MT_2 melatonin receptors present in SCN.[51] These two melatonin receptors modulate $GABA_A$ receptors in the SCN differentially.[52]; these GABA receptors reportedly both phase shift and synchronize SCN clock cells.[53]

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 which 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 h per day, with eastbound flight causing a greater prolongation of symptoms when compared to westbound flights.[54,55]

Melatonin administration has been shown to shift circadian rhythms in humans.[56-58] 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.[24,59-66] In the first placebo controlled clinical trial of this phenomenon, melatonin (5 mg dose) was administered in the early evening (18:00 h) 3 days prior to flight and for 4 days (post-flight) at 23:00 h to passengers travelling east over 8 time zones.[59] Melatonin's superiority over the placebo substance was shown by both subjective measures of jet lag, self recorded sleep parameters, mood ratings, as well as 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 8 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.[67] Melatonin administration was also found to be of benefit to air-crew members whose jet lag symptoms were significantly reduced following the therapeutic regimen.[60] A meta-analysis of 10 studies using melatonin to alleviate jet lag symptoms found that melatonin taken at bedtime (22:00 h) at the destination of the flight effectively decreased the symptoms of jet lag.[68] The dose of melatonin varied from 0.5 mg to 5.0 mg /day.

A study was conducted on a group of elite sports competitors who travelled from Buenos Aires to Tokyo (crossing 12 time zones) to participate in the final games of an international soccer competition.[58] 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 h) in the morning, and from 15:00 to 18:00 h in the afternoon. The purpose of this scheduling was to cover the phase delay and phase advance effects of light symmetrically, as this will influence the phase response curve.[69.] 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 actograms derived from sleep log data revealed that subjects became synchronized within 24 -48 h, well in advance of what would have been expected in the absence of such a treatment schedule.[58] 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 scheduled combined 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 non-athletes. In a study of the effects of melatonin plus other interventions on jet lag, sedentary volunteers, 75 subjects 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.[70] 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.[70] 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 h of flight without any treatment, which is 7 days, 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.[24] For travel of 11-13 h, 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.[42]

Analysis of the evidence reviewed above indicates that oral administration of melatonin is the best pharmacological treatment currently available for reducing the symptoms of jet lag. Hence we conclude that strategically timed administration of melatonin is helpful for readjusting the body clock during rapid time-zone transitions and could help millions of air-travellers who suffer from jet lag symptoms.

Potential use of melatonin agonists in jet lag

Ramelteon (Rozerem^{TM}), a MT_1/MT_2 melatonin receptor agonist, has been shown in randomized double-blind placebo controlled trials to be effective for treating insomnia.[71-73] It also has been shown to accelerate re-entrainment of circadian rhythms after an 8 h phase advance of the light –dark cycle in rodents.[74] Compared to 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.[75] In addition to its efficacy for treating insomnia, its safety for treating chronic insomnia has been shown in various studies.[76-79]

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 yrs) for 6 days.[80] Ramelteon's significant promotion of phase-advance shifts in the target subjects demonstrated its efficacy for treating CRSD. A recent placebo-controlled study included 110 healthy adults with a history of jet lag sleep disturbances and flying eastward across five time zones from Hawaii to the east coast of the US.[81] Ramelteon (1-8 mg) was administered 5 min before bedtime (local time) for four nights. Sleep parameters were measured using polysomnography on nights 2, 3, and 4 while next-day residual effects were assessed using psychomotor and memory function tests.[81] Compared to placebo, there was a significant decrease in mean latency to persistent sleep on nights 2-4 with ramelteon 1 mg, but not with 4 or 8 mg doses. The lack of significant reductions at higher doses could be due to the small sample size used for study (n=27 for each ramelteon group) No consistent significant differences were observed with ramelteon vs. placebo on measures of next-day residual effects except on day 4 where participants in all ramelteon groups performed significantly worse.[81] In view of its circadian phase shifting effects, ramelteon could be proposed as a potential therapy for inducing rapid resynchronization following time zone transition of jet travelers. However, further studies on large samples and with more than 8 h phase shifts of jet travel are needed to test the efficacy of ramelteon in different doses in improving sleep quality and day time performance and alertness in healthy adults.

Vanda Pharmaceutical has completed phase 2 and 3 studies on the melatonin MT_1/MT_2 agonist tasimelteon and a randomized controlled trial of for transient insomnia after sleep time shift was recently published.[82] 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.[82] 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 travelled both eastward and westward also frequently report that they have experienced depressive symptoms.[83-85] Over a six 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.[85] 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 were found to be similar among groups the number of relapses occurring conjointly with jet lag was found to be significantly greater in people crossing 7 or more time zones.[85] In earlier studies depression was noted in passengers with westbound flights and mania with eastbound flights.[83,84] It has been suggested that the transient desynchronization seen in jet travelers can trigger affective disorders.[86]

The hypothesis that various subtypes of affective disorders might be the result of rhythm failures (i.e., that they were linked to “free running rhythms”) was first proposed by Halberg et al..[87] A “free running rhythm” refers to the genetically determined internal rhythm that a healthy individual displays when isolated from all

external time cues. When dissociated from these external cues the individually generated rhythm varies somewhat from the normal daily pattern (humans usually showing periods longer than 24 h). A rhythm is said to be “phase advanced” when its peak occurs earlier than its normal pattern and is said to be “phase delayed” when it occurs later.

It has been suggested that internal phase angle disturbances, desynchronizations among various endogenous rhythms, i.e., when these rhythms go in and out of phase with each other, may lie at the heart of depressive disorders.[88,89] 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.[18,42] Evidence from epidemiological and electroencephalographic studies additionally implicate sleep disturbances as key factors in the pathogenesis of depressive illness.[90] 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.[91-93] and demonstrate a variety of polysomnographic abnormalities.[94] and further that 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.[95,96] Hence an ideal antidepressant should 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 $5HT_{2c}$ receptor antagonist.[97,98]This dual mechanism of action is unique and is the basis for its antidepressant efficacy and for mitigating sleep/wakefulness rhythm disturbances. The effectiveness of agomelatine in improving sleep quality and reducing depressive symptoms has been demonstrated in number of clinical trials.[99-102]

It has been proposed that the dysregulation of melatonin secretion underlies various circadian-rhythm sleep disorders and depression.[103] A number of clinical studies have reported that melatonin secretion is disturbed in depressives.[104-112] 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, provides a new therapeutical alternative for the treatment of mood disorders. The chronobiotic action of agomelatine was clinically evaluated in a study conducted in healthy older men. Administration of agomelatine (50 mg) or placebo to 8 healthy older adults for a period of 15 days revealed that agomelatine caused phase advances of an average of 2 h in the temperature profile as well as in the temporal organization of cortisol secretion.[113] These findings suggest that agomelatine is useful as a chronobiotic agent.

Further evidence for agomelatine's usefulness as a treatment for chronobiological disorders emerged from its application in the treatment of seasonal affective disorder (SAD). In chronobiological studies on human subjects, core body temperature and melatonin levels have been used as markers for assessing circadian phase position. Phase delay of the circadian pacemaker relative to the timing of the habitual sleep/wake cycle is considered as one of the major contributing factors in the pathophysiology of SAD.[114] Agomelatine (25mg/day administered in the evening) was used to treat 37 acutely depressed SAD patients for a period of 14 weeks, with treatment outcome being assessed by the SIGH-SAD scale and *Circascreen*, a self rating scale for the assessment of sleep and circadian rhythm disturbances.[115] Agomelatine treatment caused a significant decrease in SAD symptoms starting from 2 weeks onward.

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, intercontinental air travel also exacerbates pre-existing affective disorders, and can produce severe symptoms in at risk individuals, i.e., 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 in accordance with circadian rhythm principles, 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 to melatonin, have a longer duration of its action, can be more effective than melatonin alone in reducing the symptoms of jet lag.

Taken together, the research evidence showing the close linkage between jet lag and a number of symptoms such as disturbed sleep and transient disturbances to mood, point to the importance of applying a program of combined therapies for treating the constellation of complaints which are often reported by jet 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 as 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.

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Conflict of interest statement and disclosure statement

S.R. Pandi-Perumal is a stockholder and the President and Chief Executive Office of Somnogen Inc., a New York Corporation. He declared no competing interests that might be perceived to influence the content of this article. All remaining authors declare that they have no proprietary, financial, professional, nor any other personal interest of any kind in any product or services and/or company that could be construed or considered to be a potential conflict of interest that might have influenced the views expressed in this manuscript.

References

1 Kyriacou CP, Hastings MH. Circadian clocks: genes, sleep, and cognition. *Trends Cogn Sci.* 2010, in press.

2 Moore RY, Speh JC, Leak RK. Suprachiasmatic nucleus organization. *Cell Tissue Res.* 2002;309:89-98.

3 Morin LP, Allen CN. The circadian visual system, 2005. *Brain Res Brain Res Rev.* 2006;51:1-60.

4 Pandi-Perumal SR, Trakht I, Spence DW, et al. The roles of melatonin and light in the pathophysiology and treatment of circadian rhythm sleep disorders. *Nat Clin Pract Neurol.* 2008;4:436-447.

5 Zee PC, Manthena P. The brain's master circadian clock: implications and opportunities for therapy of sleep disorders. *Sleep Med Rev.* 2007;11:59-70.

6 Samuels C. Sleep, recovery, and performance: the new frontier in high-performance athletics. *Phys Med Rehabil Clin N Am.* 2009;20:149-59, ix.

7 Sack RL. Clinical practice. Jet lag. *N Engl J Med.* 2010;362:440-447.

8 Waterhouse J, Reilly T. Managing jet lag. *Sleep Med Rev.* 2009;13:247-248.

9 Fahey CD, Zee PC. Circadian rhythm sleep disorders and phototherapy. *Psychiatr Clin North Am.* 2006;29:989-1007.

10 Arendt J. Managing jet lag: Some of the problems and possible new solutions. *Sleep Med Rev.* 2009;13:249-256.

11 Auger RR, Morgenthaler TI. Jet lag and other sleep disorders relevant to the traveler. *Travel Med Infect Dis.* 2009;7:60-68.

12 Reilly T, Atkinson G, Waterhouse J. Travel fatigue and jet-lag. *J Sports Sci.* 1997;15:365-369.

13 Nicholson AN. Intercontinental air travel: the cabin atmosphere and circadian realignment. *Travel Med Infect Dis.* 2009;7:57-59.

14 Monk TH. Aging human circadian rhythms: conventional wisdom may not always be right. *J Biol Rhythms.* 2005;20:366-374.

15 Ariznavarreta C, Cardinali DP, Villanua M, et al. Circadian rhythms in airline pilots submitted to long-haul transmeridian flights. *Aviat Space Environ Med.* 2002;73:445-455.

16 Tresguerres J, Ariznavarreta C, Granados B, et al. Circadian urinary 6-sulphatoxymelatonin, cortisol excretion and locomotor activity in airline pilots during transmeridian flights. *J Pineal Res* 2001;31:16-22.

17 Shanahan TL, Czeisler CA. Physiological effects of light on the human circadian pacemaker. *Semin Perinatol.* 2000;24:299-320.

18 Takahashi T, Sasaki M, Itoh H, et al. Melatonin alleviates jet lag symptoms caused by an 11-hour eastward flight. *Psychiatry Clin Neurosci.* 2002;56:301-302.

19 Nicholson AN. Sleep and intercontinental flights. *Travel Med Infect Dis.* 2006;4:336-339.

20 Lowden A, Akerstedt T, Wibom R. Suppression of sleepiness and melatonin by bright light exposure during breaks in night work. *J Sleep Res.* 2004;13:37-43.

21 Roehrs T, Turner L, Roth T. Effects of sleep loss on waking actigraphy. *Sleep.* 2000;23:793-797.

22 Wegmann HM, Gundel A, Naumann M, et al. Sleep, sleepiness, and circadian rhythmicity in aircrews operating on transatlantic routes. *Aviat Space Environ Med.* 1986;57:B53-B64.

23 Samel A, Wegmann HM, Vejvoda M. Jet lag and sleepiness in aircrew. *J Sleep Res.* 1995;4:30-36.

24 Beaumont M, Batejat D, Pierard C, et al. Caffeine or melatonin effects on sleep and sleepiness after rapid eastward transmeridian travel. *J Appl Physiol.* 2004;96:50-58.

25 Sack RL. The pathophysiology of jet lag. *Travel Med Infect Dis.* 2009;7:102-110.

26 Costa G, Haus E, Stevens R. Shift work and cancer - considerations on rationale, mechanisms, and epidemiology. *Scand J Work Environ Health.* 2010;36:163-179.

27 Stevens RG, Blask DE, Brainard GC, et al. Meeting report: the role of environmental lighting and circadian disruption in cancer and other diseases. *Environ Health Perspect.* 2007;115:1357-1362.

28 Arendt J. Shift work: coping with the biological clock. *Occup Med (Lond).* 2010;60:10-20.

29 Grundy A, Sanchez M, Richardson H, et al. Light intensity exposure, sleep duration, physical activity, and biomarkers of melatonin among rotating shift nurses. *Chronobiol Int.* 2009;26:1443-1461.

30 Thorpy MJ. Managing the patient with shift-work disorder. *J Fam Pract.* 2010;59:S24-S31.

31 Bjorvatn B, Stangenes K, Oyane N, et al. Randomized placebo-controlled field study of the effects of bright light and melatonin in adaptation to night work. *Scand J Work Environ Health.* 2007;33:204-215.

32 Lemmer B, Kern RI, Nold G, et al. Jet lag in athletes after eastward and westward time-zone transition. *Chronobiol Int.* 2002;19:743-764.

33 Steenland K, Deddens JA. Effect of travel and rest on performance of professional basketball players. *Sleep.* 1997;20:366-369.

34 Waterhouse J, Edwards B, Nevill A, et al. Identifying some determinants of "jet lag" and its symptoms: a study of athletes and other travellers. *Br J Sports Med.* 2002;36:54-60.

35 Schwartz JR. Pharmacologic management of daytime sleepiness. *J Clin Psychiatry.* 2004;65 Suppl 16:46-49.

36 Caldwell JA. Fatigue in aviation. *Travel Med Infect Dis.* 2005;3:85-96.

37 Pandi-Perumal SR, Srinivasan V, Maestroni GJM, et al. Melatonin: Nature's most versatile biological signal? *FEBS Lett.* 2006;273:2813-2838.

38 Srinivasan V, Pandi-Perumal SR, Spence DW, et al. Potential use of melatonergic drugs in analgesia: mechanisms of action. *Brain Res Bull.* 2010;81:362-371.

39 Srinivasan V, Pandi-Perumal SR, Spence DW, et al. Melatonin in septic shock: Some recent concepts. *J Crit Care.* 2010.¿, in press.

40 Dijk DJ, von Schantz M. Timing and consolidation of human sleep, wakefulness, and performance by a symphony of oscillators. *J Biol Rhythms.* 2005;20:279-290.

41 Bartness TJ, Goldman BD. Mammalian pineal melatonin: a clock for all seasons. *Experientia.* 1989;45:939-945.

42 Brown GM, Pandi-Perumal SR, Trakht I, et al. Melatonin and its relevance to jet lag. *Travel Med Infect Dis.* 2009;7:69-81.

43 Claustrat B, Brun J, Chazot G. The basic physiology and pathophysiology of melatonin. *Sleep Med Rev.* 2005;9:11-24.

44 Brown GM, Pandi-Perumal SR, Trakht I, et al. The role of melatonin in seasonal affective disorder.In: Partonen T, Pandi-Perumal, S R, eds. Seasonal Affective Disorder Practice and Research, 2nd ed. Oxford: Oxford University Press, 2010: 149-162.

45 Arendt J, Skene DJ. Melatonin as a chronobiotic. *Sleep Med Rev.* 2005;9:25-39.

46 Burgess HJ, Sharkey KM, Eastman CI. Bright light, dark and melatonin can promote circadian adaptation in night shift workers. *Sleep Med Rev.* 2002;6:407-420.

47 Dubocovich ML, Delagrange P, Krause DN, et al. Nomenclature, classification and pharmacology of G protein-coupled melatonin receptors. 2010, in press.

48 Dubocovich ML, Markowska M. Functional MT_1 and MT_2 melatonin receptors in mammals. *Endocrine.* 2005;27:101-110.

49 Liu C, Weaver DR, Jin X, et al. Molecular dissection of two distinct actions of melatonin on the suprachiasmatic circadian clock. *Neuron.* 1997;19:91-102.

50 von Gall C, Stehle JH, Weaver DR. Mammalian melatonin receptors: molecular biology and signal transduction. *Cell Tissue Res.* 2002;309:151-162.

51 Hunt AE, Al Ghoul WM, Gillette MU, et al. Activation of MT_2 melatonin receptors in rat suprachiasmatic nucleus phase advances the circadian clock. *Am J Physiol Cell Physiol.* 2001;280:C110-C118.

52 Wan Q, Man HY, Liu F, et al. Differential modulation of $GABA_A$ receptor function by Mel_{1a} and Mel_{1b} receptors. *Nat Neurosci.* 1999;2:401-403.

53 Liu C, Reppert SM. GABA synchronizes clock cells within the suprachiasmatic circadian clock. *Neuron.* 2000;25:123-128.

54 Gherardin T. Jet lag. A problem for 'long haul' travellers. *Aust Fam Physician.* 1999;28:833.

55 Arendt J. Jet-lag. *Lancet.* 1998;351:293-294.

56 Kennaway DJ, Wright H. Melatonin and circadian rhythms. *Curr Top Med Chem.* 2002;2:199-209.

57 Paul MA, Miller JC, Gray GW, et al. Melatonin treatment for eastward and westward travel preparation. *Psychopharmacology (Berl).* 2010;208:377-386.

58 Cardinali DP, Bortman GP, Liotta G, et al. A multifactorial approach employing melatonin to accelerate resynchronization of sleep-wake cycle after a 12 time-zone westerly transmeridian flight in elite soccer athletes. *J Pineal Res.* 2002;32:41-46.

59 Arendt J, Aldhous M, Marks V. Alleviation of jet lag by melatonin: preliminary results of controlled double blind trial. *Br Med J (Clin Res Ed).* 1986;292:1170.

60 Petrie K, Dawson AG, Thompson L, et al. A double-blind trial of melatonin as a treatment for jet lag in international cabin crew. *Biol Psychiatry.* 1993;33:526-530.

61 Claustrat B, Brun J, David M, et al. Melatonin and jet lag: confirmatory result using a simplified protocol. *Biol Psychiatry.* 1992;32:705-711.

62 Lino A, Silvy S, Condorelli L, et al. Melatonin and jet lag: treatment schedule. *Biol Psychiatry.* 1993;34:587.

63 Spitzer RL, Terman M, Williams JB, et al. Jet lag: clinical features, validation of a new syndrome-specific scale, and lack of response to melatonin in a randomized, double-blind trial. *Am J Psychiatry.* 1999;156:1392-1396.

64 Samel A. Melatonin and jet-lag. *Eur J Med Res.* 1999;4:385-388.

65 Edwards BJ, Atkinson G, Waterhouse J, et al. Use of melatonin in recovery from jet-lag following an eastward flight across 10 time-zones. *Ergonomics.* 2000;43:1501-1513.

66 Revell VL, Burgess HJ, Gazda CJ, et al. Advancing human circadian rhythms with afternoon melatonin and morning intermittent bright light. *J Clin Endocrinol Metab.* 2006;91:54-59.

67 Arendt J, Skene DJ, Middleton B, et al. Efficacy of melatonin treatment in jet lag, shift work, and blindness. *J Biol Rhythms.* 1997;12:604-617.

68 Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. *Cochrane Database Syst Rev.* 2002;CD001520.

69 Czeisler CA, Kronauer RE, Allan JS, et al. Bright light induction of strong (type 0) resetting of the human circadian pacemaker. *Science.* 1989;244:1328-1333.

70 Cardinali DP, Furio AM, Reyes MP, et al. The use of chronobiotics in the resynchronization of the sleep/wake cycle. *Cancer Causes Control.* 2006;17:601-609.

71 Bellon A. Searching for new options for treating insomnia: are melatonin and ramelteon beneficial? *J Psychiatr Pract.* 2006;12:229-243.

72 Dobkin RD, Menza M, Bienfait KL, et al. Ramelteon for the treatment of insomnia in menopausal women. *Menopause Int.* 2009;15:13-18.

73 Gross PK, Nourse R, Wasser TE. Ramelteon for insomnia symptoms in a community sample of adults with generalized anxiety disorder: an open label study. *J Clin Sleep Med.* 2009;5:28-33.

74 Hirai K, Kita M, Ohta H, et al. Ramelteon (TAK-375) accelerates reentrainment of circadian rhythm after a phase advance of the light-dark cycle in rats. *J Biol Rhythms.* 2005;20:27-37.

75 Kato K, Hirai K, Nishiyama K, et al. Neurochemical properties of ramelteon (TAK-375), a selective MT1/MT2 receptor agonist. *Neuropharmacology.* 2005;48:301-310.

76 Erman M, Seiden D, Zammit G, et al. An efficacy, safety, and dose-response study of ramelteon in patients with chronic primary insomnia. *Sleep Medicine.* 2006;;7:17-24

77 Roth T, Seiden D, Wang-Weigand S, et al. A 2-night, 3-period, crossover study of ramelteon's efficacy and safety in older adults with chronic insomnia. *Curr Med Res Opin.* 2007;23:1005-1014.

78 Zammit G, Erman M, Wang-Weigand S, et al. Evaluation of the efficacy and safety of ramelteon in subjects with chronic insomnia. *J Clin Sleep Med.* 2007;3:495-504.

79 Mini L, Wang-Weigand S, Zhang J. Ramelteon 8 mg/d versus placebo in patients with chronic insomnia: post hoc analysis of a 5-week trial using 50% or greater reduction in latency to persistent sleep as a measure of treatment effect. *Clin Ther.* 2008;30:1316-1323.

80 Richardson GS, Zee PC, Wang-Weigand S, et al. Circadian phase-shifting effects of repeated ramelteon administration in healthy adults. *J Clin Sleep Med.* 2008;4:456-461.

81 Zee PC, Wang-Weigand S, Wright KP, Jr., et al. Effects of ramelteon on insomnia symptoms induced by rapid, eastward travel. *Sleep Med.* 2010;11:525-533.

82 Rajaratnam SM, Polymeropoulos MH, Fisher DM, et al. Melatonin agonist tasimelteon (VEC-162) for transient insomnia after sleep-time shift: two randomised controlled multicentre trials. *Lancet.* 2009;373:482-491.

83 Jauhar P, Weller MP. Psychiatric morbidity and time zone changes: a study of patients from Heathrow airport. *Br J Psychiatry.* 1982;140:231-235.

84 Young DM. Psychiatric morbidity in travelers to Honolulu, Hawaii. *Compr Psychiatry.* 1995;36:224-228.

85 Katz G, Knobler HY, Laibel Z, et al. Time zone change and major psychiatric morbidity: the results of a 6-year study in Jerusalem. *Compr Psychiatry.* 2002;43:37-40.

86 Srinivasan V, Spence DW, Pandi-Perumal SR, et al. Jet lag: therapeutic use of melatonin and possible application of melatonin analogues. *Travel Med Infect Dis.* 2008;6:17-28.

87 Halberg F, Vestergaard P, Sakai M. Rhythmometry on urinary 17-ketosteroid excretion by healthy men and women and patients with chronic schizophrenia; possible chronopathology in depressive illness. *Arch Anat Histol Embryol.* 1968;51:299-311.

88 Wehr TA, Wirz-Justice A. Circadian rhythm mechanisms in affective illness and in antidepressant drug action. *Pharmacopsychiatria.* 1982;15:31-39.

89 Healy D, Waterhouse JM. The circadian system and the therapeutics of the affective disorders. *Pharmacol Ther.* 1995;65:241-263.

90 Lustberg L, Reynolds CF. Depression and insomnia: questions of cause and effect. *Sleep Med Rev.* 2000;4:253-262.

91 Reynolds CF, III, Monk TH, Hoch CC, et al. Electroencephalographic sleep in the healthy "old old": a comparison with the "young old" in visually scored and automated measures. *J Gerontol.* 1991;46:M39-M46.

92 Bunney JN, Potkin SG. Circadian abnormalities, molecular clock genes and chronobiological treatments in depression. *Br Med Bull.* 2008;86:23-32.

93 Quera-Salva MA, Lemoine P, Guilleminault C. Impact of the novel antidepressant agomelatine on disturbed sleep-wake cycles in depressed patients. *Hum Psychopharmacol.* 2010;25:222-229.

94 Riemann D, Berger M, Voderholzer U. Sleep and depression--results from psychobiological studies: an overview. *Biol Psychol.* 2001;57:67-103.

95 Lam RW. Sleep disturbances and depression: a challenge for antidepressants. *Int Clin Psychopharmacol.* 2006;21 Suppl 1:S25-S29.

96 Moltzen EK, Bang-Andersen B. Serotonin reuptake inhibitors: the corner stone in treatment of depression for half a century--a medicinal chemistry survey. *Curr Top Med Chem.* 2006;6:1801-1823.

97 Yous S, Andrieux J, Howell HE, et al. Novel naphthalenic ligands with high affinity for the melatonin receptor. *J Med Chem.* 1992;35:1484-1486.

98 Millan MJ, Gobert A, Lejeune F, et al. The novel melatonin agonist agomelatine (S20098) is an antagonist at 5-hydroxytryptamine2C receptors, blockade of which enhances the activity of frontocortical dopaminergic and adrenergic pathways. *J Pharmacol Exp Ther.* 2003;306:954-964.

99 Loo H, Hale A, D'haenen H. Determination of the dose of agomelatine, a melatoninergic agonist and selective 5-HT_{2C} antagonist, in the treatment of major depressive disorder: a placebo-controlled dose range study. *Int Clin Psychopharmacol.* 2002;17:239-247.

100 Kennedy SH, Emsley R. Placebo-controlled trial of agomelatine in the treatment of major depressive disorder. *Eur Neuropsychopharmacol.* 2006;16:93-100.

101 Montgomery SA. Major depressive disorders: clinical efficacy and tolerability of agomelatine, a new melatonergic agonist. *Eur Neuropsychopharmacol.* 2006;16 Suppl 5:S633-S638.

102 Kupfer DJ. Depression and associated sleep disturbances: patient benefits with agomelatine. *Eur Neuropsychopharmacol.* 2006;16 Suppl 5:S639-S643.

103 Srinivasan V, Smits M, Spence W, et al. Melatonin in mood disorders. *World J Psychiatry*. 2006;7 (3):138-151.

104 Branchey L, Weinberg U, Branchey M, et al. Simultaneous study of 24-hour patterns of melatonin and cortisol secretion in depressed patients. *Neuropsychobiology.* 1982;8:225-232.

105 Claustrat B, Chazot G, Brun J, et al. A chronobiological study of melatonin and cortisol secretion in depressed subjects: plasma melatonin, a biochemical marker in major depression. *Biol Psychiatry.* 1984;19:1215-1228.

106 Nair NP, Hariharasubramanian N, Pilapil C. Circadian rhythm of plasma melatonin in endogenous depression. *Prog Neuropsychopharmacol Biol Psychiatry.* 1984;8:715-718.

107 Beck-Friis J, Kjellman BF, Aperia B, et al. Serum melatonin in relation to clinical variables in patients with major depressive disorder and a hypothesis of a low melatonin syndrome. *Acta Psychiatr Scand.* 1985;71:319-330.

108 Wehr TA, Sack DA, Rosenthal NE. Antidepressant effects of sleep deprivation and phototherapy. *Acta Psychiatr Belg.* 1985;85:593-602.

109 Rubin RT, Heist EK, McGeoy SS, et al. Neuroendocrine aspects of primary endogenous depression. XI. Serum melatonin measures in patients and matched control subjects. *Arch Gen Psychiatry.* 1992;49:558-567.

110 Sekula LK, Lucke JF, Heist EK, et al. Neuroendocrine aspects of primary endogenous depression. XV: Mathematical modeling of nocturnal melatonin secretion in major depressives and normal controls. *Psychiatry Res.* 1997;69:143-153.

111 Crasson M, Kjiri S, Colin A, et al. Serum melatonin and urinary 6-sulfatoxymelatonin in major depression. *Psychoneuroendocrinology.* 2004;29:1-12.

112 Tuunainen A, Kripke DF, Elliott JA, et al. Depression and endogenous melatonin in postmenopausal women. *J Affect Disord.* 2002;69:149-158.

113 Leproult R, Van Onderbergen A, L'hermite-Baleriaux M, et al. Phase-shifts of 24-h rhythms of hormonal release and body temperature following early evening administration of the melatonin agonist agomelatine in healthy older men. *Clin Endocrinol (Oxf).* 2005;63:298-304.

114 Koorengevel KM, Beersma DG, den Boer JA, et al. A forced desynchrony study of circadian pacemaker characteristics in seasonal affective disorder. *J Biol Rhythms.* 2002;17:463-475.

115 Pjrek E, Winkler D, Konstantinidis A, et al. Agomelatine in the treatment of seasonal affective disorder. *Psychopharmacology (Berl).* 2007;190:575-579.