Circadian rhythm sleep disorder

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Circadian Rhythm Sleep Disorders

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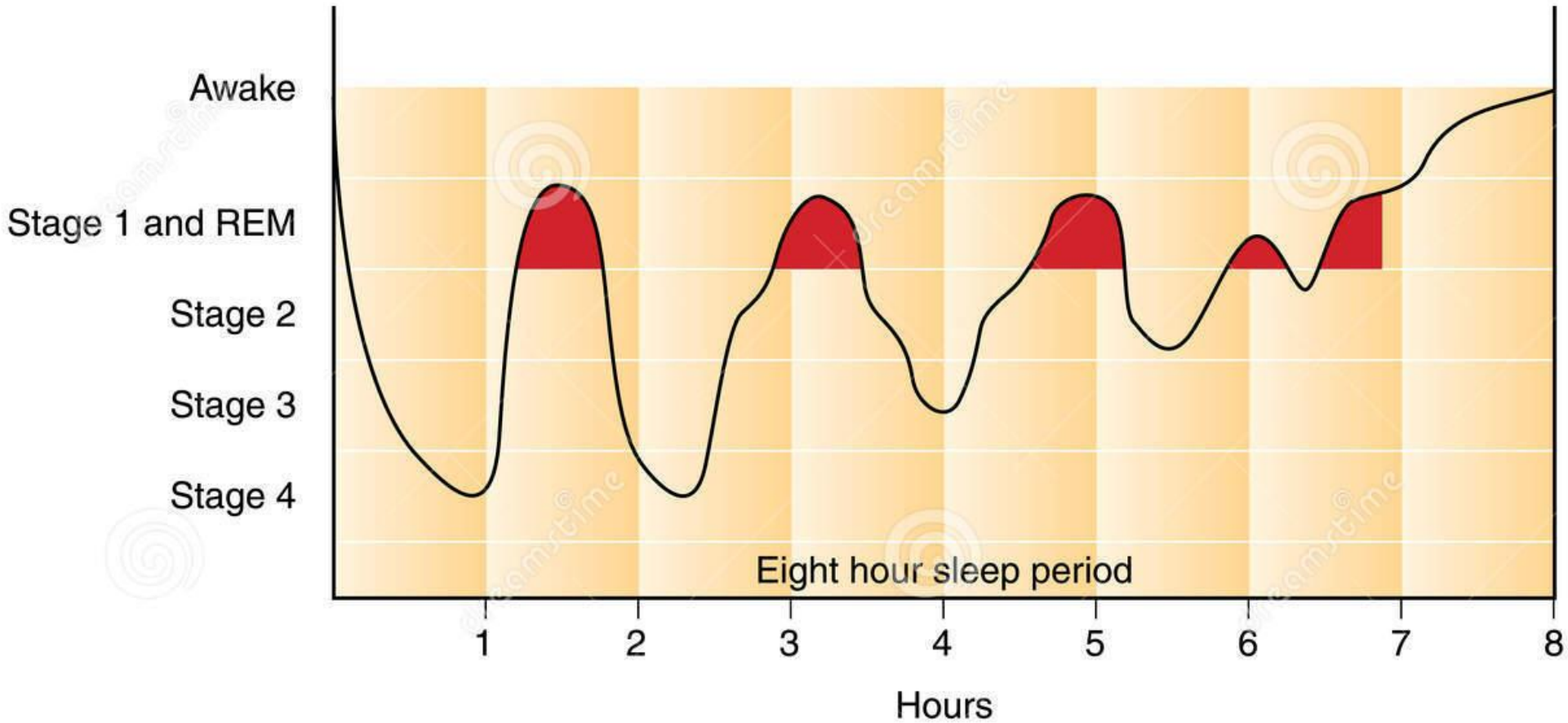
Normal pattern of sleep

- Sleep latency is the time between going to bed and falling asleep
- When going to bed, people usually fall asleep within 10-20 min
- REM latency is the time between asleep(NREM period) and entering the initial REM period
- REM latency is about 90-120 min
- NREM-REM cycle repeats throughout the night with a periodicity of approximately 90 min
- REM periods develop 4 or 5 times in total, but in the latter half of the night they lengthen and occur more frequently

Normal pattern of sleep

- The tendency toward REM sleep peaks, body temperature falls to its lowest point (the nadir)
- The final REM period typically merges with awakening
- People can most easily recall their final dream, which may incorporate surrounding morning household activities
- *sleep efficiency* is the ratio of the total time asleep to the time in bed.
- Reduced sleep efficiency, with a ratio significantly less than 1.0, characterizes insomnia and other disorders

Normal pattern of sleep



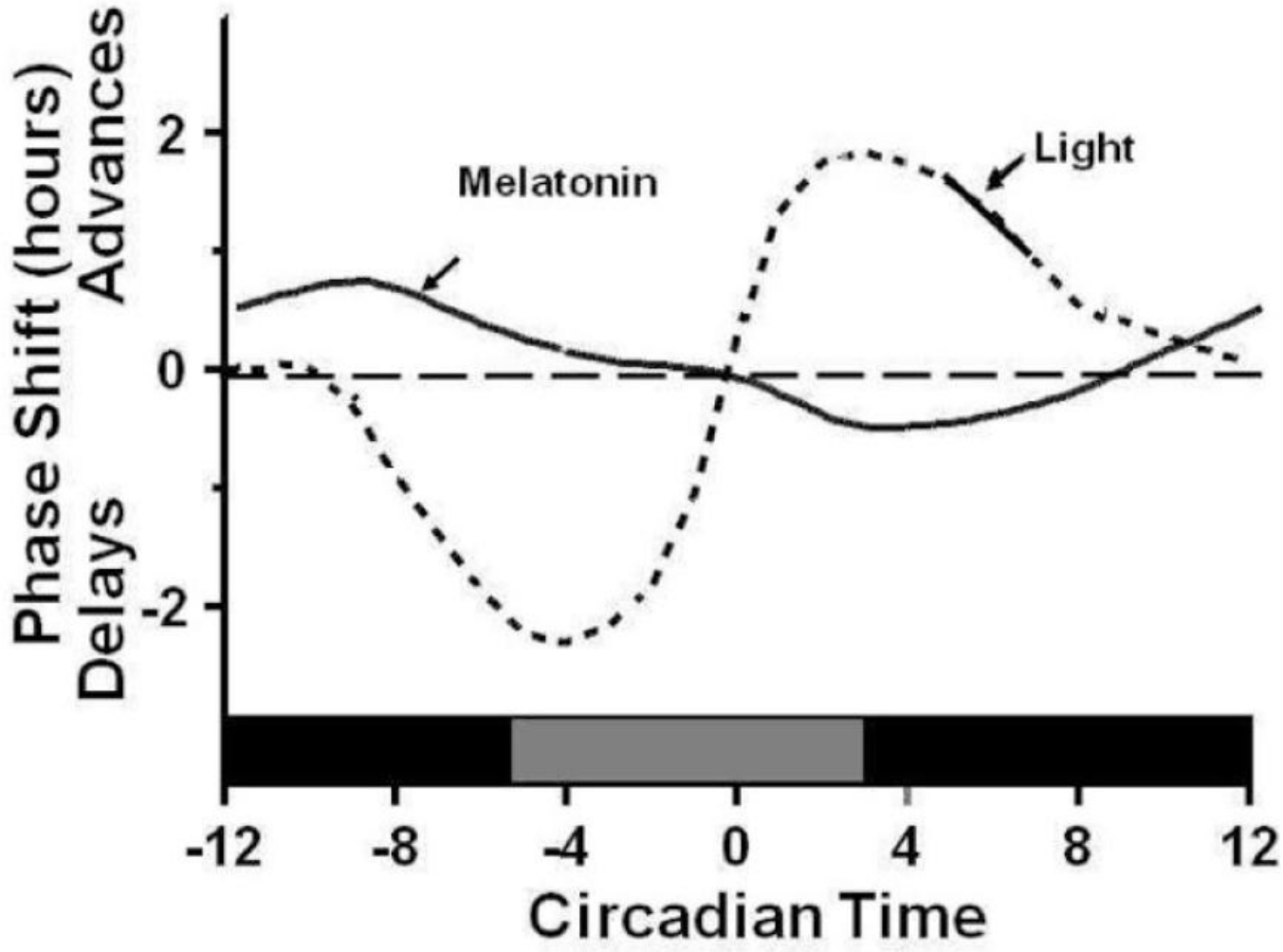
Circadian rhythm

- The endogenous circadian rhythm is synchronized or entrained to the 24 hour rhythm of the external environments daily by synchronizing agents, including light, physical activity, social behaviors and melatonin
- The light is the most influential entraining agent
- Exposure of light in the biological evening or early night will delay the circadian pacemaker
- Exposure of light in the biological morning will advance the circadian pacemaker
- There is a dead zone in the middle of the day where bright light exposure has no effect on the timing of circadian rhythms

Circadian rhythm

- The melanopsin containing retinal ganglion cell is the primary circadian photoreceptor and most sensitive to blue light
- The photic information reaches the suprachiasmatic nucleus (SCN) through a direct pathway the retinohypothalamic tract, and an indirect pathway from the optic tract to the intergeniculate leaflet and then to the SCN via the geniculohypothalamic tract
- The SCN signals the pineal gland via the superior cervical ganglion to inhibit the production of melatonin, an important entraining agent produced by the pineal gland
- In darkness, this inhibition effect is removed and the release of melatonin feeds back to inhibit the firing rate of SCN neurons permitting the sleep drive

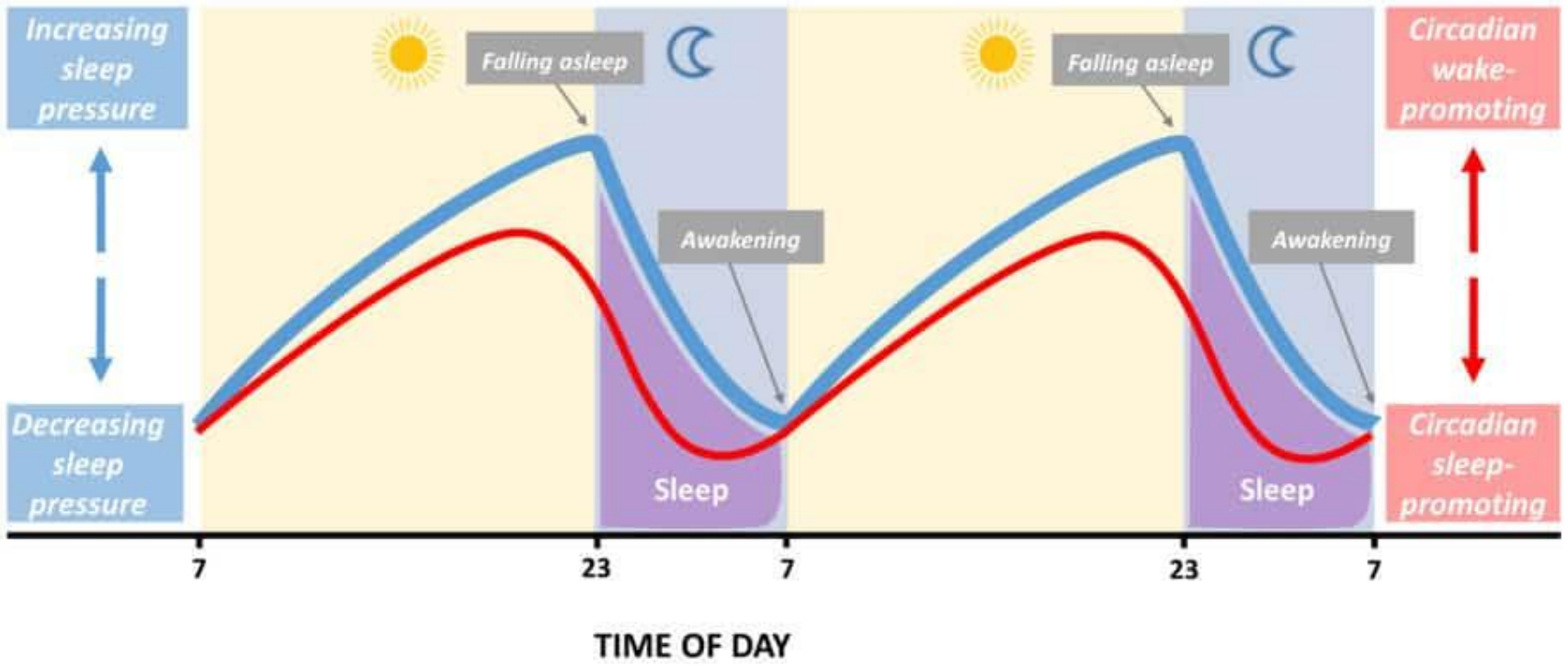
Circadian rhythm



Circadian rhythm

- The sleep-wake cycle is regulated by a complex interaction between the homeostatic process (a drive for sleep which builds up during wakefulness and declines during sleep) and circadian process (a sleep-wake independent 24-hour oscillatory rhythm that modulates sleep propensity)

Circadian rhythm



Sleep hygiene

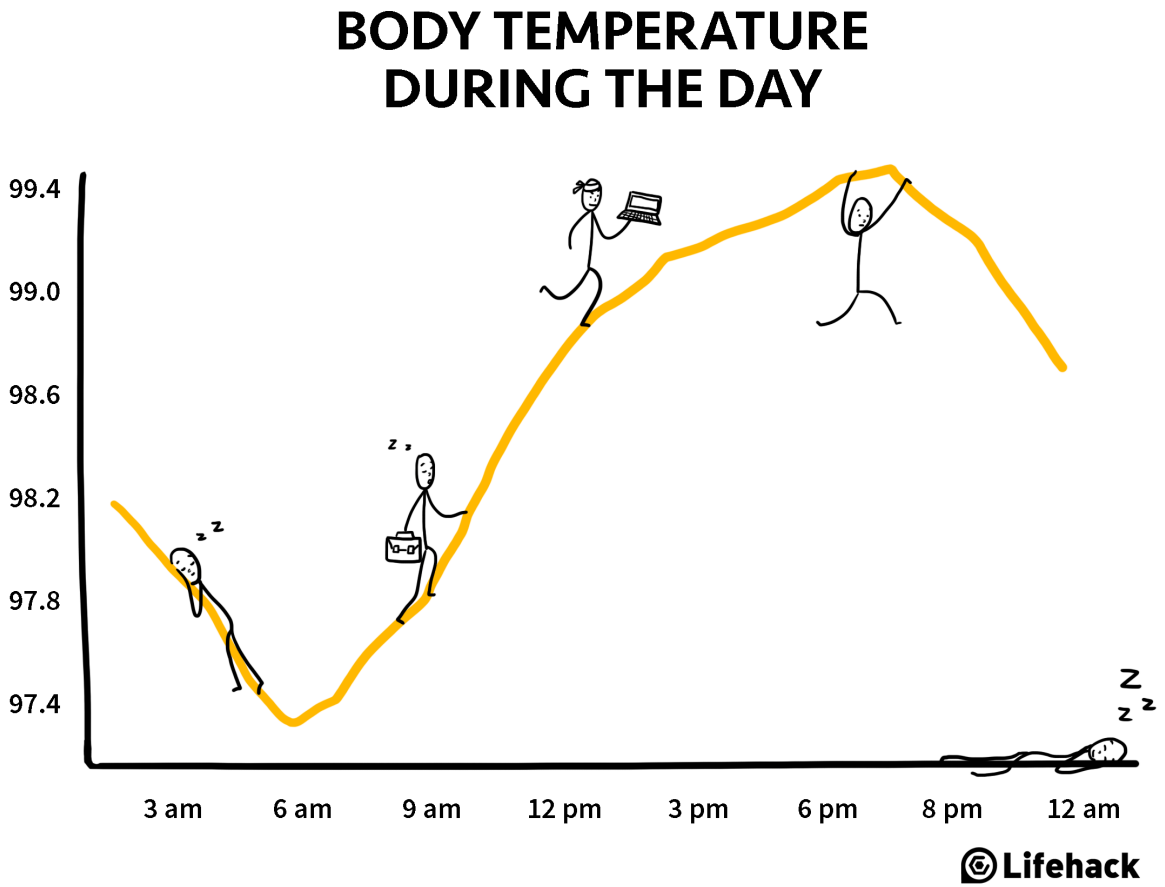
Circadian rhythm sleep disorder

- CRSDs arise from a chronic or recurrent pattern of sleep and wake disturbance that is due to dysfunction of the circadian clock system, or misalignment between the timing of the endogenous circadian rhythm and externally imposed social and work cycles, that result in clinically significant functional impairments
- CRSDs can be categorized according to their postulated underlying mechanisms: 1) the endogenous circadian clock itself is altered (delayed sleep phase disorder, advanced sleep phase disorder, irregular sleep wake rhythm, and free-running disorder); 2) the external environment and/or social circumstances are altered relative to the endogenous circadian clock (jet lag and shift work disorder)

Circadian rhythm sleep disorder

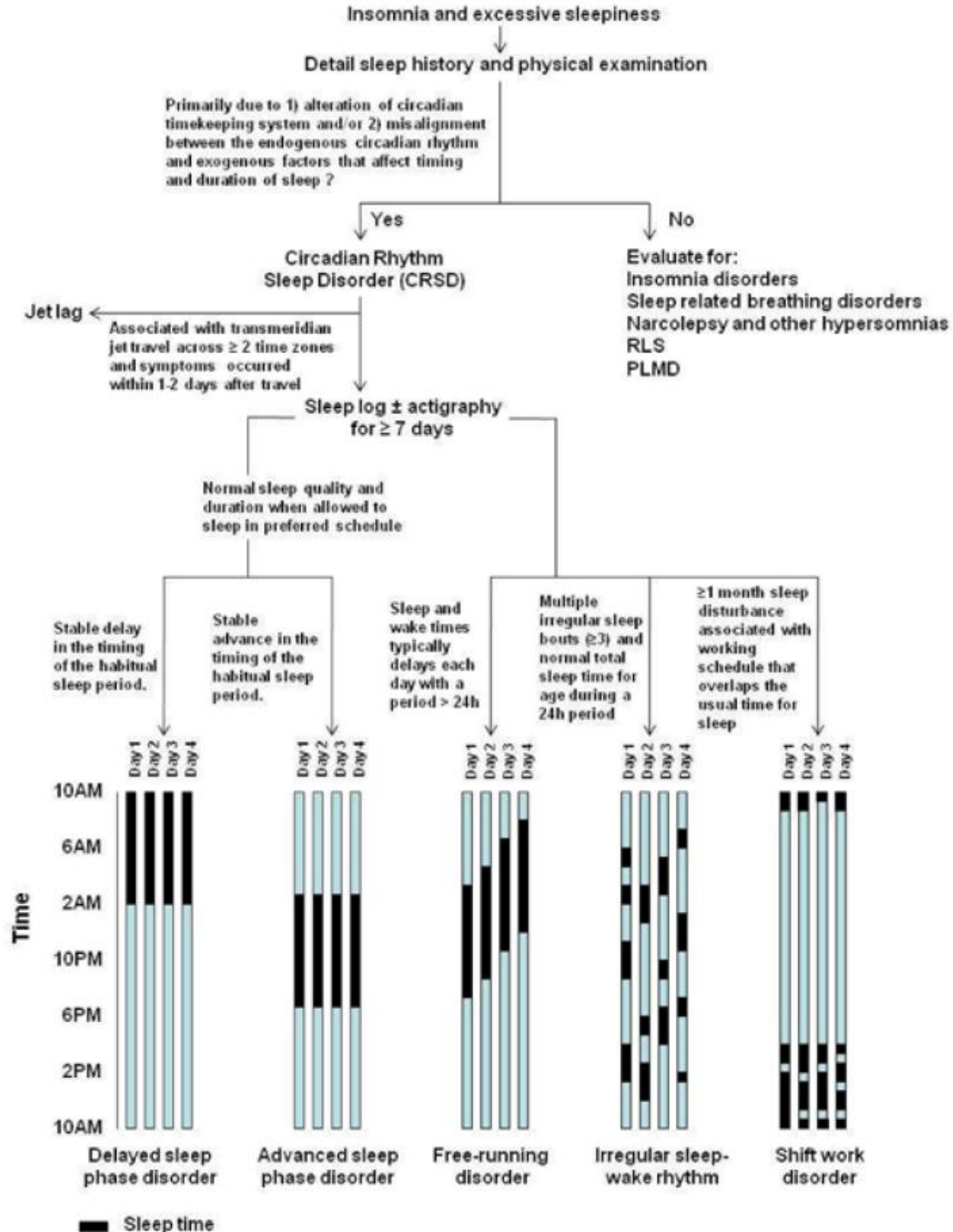
- The diagnosis of CRSD is based on a detailed history of the patient's sleep and wake pattern, and diagnostic tools, such as a sleep diary and actigraphy
- Core temperature and melatonin are useful diagnostic tools that can be used to confirm the diagnosis
- Melatonin rhythm and body temperature rhythm are reliable biological phase markers of the endogenous circadian rhythm and exhibit distinct phase relationships with the sleep-wake rhythm. Regulated by the SCN, and under dim light condition, the pineal gland begins to secrete melatonin (Dim light melatonin onset or DLMO) about 2-2.5 hours before sleep onset.
- The nadir of the core body temperature rhythm occurs approximately 2 hours before habitual sleep offset

Circadian rhythm sleep disorder



Circadian rhythm sleep disorder

- Delayed sleep phase disorder
- Advanced sleep phase disorder
- Non-24 hour sleep-wake disorder
- Irregular sleep-wake rhythm disorder
- Shift work disorder
- Jet lag


Insomnia and excessive sleepiness
Detail sleep history and physical examination
Primarily due to 1) alteration of circadian timekeeping system and/or 2) misalignment between the endogenous circadian rhythm and exogenous factors that affect timing and duration of sleep ?
Yes
No
Circadian Rhythm Sleep Disorder (CRSD)
Evaluate for:
Insomnia disorders
Sleep related breathing disorders
Narcolepsy and other hypersomnias
RLS
PLMD
Jet lag
Associated with transmeridian jet travel across ≥ 2 time zones and symptoms occurred within 1-2 days after travel
Sleep log ± actigraphy for ≥ 7 days
Normal sleep quality and duration when allowed to sleep in preferred schedule
Stable delay in the timing of the habitual sleep period.
Stable advance in the timing of the habitual sleep period.
Sleep and wake times typically delays each day with a period > 24h
Multiple irregular sleep bouts (≥3) and normal total sleep time for age during a 24h period
≥1 month sleep disturbance associated with working schedule that overlaps the usual time for sleep
Day 1
Day 2
Day 3
Day 4
Time
10AM
6AM
2AM
10PM
6PM
2PM
10AM
Delayed sleep phase disorder
Advanced sleep phase disorder
Free-running disorder
Irregular sleep-wake rhythm
Shift work disorder
Sleep time

Delayed sleep phase disorder

- Delayed sleep phase disorder (DSPD) is a sleep disorder in which there is a stable delay of the major sleep episode relative to the required sleep/wake clock time
- This delayed pattern leads to chronic symptoms of insomnia and excessive sleepiness associated with impairment in daytime functioning

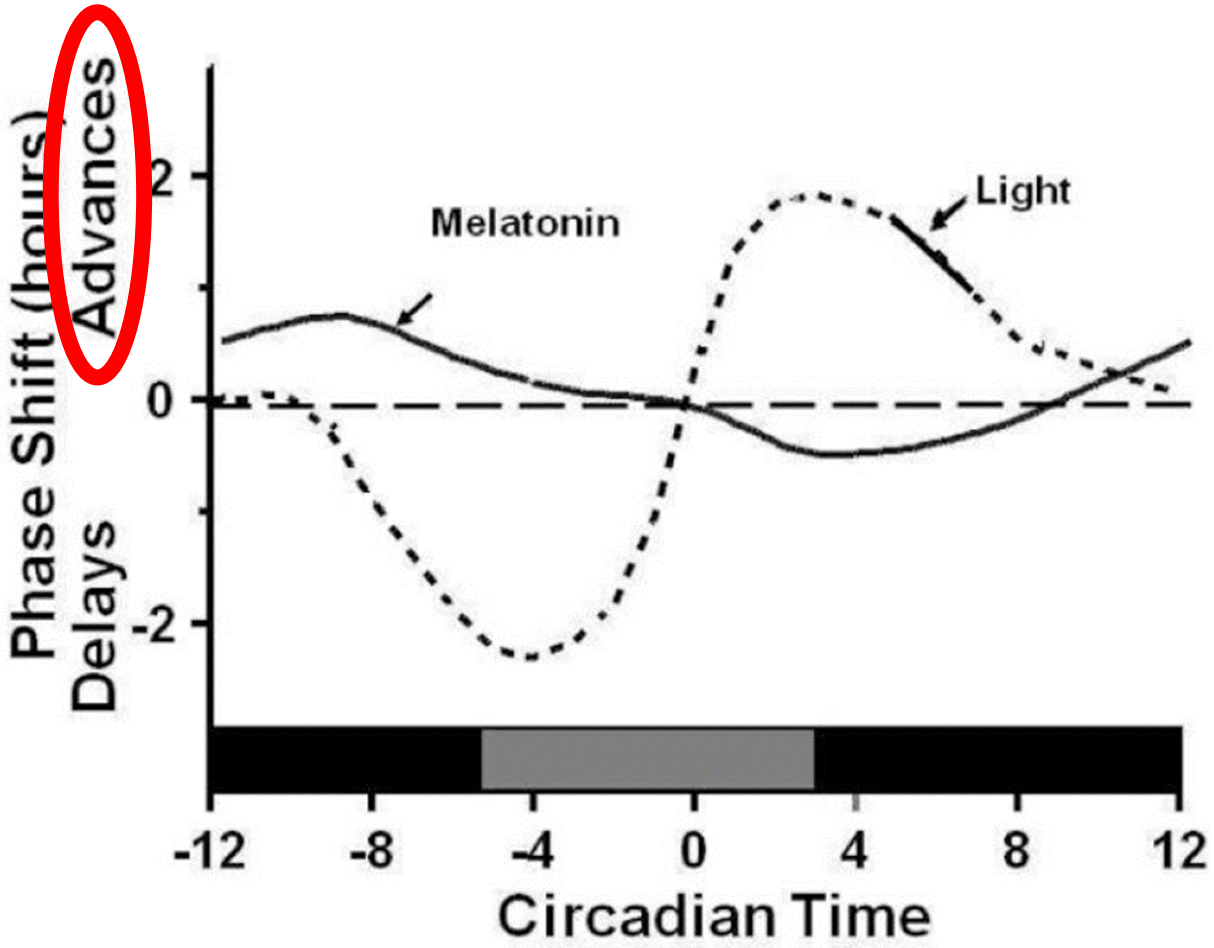
Delayed sleep phase disorder

- Epidemiology and risk factor
  - DSPD is the most common CRSD with an estimated prevalence of 0.17% in the general population
  - It has been estimated that 5-10% of chronic insomnia patients in sleep clinics have DSPD
  - Several studies indicate a genetic predisposition for DSPD
  - A polymorphism of Aryl alkylamine N-acetyltransferase and the frequency of HLA-DR1 were found to be significantly higher in the patients with DSPD when compared with healthy controls

Delayed sleep phase disorder

- Pathophysiology
- In addition to genetic vulnerability, physiological, behavioral and environmental factors likely play important roles in the development of DSPD
  - An unusually long endogenous circadian period may alter the relationship between sleep onset or offset with the timing of other endogenous circadian rhythms. For example, patients with DSPD have been shown to have a greater interval between sleep offset and nadir of core body temperature
  - Alteration in entrainment mechanisms. Patients have been shown to have a hypersensitivity of melatonin suppression to light at night. There is also evidence that the advance portion of the PRC to light in DSPD patients may be smaller than usual

Delayed sleep phase disorder



Delayed sleep phase disorder

- Pathophysiology
- In addition to genetic vulnerability, physiological, behavioral and environmental factors likely play important roles in the development of DSPD
  - Altered homeostatic process indicated by the alterations in slow-wave activity and sleep propensity in response to sleep deprivation
  - Behavioral factors precipitate and perpetuate DSPD. For example, the delayed sleep and wake times of patients with DSPD is often associated with less light exposure in the phase advance portion of the PRC curve (morning) and more light exposure in the phase delay portion of the PRC curve (evening).

Delayed sleep phase disorder

- Clinical Features
  - DSPD typically present with symptoms of chronic difficulty falling asleep before 2 am-6 am and inability to wake up in the morning
  - When allowed to choose their natural preferred schedules, their sleep is usually of normal quality and duration for age.
  - When attempting to comply with their school and occupational obligations, sleep duration is curtailed, resulting in chronic partial sleep deprivation and associated excessive daytime sleepiness and impairment of daily functioning.

Delayed sleep phase disorder

- Diagnosis
  - The diagnosis of DSPD is largely based on obtaining a detailed sleep history of a sleep and wake pattern that is chronically and stably delayed. A sleep dairy and/or wrist actigraphy for at least 7 consecutive days (longer if possible) is indicated to establish the habitually delayed sleep/wake pattern.
  - In addition, biological markers of circadian timing can be useful and are desirable if available. Dim light melatonin onset (DLMO)and nadir of core body temperature have been used in clinical practice and demonstrate as expected a delayed phase.
  - Nocturnal polysomnography is not indicated unless there is suspicion of concomitant disorders such as sleep disordered and other causes of insomnia or daytime sleepiness.
  - DSPD is strongly associated with anxiety and depression, so mood disorders screening should be considered in all patients

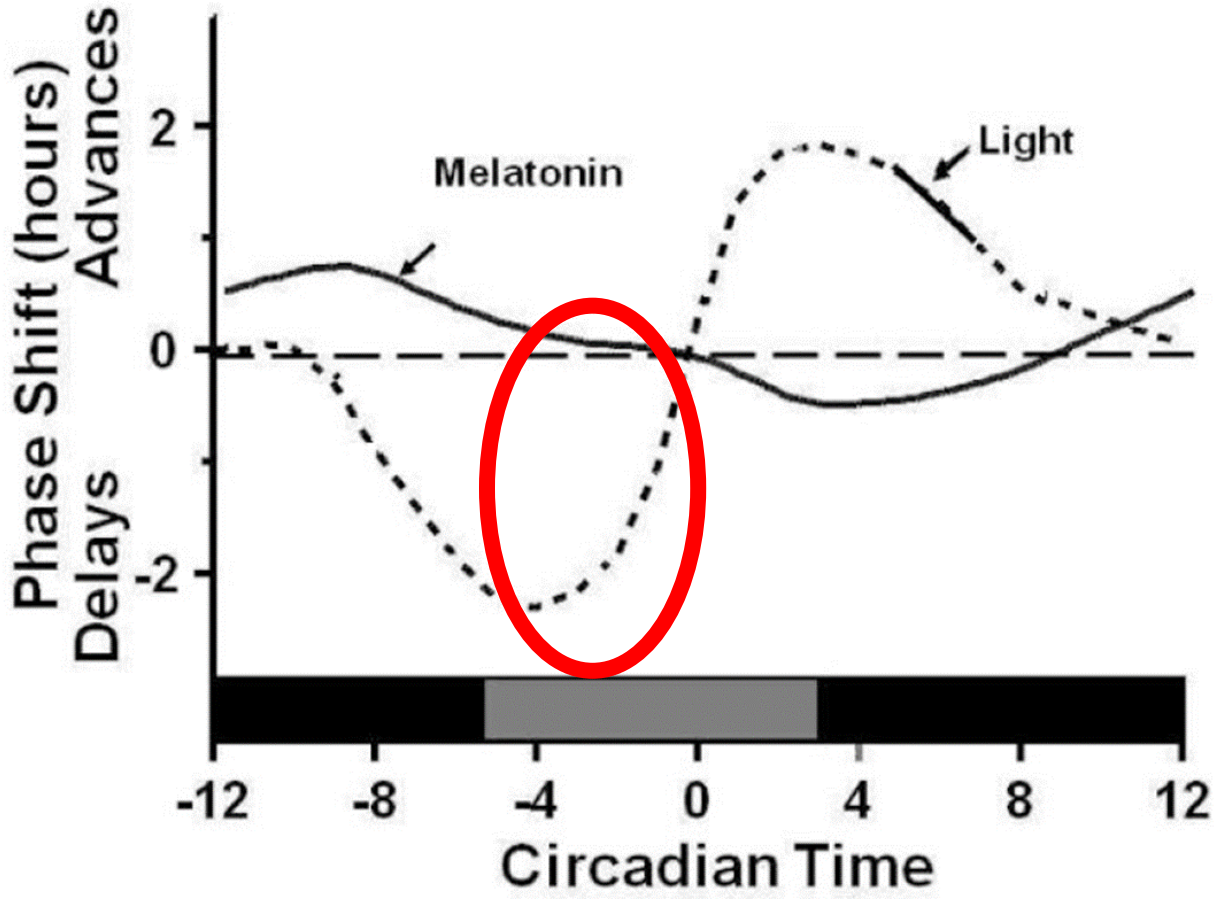
Delayed sleep phase disorder

- Treatment
  - The management of DSPD requires a combined approach using behavioral techniques, manipulation of light/dark exposure, and in some patients, pharmacological agents
  - Chronotherapy is a treatment in which the sleep and wake times are progressively delayed by about 3 hours every 2 days until a final earlier bedtime schedule is achieved and maintained

Delayed sleep phase disorder

- Treatment
  - Timed bright light therapy is one of the most commonly used treatments for DSPD
  - Exposure to light in the biological evening or early night phase delays circadian rhythms
  - Exposure to light in the morning results in phase advances
  - Bright light of 2,000 to 2,500 lux for 2 hours in the biological morning combined with avoidance of bright light exposure in the biological night can effectively achieve earlier sleep and wake times in DSPD patients.
  - Exposure to bright light between 7-9 am is usually effective for most DSPD patients
  - For patients who are more severely delayed (whose endogenoussleep time is after 3 AM and wake time after 9 am, the time of morning light exposure should be given later in the morning (shortly after awakening) to avoid light exposure before the nadir of core body temperature which could further delay circadian rhythms

Delayed sleep phase disorder



Delayed sleep phase disorder

- Treatment
  - Some of the practical limitations of chronotherapy and timed bright light therapy, the benefit of taking melatonin in the evening has been investigated. Appropriately timed melatonin (in the early evening) has been shown to decrease sleep latency, increase sleep duration and improve function in DSPD patients. One small placebo controlled study in DSPD patients showed that administration of melatonin 0.3 or 3mg about 6 hours prior to their sleep time, resulted in the largest phase advances of sleep and wake times. Although melatonin is indicated as a treatment for DSPD, large randomized placebo-controlled studies are still needed to establish a standard clinical approach for its use.
  - In addition to light and melatonin, treatment of DSPD should also include proper sleep hygiene, such as adherence to regular sleep-wake times and structured social and physical activity schedules, and address other factors, such as comorbid psychopathology and other sleep disorders.

Advanced sleep phase disorder

- Advanced Sleep Phase Disorder (ASPD) is a sleep disorder in which there is a stable advance of the major sleep period, characterized by habitual and involuntary sleep onset and wake-up times that are several hours earlier than the desired or conventional clock time.

Advanced sleep phase disorder

- Epidemiology and risk factor
  - ASPD is more common among middle and older adults. The estimated prevalence of ASPD is about 1% in middle-age adults. A genetic basis has been clearly demonstrated in familial ASPD. Missense mutations located in two different genes have been reported to co-segregate with the ASPD phenotype

Advanced sleep phase disorder

- Pathophysiology
  - In addition to the genetic factors in familial ASPD, a shortened endogenous circadian period has been postulated to be involved in sporadic cases. Other proposed mechanisms include alterations of entrainment mechanisms, such as increased retinal response to light in the morning, or increased early morning light exposure, both of which can perpetuate the advanced circadian phase.

Advanced sleep phase disorder

- Clinical Features
- Patients with ASPD typically present with complaints of sleepiness in the late afternoon or early evening and difficulty maintaining asleep in the early morning hours. Most report sleep onset between 6 pm-9 pm and wake time of 2 am-5 am. Even when sleep time is voluntarily delayed due to social and occupational obligations, patients continue to wake up earlier than desired, resulting in chronic partial sleep deficiency.

Advanced sleep phase disorder

- Diagnosis
  - The diagnosis of ASPD largely relies on a detailed sleep history of a stable advance in sleep and wake times. When allowed to sleep at their advanced endogenous sleep time, sleep quality and duration are normal for age.
  - A sleep dairy and/or wrist actigraphy for at least 7 consecutive days is recommended to establish the habitual advanced sleep/wake pattern. Measurement of DLMO is desirable if available and can help confirm the advanced circadian rhythm.
  - Nocturnal polysomnography is not indicated, except when the history suggests the presence of other sleep disorders, such as sleep apnea(common in older adults).

Advanced sleep phase disorder

- Treatment
  - A combined approach with timed bright light exposure for 2 hours in the evening, planned sleep and wake scheduling and adherence to good sleep hygiene is recommended by the AASM Practice Parameters.
  - Bright light exposure in the evening, typically between 7-9 pm, has been shown to delay the phase of circadian rhythms and improve sleep efficiency. Melatonin can theoretically delay circadian rhythms if taken in the early biological morning, but clinical evidence of its efficacy or safety for the treatment of ASPD is lacking.
  - Hypnotic agents are can be useful for the management of sleep maintenance symptoms associated with ASPD, they are not approved by the FDA for the treatment of ASPD.

Non-24 hour sleep-wake disorder

- Non-24 Hour Sleep Wake Disorder (N24HSWD) is characterized by a chronic or recurring pattern of sleep and wake times that are not stably entrained to the 24-hour environmental cycle. There is typically a predicable drift over weeks (usually to later and later times) of sleep onset and wake times.

Non-24 hour sleep-wake disorder

- Epidemiology and risk factor
  - N24HSWD affects approximately 50% of blind people and is thought to be rare in sighted persons. Sighted patients with N24HSWD are generally evening chronotypes, or may have a history of DSPD. The largest case series of N24HSWD in sighted subjects reported cases identified over a 10-year period.
  - The etiology of N24HSWD in the blind is the absence or near absence of light perception. The mechanism responsible in sighted individuals is less clear. The primary risk factor in sighted persons appears to be a long circadian period that is beyond the range of entrainment to a 24 hours cycle. Other mechanisms include:
    - decreased response of the circadian clock to light,
    - alteration and reduction of environmental or social cues because of psychiatric illness induced social withdrawal
    - mutation in the Casein Kinase I Epsilon (CK1ε) gene49.
  - N24HSWD has been reported in sighted individuals following traumatic brain injury but the mechanism is poorly understood.

Non-24 hour sleep-wake disorder

- Clinical Features
- Patients with N24HSWD typically complain of insomnia, difficulty waking up in the morning, excessive daytime sleepiness and inability to meet their social and occupational obligations. Since the timing of the sleep-wake cycle is progressively changing (usually to later and later times), there is a history of both symptomatic and asymptomatic episodes. At times when the endogenous circadian rhythm is in phase with the conventional sleep and wake time, their sleep is usually normal, whereas when the nonentrained circadian pacemaker is out of phase with the conventional sleep and wake schedules, they have symptoms of insomnia and excessive sleepiness.

Non-24 hour sleep-wake disorder

- Diagnosis
  - The diagnosis is established primarily by a detailed sleep history and a sleep diary with or without concurrent actigraphy for at least 14 days
  - Actigraphy is particularly useful because depending on the length of the endogenous circadian period, a clear nonentrained pattern may not be evident for several weeks. Most sighted persons with N24HSWD have an evening chronotype, and may exhibit episodes of delayed sleep phase.
  - Unlike patients with DSPD, patients with N24HSWD cannot maintain a stable delayed sleep-wake pattern. It is important to make the distinction between DSPD and N24HSWD because treatment of DSPD with chronotherapy may precipitate the development of a N24HSWD80.

Non-24 hour sleep-wake disorder

- Treatment
- The goal of treatment of N24HSWD is to improve sleep quality and daytime function by establishing stable entrainment of the sleep-wake pattern to the 24 hour external cycle.
- In the blind, the primary approach is a combination of good sleep hygiene, structured social, school and work schedules, and low dose melatonin (0.5 mg) one hour before their preferred sleep time. Many blind patients, whose circadian period is close to 24 hours are able to can maintain entrainment with even lower nightly doses of 20-300µg

Non-24 hour sleep-wake disorder

- Treatment
- A practical approach is to start with a higher dose of melatonin (3-5 mg) for the first month 1-2 hours before bedtime. Once entrainment is established, a lower dose of 0.5 mg can be used for maintenance therapy. For sighted patients, the addition of bright light exposure in the morning, shortly after awakening is a very useful option.
- B12 has also been proposed as a treatment, but the evidence from case reports is inconclusive and is not a recommended treatment by the AASM Practice Parameters

Irregular sleep-wake rhythm disorder

- Irregular sleep-wake rhythm Disorder (ISWRD) is characterized by temporal disorganization of the circadian sleep-wake rhythm, resulting in multiple short sleep and wake bouts occurring throughout the 24 hour cycle

Irregular sleep-wake rhythm disorder

- Epidemiology, risk factor and Pathophysiology
  - The exact prevalence of the ISWR in the general population is unknown, but is commonly reported in institutionalized residents, particularly in those with dementia, children with mental retardation and individuals with traumatic brain injury.
  - The most accepted etiology is a dysfunction of the central circadian clock system due to neurodegeneration or injury. In addition, decreased exposure to synchronizing agents, such as light and structured activities during the day in institutionalized patients can decrease the strength of an already weakened circadian oscillation and thus exacerbate the temporal disorganization of sleep-wake behaviors . Other external factors such as nighttime noise and adverse effect of medications can further disrupt sleep and increase daytime naps.

Irregular sleep-wake rhythm disorder

- Clinical Features
  - Patients with ISWR or their caregivers typically report chronic symptoms of difficulty maintaining sleep during the night and excessive daytime sleepiness.

Irregular sleep-wake rhythm disorder

- Diagnosis
  - The diagnosis is made primarily by a careful history of a minimum of 3 irregular sleep-wake bouts occurring in a 24-hour cycle recorded for at least 7 days, preferably longer by sleep diary and/or actigraphy.
  - The sleep and wake episodes occur in short intervals of 1-4 hours throughout the 24 hours. Total sleep time per day may be normal for age. Poor sleep hygiene, voluntary irregular sleep-wake schedules, other medical or mental disorders with similar clinical presentation must be considered in the differential diagnosis.

Irregular sleep-wake rhythm disorder

- Treatment
- The goal of the treatment of ISWR patients is to consolidate sleep during the night and maintain wakefulness during the daytime
- A multimodal approach consisting of structured activities during the day, increasing daytime light exposure, and addressing nighttime noise and nocturia are basic for all patients with ISWRD59.
- Exposure to 3000-5000 lux bright light for 2 hours in the morning for 4 weeks improved daytime alertness, decreased napping, consolidated nighttime sleep and reduced nocturnal agitation

Irregular sleep-wake rhythm disorder

- Treatment
  - Several randomized controlled studies showed that the combination of increasing daytime light exposure and social activity, evening melatonin administration, structured physical activity, and minimizing nighttime light and noise exposure are helpful for improving the robustness of rest/activity rhythms and reducing the nighttime awakenings in institutionalized residents with disrupted sleep/wake patterns.
  - The evidence for the efficacy of melatonin as a single treatment has been best inconsistent in older adults and in patients with dementia and thus n recommended. Treatment with melatonin alone was found to be associated withdrawn behavior and mood disturbance in one study.
  - Melatonin may more effective in children with ISWR and mental retardation. Melatonin 3 administered in the evening increased nighttime sleep duration, improved sleep efficiency, and reduced daytime naps in these children

Wrap up

Table 1

Overview of clinical features and treatment of circadian rhythm sleep disorders (CRSD) *

Disorder	Clinical Features	Treatment
Delayed leep phase disorder (DSPD)	Stable delay of the major sleep period, resulting in difficulty falling asleep at night and difficulty waking up in the monring	Bright ight therapy 2,000-2:500 lux for 2 hours at or 2-3hours prior to habitual rise time 0.5 mg-3mg melatonin 5-7h prior to steep time
Advanced sleep phase disorder (ASPD)	Stable advance of the major sleep period, resulting in difficulty staying awake in the evening and difficulty maintaining asleep in the morning	Bright light therapy 2,000-2,500 iux for 2h in evening (around 7-9pm)
Non-24 Hour Sleep Wake Disorder (N24HSWD)	Chronic and steady 1 to 2 hours daily delay of sleep and wake schedule resutting in insomnia, difficulty waking up in the morning and excessive daytime sleepiness	Blind - 0 5mg melatonin 1h before preferred bedtime. Sighted - morning bright light therapy at rise time and/or night melatonin administration
Irregular Sleep-Wake Rhythm (ISWR)	Absence of a clearly discernable sleep-wake circadian rhythm resulting in insomnia and/or excessive daytime sleepiness	Increase daytime light exposure and social activity Minimize nighttime light and noise exposure Evening melatonin administration combined with daytime light exposure

* Sleep hygiene is an important component to treat CRSD.

Shift work disorder

- SWD occurs when work hours are scheduled during the habitual sleep ti resulting in chronic complaints of insomnia and excessive daytime sleepiness, result impairment of function that are temporarily associated with the unconventional wo schedules.

Shift work disorder

- Epidemiology, risk factor and Pathophysiology
  - Most shift workers do not have SWD. The estimated prevalence of SWD is ~10 in night and rotating shift workers. Factors that influence the ability to cope with shift work include age, type of work schedule, domestic responsibilities, diurnal preference, commute time, and other sleep disorders (e.g., sleep apnea, narcolepsy). Sleep disturbance is most commonly associated with night or early morning shifts

Shift work disorder

- Clinical Features
  - SWD is characterized by symptoms of insomnia and excessive sleepiness when patients sleep or work at an adverse circadian phase relative to their endogenous circadian sleep and wake propensity rhythm. These impairments persist despite optimizing environmental conditions for sleep. As a result, most patients, particularly night workers are chronically sleep deprived by 1-4 hours per day. Chronic partial sleep deprivation associated with SWD can result in reduced alertness and performance capacity. Excessive sleepiness usually occurs during the shift (mainly night or early morning) when the circadian propensity for sleep is high. These symptoms may persist on days off or for several days after the last work shift. In addition, the unconventional work schedule often interferes with family time and impaired social relationships.

Shift work disorder

- Clinical Features
  - Other symptoms of SWD include chronic fatigue, malaise, mood disorder, gastrointestinal problems and decreased libido. Risk of alcohol and substance abuse is increased, as is the risk of weight gain, hypertension, cardiovascular disease and breast and endometrial cancer. In addition to the medical co-morbidities, SWD is associated with significant loss of productivity, increased health care utilization and increased risk for personal and public safety.

Shift work disorder

- Diagnosis
  - The diagnosis of SWD is reliant on obtaining a careful sleep and work history that documents the chronic impairments in sleep and functioning occur in relation to the shift work schedule. A sleep diary and/or actigraphy for at least 7 days, but preferably longer are useful tools to determine the relationship between sleep and work.
  - Polysomnography is not specifically indicated, but is recommended to evaluate for other co-morbid sleep disorders such as sleep disordered breathing, primary hypersomnia and parasomnias

Shift work disorder

- Treatment
  - The goal of treatment is to improve sleep quality, alertness and performance at work and overall quality of life. Although symptomatic management may be necessary during the course of adaptation to shift work, the ideal approach is to ensure good sleep hygiene and to realign circadian rhythms with the work schedule.
  - Short-acting hypnotic medications can be used to treat associated insomnia, but they are not FDA approved specifically for the treatment of SWD Appropriate alignment of circadian rhythms will improve sleep quality, increase alertness and performance during the shift, and safety. The bulk of the treatment data comes from night shift workers. In night workers,
  - The aim is to induce a delay shift of circadian rhythms, so that alertness is highest during the night (work) and sleep propensity is highest during the late morning and afternoon.

Shift work disorder

- Treatment
  - Bright light exposure (continuous or intermittent) 2,500 to 9,500 lux started early of the night shift and terminated approximately 2 hours before the end of the shift (induces a phase delay) and/or wearing dark glasses or blue light blocking glasses to avoid light exposure in
  - the morning after the night shift (avoiding advance shift) facilitate circadian rhythm adaptation. The combination bright light exposure at work and avoidance of bright
  - light in the morning is the most effective approach.

Shift work disorder

- Treatment
  - However, there is some concerns about the use of dark goggles when driving because of the alerting effect of bright light. Melatonin can potentially induce a delay shift of circadian rhythms when administered in the morning in night workers. Although administration of melatonin before bedtime in night SWD patients has been shown to improve daytime sleep duration, it does not appear to significantly improve alertness. Excessive sleepiness is perhaps the most debilitating problem for many patients with SWD, and can persist despite therapies aimed at improving sleep quality.
  - A short 1-2 hours nap 2-3 hours prior to the shift work, or even relatively short duration (20 minutes) naps at work when possible can decrease sleepiness.
  - Wake-promoting agents such as caffeine and modafinil can also be used to improve alertness and performance during the night shift.

Shift work disorder

- Treatment
- The combination of naps and intermittent low dose caffeine can further improve alertness during work. Modafinil was approved by FDA for the treatment of excessive sleepiness associated with SWD. Modafinil 200 mg taken at the beginning of the shift has been shown to decrease sleepiness, and improve performance on Psychomotor Vigilance Test in patients with SWD. However, it should be noted that residual sleepiness on average remained in the pathologic range. Similar effect was observed in one recent study using armodafinil 150 mg. provides an example to illustrate the timely treatment strategy for SWD.

Jet lag

- Jet lag is characterized by symptoms of difficulty falling asleep or staying asleep, daytime sleepiness, and general malaise due to a temporary misalignment of the internal circadian system with the external physical environment associated with rapid travel across multiple time zones.

Jet lag

- Clinical Presentation and Diagnosis
- The diagnosis of jet lag as a disorder is established by a history of symptoms of insomnia and excessive sleepiness that is temporally associated with travel across more than two time zones. The severity of the clinical symptoms depends on the direction of travel and the number of time zone crossed. These symptoms typically subside within a few days or up to one week. However, for frequent travelers, the symptoms and functional impairments can be chronic and severe, prompting them to seek treatment.

Jet lag

- Clinical Presentation and Diagnosis
  - In general, it is more difficult to adapt to eastward travel.
  - For eastward travelers, the symptoms at the destination include difficulty falling asleep, excessive daytime sleepiness and decreased daytime performance especially in the morning.
  - For westward travelers, falling asleep is less problematic than maintaining asleep, and early evening sleepiness and decreased performance are especially troublesome. Other common associated symptoms of jet lag include: 1) altered appetite and gastrointestinal function, 2) general malaise 3) fatigue and 4) mood disturbance. Other sleep disorders causing insomnia and/or excessive daytime sleepiness should be considered.

Jet lag

- Treatment
- The main treatment goal for jet lag is to accelerate realignment of the endogenous circadian rhythm to the destination's time zone. Circadian adaptation after eastward travel requires advancing the phase of circadian rhythms, whereas westward travel usually requires a phase delay. Phase advancement after eastward travelling is more difficult than phase delay after westward travelling, because the endogenous period of human circadian rhythms is slightly longer than 24h.

Jet lag

- Treatment
- Circadian synchronizing agents such as timed bright light exposure and exogenous melatonin are recommended. The timing of light exposure depends primarily on the direction of travel and the number of time zones crossed.
- For eastward flights, one can begin to advance the timing of circadian rhythms by bright light upon awakening and avoiding light exposure in the evening. On the other hand, at the destination, one should avoid bright light too early in the morning, but increase exposure to light in the late morning and exposure to afternoon for the first 2-3 days.
- If flying westward, at the destination, one should stay awake during the daylight hours, increase light exposure in the afternoon and early evening and avoid napping prior to bedtime at the destination.

Jet lag

- Treatment
- Although there are no FDA approved pharmacologic therapies for jet lag, results from several studies support the use of melatonin (0.5 to 5 mg) for alleviating jet lag symptoms with eastward travel.
- One recent placebo controlled study showed that bedtime administration of ramelteon (1 mg), a melatonin receptor agonist, reduced sleep latency in subjects travelling eastward across five time zones. However, this effect was only seen under dim light conditions, indicating that light is still the most powerful stimulus for phase re-setting of circadian rhythms.

Jet lag

- Treatment
- Other pharmacological agents, including caffeine, armodafinil and short acting hypnotics have been studied for the management symptoms of insomnia and excessive sleepiness associated with jet lag. Wake promoting agents, such as caffeine and armodafinil 150 mg have been shown to have beneficial effects on alertness and fatigue when flying eastward.
- Short acting hypnotics, such as zolpidem 10mg given for 3 consecutive nights immediately after travel may be effective for improving sleep quality and duration.

Jet lag

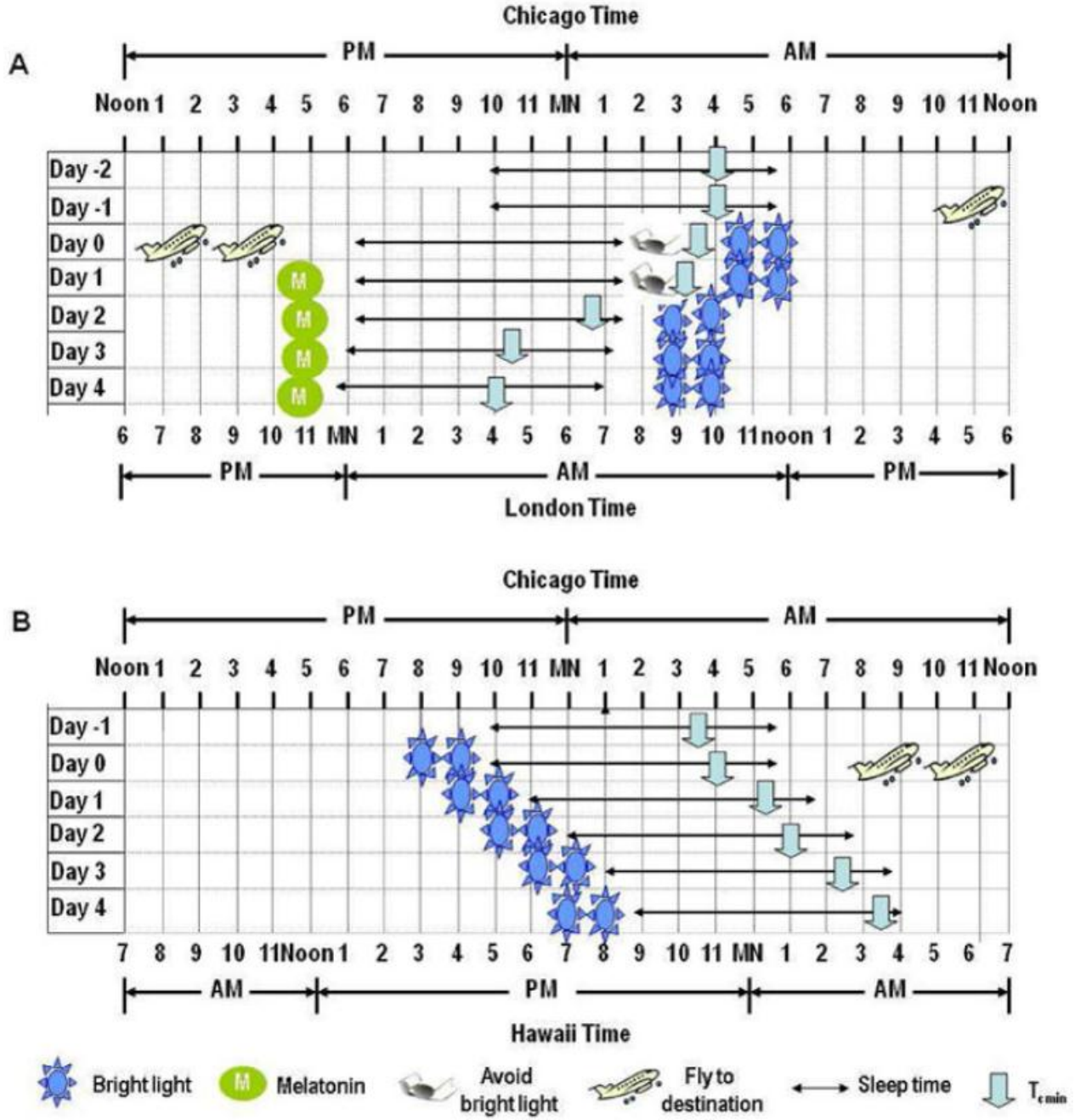


Figure 7. Strategies to accelerate circadian adaption to jet lag

Thank you for attention