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Review

Circadian rhythm sleep disorders

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Abstract

In modern societies, there has been an increasing awareness of persistent circadian rhythm sleep disorders. In our 24-h society, under conditions which may disrupt normal day-night activities such as shift work, jet lag, affective disorders, or intense bright light late at night, a desynchronization of circadian rhythms can occur resulting in circadian rhythm sleep disorders.

Circadian rhythms are major features of adaptation to our environment. In mammals, circadian rhythms are generated and regulated by a circadian timing system. Disorders of circadian timing primarily affect entrainment function to the normal day-night cycle. The major feature of these disorders is a misalignment between the patient's sleep pattern and the sleep pattern that is desired or regarded as the societal norm. These disorders are classified as circadian rhythm sleep disorders in ICSD-2 (the International Classification of Sleep Disorders: second edition; 2005), consisting of: 1) Delayed sleep phase type characterized by a persistent inability to fall asleep and arise at conventional clock times; the phase of the sleep-wake cycle is delayed. 2) Advanced sleep phase type: affected individuals complain of sleepiness in the late afternoon or early sleep onset, and early morning awaking. 3) Irregular sleep-wake type consisting of temporally disorganized sleep period: there is no major sleep period, instead patients presents variable episodes in sleeping and waking behaviors. 4) Free-running type which consists of a chronic steady pattern comprising one- to two-hour daily delays in sleep onset and wake times in an individual living in society. 5) Jet lag type. 6) Shift work type: the shift workers complain of difficulty initiating and maintaining sleep and poor sleep quality.

For these patients with circadian rhythm sleep disorders, chronobiological treatments such as resetting daily-life schedule, enforcement of zeitgebers, bright light therapy, melatonin, or vitamin B_{12} treatment are effective.

Key words: clock, delayed sleep phase disorder, shift work, melatonin

Introduction

Circadian Rhythm

From the Latin circa, "about", and diem, "a day", meaning literally "about a day", circadian rhythm is the twenty-four-hour cycle of light/dark, wakefulness/sleep to which most human physiologic processes are set. Many biological activities are restricted to specific times of day. In the absence of external timing cues, some of these processes remain rhythmic ("free run") with approximately 24-h (circadian) periods. The features of these self-sustaining oscillations have suggested the existence of an endogenous timekeeping mechanism. This circadian pacemaker receives input (afferent) pathways for synchronization (entrainment) to light-dark cycles and expresses its rhythmicity through output (efferent) pathways. The pacemaker works as a clock because its endogenous period is adjusted to the external 24-h period, primarily by light-induced phase shifts that reset the pacemaker's oscillation.

This circadian "clock" in mammals was located in the suprachiasmatic nucleus (SCN). Destruction of the SCN results in the complete absence of a regular sleep/wake rhythm. Contributing to this clock are photo receptors found in the retina, known as melanopsin ganglia. These cells, which contain a photo pigment known as melanopsin, follow the retinohypothalamic tract, leading to the SCN. The SCN takes the information on day length from the retina, interprets it, and passes it on to the pineal gland, which then secretes the hormone melatonin in response. Secretion of melatonin peaks at night and decreases during the day. The SCN does not appear to be able to react rapidly to changes in the light/dark cues. Recent evidence indicates that circadian rhythms are found in many cells in the body, outside of the SCN "master clock."

From the evolutionary perspective, the circadian clock has one major role to play in ensuring the survival of the individual: to regulate the phase of a multitude of circadian rhythms such that specific phase points of these rhythms occur at optimal times relative to each other (internal synchronization) or relative to the external environment (external synchronization).

Cues from the environment (zeitgebers) ensure that the internal rhythms reset each day to the external rhythms, with light being the major environmental time cue. In humans living in temporal isolation, an environment without time cue, the cycles of sleep and waking behavior persist in a free-running state with period that usually longer than 24-h. The maintenance of this free-running sleep-wake rhythm is accountable only by the action of the circadian clock.

Circadian Rhythm Sleep Disorders

In modern societies, there has been an increasing awareness of persistent circadian rhythm sleep disorders. In our 24-h society, under conditions which may disrupt normal day-night activities such as shift work, jet lag, affective disorders, or intense bright light late at night, a desynchronization of circadian rhythms can occur resulting in circadian rhythm sleep disorders. Circadian rhythm sleep disorders can be divided into two major groups: (1) when the physical environment is altered relative to internal circadian timing (shift work, jet lag); and (2) the circadian timing system is altered relative to the external environment (delayed sleep phase syndrome, non-24-hour sleep-wake syndrome, advanced sleep phase syndrome, irregular sleep-wake rhythm).

According to the International Classification of Sleep Disorders, the general criteria for circadian sleep disorders are (i) persistent or recurrent pattern of sleep disturbances due primarily to one of the following: alterations of the circadian timekeeping system or misalignment between the endogenous circadian rhythm and exogenous factors that affect the timing/duration of sleep; (ii) the circadian related sleep disruption leads to insomnia, excessive daytime sleepiness, or both; (iii) the sleep disturbance is associated with impairment of social, occupational, or other areas of functioning (American Academy of Sleep Medicine 2005). The International Classification of Circadian Rhythm Sleep Disorders with alternate names is presented in Table 1.

Table 1 The International Classification of Circadian Rhythm Sleep Disorders (with alternate names)

1.	Circadian Rhythm Sleep Disorder, Delayed Sleep Phase Type (Delayed Sleep Phase Disorder)
2.	Circadian Rhythm Sleep Disorder, Advanced Sleep Phase Type
3.	Circadian Rhythm Sleep Disorder, Irregular Sleep-Wake Type (Irregular Sleep-wake Rhythm)
4.	Circadian Rhythm Sleep Disorder, Free-Running Type (Nonentrained Type, Non-24-hour Sleep Wake Syndrome, Hypernychthermal Syndrome)
5.	Circadian Rhythm Sleep Disorder, Jet Lag Type (Jet Lag Disorder, Time Zone Change Syndrome, Jet Lag Syndrome)
6.	Circadian Rhythm Sleep Disorder, Shift Work Type (Shift Work Disorder)
7.	Circadian Rhythm Sleep Disorder Due to a Medical Condition
8.	Other Circadian Rhythm Sleep Disorder (Circadian Rhythm Disorder, NOS)
9.	Other Circadian Rhythm Sleep Disorder Due to Drug or Substance

1. *Circadian Rhythm Sleep Disorder, Delayed Sleep Phase Type (Delayed Sleep Phase Disorder)*

Delayed Sleep Phase Disorder (DSPS) is caused by an abnormally delayed circadian clock (Weitzman et al. 1981). Sleep onset and wake times are both significantly delayed compared to the conventional sleep-wake times. The typical patients with DSPS do not get sleepy until the early morning hours, and then sleep until the late morning or early afternoon. Subjects with DSPS are often characterized as "night owls", and when they are tested on tendencies of morningness and eveningness, they score on the eveningness end of the scale. Once asleep, the patients will have normal quality of sleep with normal sleep architecture, which will last a normal time

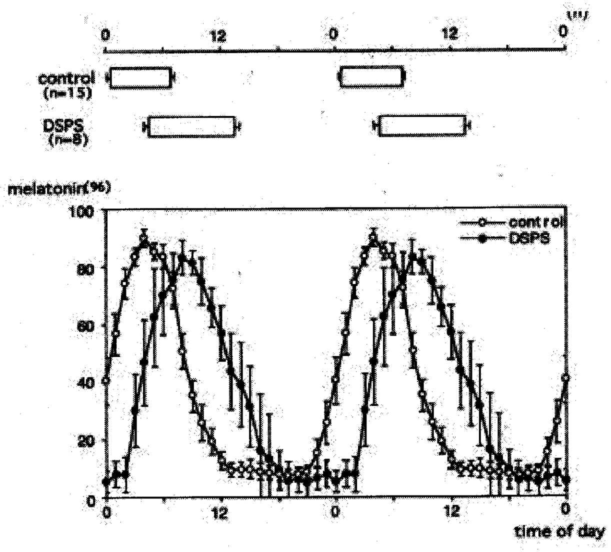

Fig. 1 Melatonin profiles and sleep episodes of delayed sleep phase syndrome (DSPS) patients and controls. Melatonin profiles and sleep episodes of DSPS patients and normal controls are shown in a double-plot format. Melatonin concentrations are expressed as the percentages of the subjects' peak values. The melatonin rhythm and the sleep phase in the DSPS patients were significantly delayed compared to those in the controls (Shibui et al. 1999)

unless it is interrupted by external disturbances (Weitzman et al. 1981). The continuing mismatch between the daily schedule required by the social environment and the individuals' circadian sleep-wake pattern creates major social, work, and academic problems. DSPS patients complain of headache, loss of appetite, depressed mood, and loss of concentration. In addition to sleep period, rhythms of various physiologic cycles, including those of melatonin in plasma (Figure 1), urinary melatonin metabolite excretion, and core body temperature, have been reported to be significantly delayed in patients with DSPS (Ozaki et al. 1988, Oren et al. 1995, Ozaki et al. 1996, Shibui et al. 1999).

Although no study has systematically investigated all age groups, DSPS has been found to be low in the general population in Japan, 0.13% among 15–54 years (Yazaki et al. 1999). Meanwhile in adolescents DSPS is reportedly a common source of insomnia (Pelayo et al. 1988, Carskadon et al. 1993, Schuen and Millard 2000). In Japan, half of adult patients with DSPS had their symptoms appeared in childhood or adolescence (Yamadera et al. 1996) and may have been caused by long vacation (day and night reversed) and by the exhausting preparation period for university exams. The number of cases of DSPS and related disorders seems to have increased in the last few decades as a result of modern life, TV watching and computer games or night work, all of them causing the delay of sleep onset time. As a result, people sleep in the train, library, class and everywhere to compensate their lack of sleep, some of them clearly presenting the symptoms of delayed sleep phase syndrome. The frequencies of DSPS patients presenting at sleep disorder clinics were reported to be between 6.7–16% (Weitzman et al. 1981, Regestein and Monk 1995).

It was recently reported that 50% of DSPS patients had biological relatives with similar symptoms and a possible pedigree of one family with DSPS was found (Ancoli-Israel et al. 2001) suggesting that DSPS may have genetic component. Genetic involvement is further supported by reports of the association of DSPS with structural (Ebisawa et al. 2001) and length (Archer et al. 2003) polymorphism in the human circadian clock *period3* gene.

Treatment for DSPS includes chronotherapy, phototherapy, exogenous melatonin as a phase-shifting agent, and exogenous melatonin as hypnotic (Wyatt 2004). Regardless of the chosen treatment, after the patient reaches the goal bedtime and rising time, the need for rigid adherence to the new sleep schedule, 7 days a week, is required from the patient. Bright light has been shown to have acute phase-shifting effects on human circadian rhythms ; bright light in the evening produces a phase delay and in the morning phase advance. On the basis of this phase-shifting effect, bright light exposure in the morning together with light restriction in the evening needs to be maintained. On the long term behavioral change is also required from the patient.

2. *Circadian Rhythm Sleep Disorder, Advanced Sleep Phase Type*

Advanced Sleep Phase Syndrome (ASPS) is a disorder in which the major sleep episode is advanced in relation to the desired clock time. Affected individuals complain of sleepiness in the late afternoon or early evening, early sleep onset, and early morning awakening. When individuals are allowed to maintain advanced schedule, sleep itself is normal for the person's age. Later bedtimes due to social and professional obligations can lead to chronically insufficient sleep and excessive daytime sleepiness. Individuals with ASPS have fewer problems to adjust to earlier schedule than those with DSPS, because societal constraints on bed time are less rigid than on wake time, and individuals may choose professions that are in phase with their circadian clock.

ASPS is less frequently reported than DSPS as it is perceived less frequently as a pathologic condition (Ando et al. 1995). Several familial cases of ASPS have been reported and evidence is mounting to support the notion of genetic heterogeneity of familial ASPS cases in humans (Jones et al. 1999, Satoh et al. 2003).

The therapeutic approaches to treat ASPS include chronotherapy, bright light therapy and melatonin (Moldofsky et al. 1986, Campbell et al. 1993, Lewy et al. 1996).

3. *Circadian Rhythm Sleep Disorder, Irregular Sleep-Wake Type (Irregular Sleep-wake Rhythm)*

Individuals with irregular sleep-wake disorder lack of a well-defined circadian sleep-wake cycle. The sleep-wake pattern temporarily disorganized, and there is no major sleep period, instead patients present with three or more sleep episodes of varying length during a 24-hour period. Patients present with this disorder have symptoms of insomnia and excessive sleepiness, depending on the time of the day.

The prevalence in the general population is unknown but estimated to be rare. Clinical management of the disorder aims to improve the amplitude of circadian rhythms and their alignment with the external environment by increasing exposure to synchronizing agents, such as bright light and structured social and physical activities (Yamadera et al. 1996).

4. *Circadian Rhythm Sleep Disorder, Free-Running Type (Nonentrained Type, Non-24-hour sleep-wake syndrome)*

Non-24-hour sleep-wake syndrome is a rare condition that is characterized by a chronic steady pattern of about 1-hour delays in spontaneous sleep-onset and wake times in individuals living under normal environmental conditions. It occurs because the intrinsic circadian pacemaker is not entrained to a 24-hour period or is free running with a non-24-hour period (usually slightly longer, Figure 2., (Hayakawa et al. 2005). Because most individuals must maintain a regular sleep-wake schedule, the clinical picture is of periodically recurring problems with sleep initiation, sleep maintenance, and rising, as the circadian cycle of wakefulness and sleep propensity moves in and out of synchrony with a fixed sleep period time.

Most individuals with nonentrained circadian rhythms are totally blind, and the failure to entrain circadian rhythms is related to the lack of photic input to the circadian pacemaker. The disorder is rare in sighted people, social and behavioral factors may contribute to the development of it. Data from a large cohort of sighted patients suffering from non-24-hour sleep-wake syndrome indicate that the onset of disorder occurs predominantly in the teens and 20s (Hayakawa et al. 2005).

Melatonin is recommended as the initial treatment of choice in blind and sighted individuals with this disorder and vitamin B_{12} has been reported to be effective, although the mechanism is unknown (Okawa et al. 1990). Bright light entrainment is also a possibility in sighted individuals and in blind individuals who posses intact photic suppression of melatonin. Entrainment by non-photic stimuli (structured social cues) alone has not been successful.

5. *Circadian Rhythm Sleep Disorder, Jet Lag Type (Jet Lag Disorder)*

With the advancement of aviation our globe "has shrunk" and humans move rapidly across time zones, an extremely unnatural act that humans have never experienced throughout

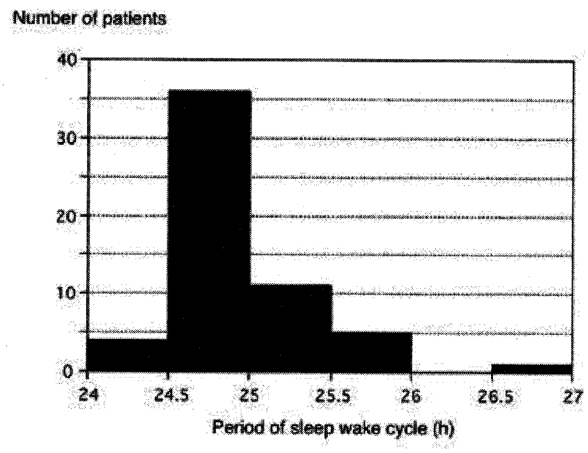

Fig. 2 Distribution of periods of the sleep-wake cycles in a group of sighted patients. The periods of the sleep-wake cycles for 57 patients are plotted with a 0.5-hour bin. The highest frequency was found at between 24.5 and 25 hours. Mean, median, and SD of the period were 24.9, 24.8, and 0.4 hours, respectively

their history until recently. Worldwide, approximately half-million people are reported to be airborne at any given time, and many of them are crossing several time zones.

The rapid travel across time zones leads to a temporary mismatch or lack of synchrony between the timing of sleep and wake cycle generated by the endogenous circadian clock and that of the sleep wake pattern according to the local time cues (Arendt and Marks 1982). Symptoms of jet lag include difficulty in sleeping at night, daytime sleepiness and fatigue, impairment performance during the new daylight hours, general malaise and gastrointestinal symptoms. The severity of symptoms is dependent on the number of time zones traveled and the direction of the travel. Eastward travel (requiring advancing circadian rhythms and sleep-wake hours) is usually more difficult to adjust to than westward travel. While "jet lag" may be nuisance for the occasional long-distance traveler, it is very disruptive to the frequent travelers and potentially dangerous for the individual who are responsible for moving the planes and people rapidly across time zones (Samel et al. 1995, Samel et al. 1997).

To help adaptation to the new environment when this is desirable, it is important to exploit the acute effects of the environment, of behavior and of medication, together with strategies designed to hasten the adaptation of the internal clock (Table 2). Appropriately timed exposure to bright light speeds up the adjustment to the new time zone, while outdoor exercises may also help. Pharmacological approach includes the use of short-acting hypnotic agents during the flight (to sleep during the destination nighttime) and for the first few days ; administering correctly timed melatonin ; and the use of vitamin B_{12}.

Table 2 Recommendations for travelers crossing multiple time zones

Where possible, choose daytime flights to minimize the loss of sleep and fatigue.
Avoid large high-fat meals out of phase and caffeine and alcohol during the night.
Drink a lot of water.
Avoid making critical decisions or attending important meetings on the first day after arrival.
Avoid driving long distances on the first day after arrival.
Avoid or seek bright light according to designed strategies.
Consider using medication with the advice of your physician (short-acting hypnotics or melatonin).

6. *Circadian Rhythm Sleep Disorder, Shift Work Type (Shift Work Disorder)*

Working at night is an inherently unnatural act. Modern society has evolved into a world filled with around-the-clock activities that range from essentials such as health care, public safety to conveniences such as shopping and entertainment. Approximately one fifth of all employers in the developed world are engaged in some form of work that requires their presence outside of the "standard" 7am to 6pm working day on regular basis, and thus be regarded as "shift workers". This figure is expected to rise as second jobbing and mandatory overtime increases. According to a survey by the Health, Labor and Welfare Ministry about 20 percent of companies in Japan have employees who work after 10 p.m., and half of them operate on rotating shifts. The fastest growing sector in Japan is the service sector and with the emergence of a 24-h society, the number of workers on night shifts continues to increase.

The shift worker's most common complaints are difficulty initiating and maintaining sleep and poor sleep quality. They may develop chronic fatigue, drowsiness, and doze off at work with the disrupted sleep. Shift workers are also reported to have higher incidence of chronic depression, emotional problems, family life dysfunction, excessive drugs and alcohol use, ulcers, myocardial infarction, gastrointestinal disease, increased accident risk than in the general population (Akerstedt 2003).

Although listed within circadian rhythm-related sleep disorders, shift work intolerance is a problem that should not be regarded as solely a circadian rhythm issue or a sleep disorder issue, or a social and domestic issue. Rather, it is a complex interaction of these factors (Figure3), with each factor influencing both of the other factors and the final outcome

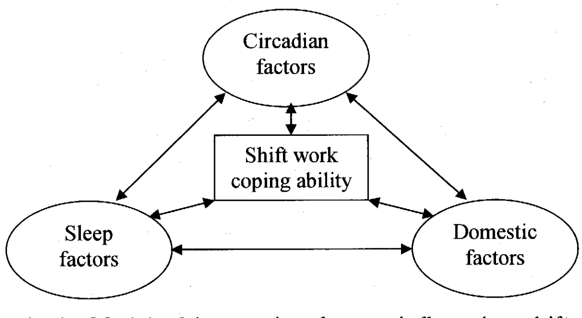

Fig. 3 Model of interacting factors influencing shift work coping ability

Table 3 Risk factors that are likely to cause problems coping with shift work

In individuals	At work places
History of gastrointestinal complaints	More than five third shifts in a row without off-time days
Age older than 50 years	More than four 12-hour night shifts in a row
Working second job for pay ("moonlighting")	First-shift starting times earlier than 7 : 00 am
Heavy domestic workload	Rotating hours that change once peer week (weekly rotation)
"Morning-type" orientation ("lark")	Less than 48 hours of time off after a run of third-shift work
History of sleep disorders	Excessive regular overtime
Psychiatric illness	Backward rotating hours (first to third to second shift)
History of alcohol or drug abuse	Excessive weekend working
Epilepsy, Diabetes, Heart disease	Long commuting times
	12 hour shifts involving critical monitoring tasks, or a heavy physical workload
	Split shifts with inappropriate break period lengths
	Shifts without appropriate shift breaks
	12 hour shifts with exposure to harmful agents and substances

of shift work tolerance (Monk 1988). Risk factors associated with coping difficulties with shift work can be divided individual and work place risks and presented in Tables 3. Prevention and coping strategies of shift work disorder requires employee and management education (Kogi 2001, Knauth and Hornberger 2003). Employee education program should emphasize how circadian, sleep, and domestic factors influence shift work coping ability and employees should be taught how to maintain good sleep hygiene and how to manipulate zeitgebers for their advantage. Management should be aware that increasing medical, recruiting, and retraining costs resulting from poor employee morale, higher job turnover, increased accidents, ill-health, and absenteeism rates become a financial burden to the company. Management should learn of the different shift systems that are available besides traditional ones and they should recognize the factors that influence the optimal shift work selection.

7. *Circadian Rhythm Sleep Disorder Due to a Medical Condition*

The etiology of this type of circadian rhythm sleep disorder is an underlying primary medical or neurological condition. Depending on the underlying neurological or medical disorder, patients may present with a variety of symptoms, including insomnia and excessive sleepiness. The sleep-wake pattern may range from alterations in phase to irregular sleep-wake pattern.

Several medical and neurological conditions have been associated with circadian rhythm disturbances, such as dementia, movement disorders, blindness, hepatic encephalopathy (Ancoli-Israel et al. 1989, Sack et al. 1992, Bliwise et al. 1995, Steindl et al. 1995). However, in most cases the specific mechanisms by which the underlying neurological or medical conditions result in alterations in circadian rhythms are unknown.

8. *Other Circadian Rhythm Sleep Disorder and other Circadian Rhythm Sleep Disorder Due to Drug or Substance*

Finally, a disorder that satisfy the criteria of a circadian sleep disorder described earlier and are not due to drug or substance abuse ; and do not meet criteria for other circadian sleep disorders belong to other circadian rhythm sleep disorder category, while a disorder that also satisfy the criteria of a circadian sleep disorder and are due to drug or substance abuse ; and do not meet criteria for other circadian sleep disorders belong other circadian rhythm sleep disorder due to drug or substance category.

Conclusion

The impact of these disorders is probably larger than estimated in terms of numbers, misdiagnosis, and health consequences. Many of the proposed therapies, including light therapy, are often considered experimental by the health insurance industry, hence not supported ; health economic studies are urgently required to establish the cost-effectiveness of these therapies. Meanwhile, application of our expanding knowledge of basic human circadian and sleep physiology to clinical practice remains an important task.

References

Akerstedt T: Shift work and disturbed sleep/wakefulness. Occup Med (Lond) 53: 89–94, 2003

American Academy of Sleep Medicine: International classification of sleep disorders: Diagnostic and coding manual. 2nd ed. Westchester, Illinois, American Academy of Sleep Medicine, 2005

Ancoli-Israel S, Parker L, Sinaee R, Fell RL, Kripke DF: Sleep fragmentation in patients from a nursing home. J Gerontol 44: M18–21, 1989

Ancoli-Israel S, Schnierow B, Kelsoe J, Fink R: A pedigree of one family with delayed sleep phase syndrome. Chronobiol Int 18: 831–840, 2001

Ando K, Kripke DF, Ancoli-Israel S: Estimated prevalence of delayed and advanced sleep phase syndromes. Sleep Res 24: 509, 1995

Archer SN, Robilliard DL, Skene DJ, Smits M, Williams A, Arendt J, von Schantz M. A: A length polymorphism in the circadian clock gene Per3 is linked to delayed sleep phase syndrome and extreme diurnal preference. Sleep 26: 413–415, 2003

Arendt J, Marks V: Physiological changes underlying jet lag. Br Med J (Clin Res Ed) 284: 144–146, 1982

Bliwise DL, Watts RL, Watts N, Rye DB, Irbe D, Hughes M: Disruptive nocturnal behavior in Parkinson's disease and Alzheimer's disease: J Geriatr Psychiatry Neurol 8: 107–110, 1995

Campbell SS, Dawson D, Anderson MW: Alleviation of sleep maintenance insomnia with timed exposure to bright light. J Am Geriatr Soc 41: 829–836, 1993

Carskadon MA, Vieira C, Acebo C: Association between puberty and delayed phase preference. Sleep 16: 258–262, 1993

Ebisawa T, Uchiyama M, Kajimura N, Mishima K, Kamei Y, Katoh M, Watanabe T, Sekimoto M, Shibui K, Kim K, Kudo Y, Ozeki Y, Sugishita M, Toyoshima R, Inoue Y, Yamada N, Nagase T, Ozaki N, Ohara O, Ishida N, Okawa M, Takahashi K, Yamauchi T: Association of structural polymorphisms in the human period3 gene with delayed sleep phase syndrome. EMBO Rep 2: 342–346, 2001

Hayakawa T, Uchiyama M, Kamei Y, Shibui K, Tagaya H, Asada T, Okawa M, Urata J, Takahashi K: Clinical analyses of sighted patients with non-24-hour sleep-wake syndrome: a study of 57 consecutively diagnosed cases. Sleep 28: 945–952, 2005

Jones CR, Campbell SS, Zone SE, Cooper F, DeSano A, Murphy PJ, Jones B, Czajkowski L, Ptacek LJ: Familial advanced sleep-phase syndrome: A short-period circadian rhythm variant in humans. Nat Med 5: 1062–1065, 1999

Knauth P, Hornberger S: Preventive and compensatory measures for shift workers. Occup Med (Lond) 53: 109–116, 2003

Kogi K: Healthy shiftwork, healthy shiftworks. J Hum Ergol (Tokyo) 30: 3–8, 2001

Lewy AJ, Ahmed S, Sack RL: Phase shifting the human circadian clock using melatonin. Behav Brain Res 73: 131–134, 1996

Moldofsky H, Musisi S, Phillipson EA: Treatment of a case of advanced sleep phase syndrome by phase advance chronotherapy. Sleep 9: 61–65, 1986

Monk TH: Coping with the stress of shift work. Work Stress 2: 169–172, 1988

Okawa M, Mishima K, Nanami T, Shimizu T, Iijima S, Hishikawa Y, Takahashi K: Vitamin B12 treatment for sleep-wake rhythm disorders. Sleep 13: 15–23, 1990

Oren DA, Turner EH, Wehr TA: Abnormal circadian rhythms of plasma melatonin and body temperature in the delayed sleep phase syndrome. J Neurol Neurosurg Psychiatry 58: 379, 1995

Ozaki N, Iwata T, Itoh A, Kogawa S, Ohta T, Okada T, Kasahara Y: Body temperature monitoring in subjects with delayed sleep phase syndrome. Neuropsychobiology 20: 174–177, 1988

Ozaki S, Uchiyama M, Shirakawa S, Okawa M: Prolonged interval from body temperature nadir to sleep offset in patients with delayed sleep phase syndrome. Sleep 19: 36–40, 1996

Pelayo R, Thorpy M, Govinski P: Prevalence of delayed sleep phase syndrome among adolescents. Sleep Res 17: 392 1988

Regestein QR, Monk TH: Delayed sleep phase syndrome: a review of its clinical aspects. Am J Psychiatry 152: 602–608, 1995

Sack RL, Lewy AJ, Blood ML, Keith LD, Nakagawa H: Circadian rhythm abnormalities in totally blind people: incidence and clinical significance. J Clin Endocrinol Metab 75: 127–134, 1992

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

Samel A, Wegmann HM, Vejvoda M: Aircrew fatigue in long-haul operations. Accid Anal Prev 29: 439–452, 1997

Satoh K, Mishima K, Inoue Y, Ebisawa T, Shimizu T: Two pedigrees of familial advanced sleep phase syndrome in Japan. Sleep 26: 416–417, 2003

Schuen JN, Millard SL: Evaluation and treatment of sleep disorders in adolescents. Adolesc Med 11: 605–616, 2000

Shibui K, Uchiyama M, Okawa M: Melatonin rhythms in delayed sleep phase syndrome. J Biol Rhythms 14: 72–76, 1999

Steindl PE, Finn B, Bendok B, Rothke S, Zee PC, Blei AT: Disruption of the diurnal rhythm of plasma melatonin in cirrhosis. Ann Intern Med 123: 274–277, 1995

Weitzman ED, Czeisler CA, Coleman RM, Spielman AJ, Zimmerman JC, Dement W, Richardson G, Pollak CP: Delayed sleep phase syndrome. A chronobiological disorder with sleep-onset insomnia. Arch Gen Psychiatry 38: 737–746, 1981

Wyatt JK: Delayed sleep phase syndrome: pathophysiology and treatment options. Sleep 27: 1195–1203, 2004

Yamadera H, Takahashi K, Okawa M: A multicenter study of sleep-wake rhythm disorders: clinical features of sleep-wake rhythm disorders. Psychiatry Clin Neurosci 50: 195–201, 1996

Yamadera H, Takahashi K, Okawa M: A multicenter study of sleep-wake rhythm disorders: therapeutic effects of vitamin B12, bright light therapy, chronotherapy and hypnotics. Psychiatry Clin Neurosci 50: 203–209, 1996

Yazaki M, Shirakawa S, Okawa M, Takahashi K: Demography of sleep disturbances associated with circadian rhythm disorders in Japan. Psychiatry Clin Neurosci 53: 267–268, 1999