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Therapeutics for Circadian Rhythm Sleep Disorders

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Synopsis

The sleep-wake cycle is regulated by the interaction of endogenous circadian and homeostatic processes. The circadian system provides timing information for most physiological rhythms, including the sleep and wake cycle. In addition, the central circadian clock located in the suprachiasmatic nucleus of the hypothalamus has been shown to promote alertness during the day. Circadian rhythm sleep disorders arise when there is a misalignment between the timing of the endogenous circadian rhythms and the external environment or when there is dysfunction of the circadian clock or its entrainment pathways. The primary synchronizing agents of the circadian system are light and melatonin. Light is the strongest entraining agent of circadian rhythms and timed exposure to bright light is often used in the treatment of circadian rhythm sleep disorders. In addition, timed administration of melatonin, either alone or in combination with light therapy has been shown to be useful in the treatment of the following circadian rhythm sleep disorders: delayed sleep phase, advanced sleep phase, free-running, irregular sleep wake, jet lag and shift work.

Keywords

circadian rhythm sleep disorders; treatment; melatonin; light therapy; sleep

Introduction

Circadian rhythm sleep disorders (CRSD) are due to a misalignment between the timing of the endogenous circadian rhythm and the desired or socially acceptable sleep-wake schedule, or dysfunction of the circadian pacemaker and its afferent/efferent pathways. CRSDs include delayed sleep phase disorder, advanced sleep phase disorder, non-24-hour sleep-wake disorder, irregular sleep-wake rhythm disorder, shift work sleep disorder and jet lag disorder.

The central circadian pacemaker in mammals is located in the suprachiasmatic nucleus (SCN). The endogenous period of circadian rhythms in humans is typically slightly longer than 24 hours [1]. Therefore, in order to maintain a stable relationship with the recurring daily changes in the 24-hour physical environment, circadian rhythms are entrained by light, social and physical activity cues, and melatonin. Of these, light is the strongest entraining agent for the circadian clock. Light-dark cycle information is relayed from the retina to the SCN primarily via the retinohypothalamic tract, a neural pathway that is distinct from the

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visual system [2]. The timing of light exposure is crucial, and determines its ability to effect changes in the timing of circadian rhythms. According to the phase response curve in humans, exposure to bright light in the early morning (after the nadir of the core body temperature rhythm) induces phase advances, whereas light exposure in the evening (before the nadir of the core body temperature rhythm) delays the phase of circadian rhythms [3] [Figure 1].

Although less potent than bright light, melatonin also has circadian phase shifting properties. The timing of melatonin release from the pineal gland is regulated by the SCN and its secretion is suppressed by exposure to bright light [4]. In individuals with a typical sleep-wake schedule, endogenous melatonin levels begin to rise approximately 2 hours before sleep onset [5], and remain elevated during the habitual sleep hours. Melatonin onset measured in dim light (DLMO) has been shown to be a stable marker of circadian phase [6,7] and can be used to determine the timing of endogenous circadian rhythms in the research setting as well as in clinical practice. The phase response curve for melatonin is approximately 12 hours out of phase with that for light, but with similar crossover points [8]. Melatonin administration in the early morning (after the nadir of the core body temperature rhythm) cause phase delay shifts, whereas when given in the evening, elicit phase advance shifts [9] [Figure 1].

Because the primary synchronizing agents of the circadian system are the light/dark cycle and melatonin, timed exposure to bright light and administration of melatonin have often been used as treatments of circadian rhythm sleep disorders. Although we will focus on pharmacologic therapies, it is important to note that timed exposure to bright light is an indication as either a guideline or option by the American Academy of Sleep Medicine (AASM) Clinical Practice Parameters for the treatment of most CRSDs [10]. Exogenous melatonin is widely used as a pharmacological treatment and is recommended as either a guideline or option by the AASM Clinical Practice Parameters for the treatment of CRSDs. Melatonin is classified as a nutritional supplement and has been approved by FDA as a treatment for sleep disorders.

Delayed Sleep Phase Disorder

Delayed sleep phase disorder (DSPD) is one of the most common of the circadian rhythms sleep disorders. Limited data suggests that the prevalence rate is about 1.7% in the general population [13] and 7% of those with insomnia complaints [7]. Onset of this disorder typically occurs during adolescence or early adulthood [11,14].

DSPD often presents as sleep-onset insomnia and/or excessive morning sleepiness associated with the chronic inability to fall asleep and wake up at socially acceptable times as required for work or school [11]. Sleep onset time typically occurs between 2 am to 6 am, and wake times delayed into the late morning or early afternoon. When unrestricted by an imposed schedule, sleep latency and duration are normal [12]. Waking in the early morning (i.e. 6-8 am) is very difficult for these patients, often requiring multiple alarms and the assistance of family members. DSPD patients report excessive sleepiness and impaired functioning in the morning, with marked improvement in alertness in the evening/night.

According to the International Classification Sleep Disorders (ICSD-2) the diagnosis is made by a history of a stable delay of the major sleep period relative to the desired sleep and wake times for at least 1-3 months, and is accompanied by clinically significant insomnia and/or excessive sleepiness [18]. When allowed to sleep at the preferred delayed sleep phase, sleep quality and duration are typically within the normal range for age. In addition, sleep logs or actigraphy monitoring for at least 7 days is recommended to confirm a delayed

pattern of the habitual sleep and wake cycle [18]. These diagnostic features and those for other CRSDs are listed with guidelines for assessment and treatment in Table 1.

Although the exact etiology of DSPD is unknown, it has been suggested that genetic predisposition, a longer than average endogenous circadian period or alterations in entrainment pathways can result in a delayed circadian phase [11,14]. There is evidence of increased sensitivity to the phase shifting effect of evening light in DSPD patients [15]. Thus, exposure to even moderate levels of light in the evening could delay circadian rhythms, as well as suppress the normal rise in melatonin in the evening, resulting in the delayed onset of the sleep-wake cycle [15]. Furthermore, the typical late rise time of patients with DSPD reduces exposure to morning light in the phase advance zone of the phase response curve, which will perpetuate or exacerbate the already delayed circadian phase. In addition, recent evidence indicates that genetic mechanisms may also play a role. For example, the DSPD phenotype has been associated with polymorphisms of the circadian genes, *Clock* [16] and *Per3* [17].

Therapeutic Approaches

Patients with DSPD commonly experience repeated unsuccessful attempts at trying to fall asleep earlier, and often resort to the use of sedating medications and alcohol [11]. Effective treatment requires a multimodal approach aimed to re-align circadian rhythms with the desired sleep and wake schedule. Non-pharmacological approaches including adherence to good sleep hygiene, avoidance of bright light in the evening and increasing light exposure in the morning are basic in any treatment program for DSPD. Based on the strength of evidence, the AASM practice parameters recommend timed morning light exposure and/or appropriately timed melatonin administration as effective treatments for DSPD [10].

Numerous studies have demonstrated the ability of appropriately timed bright broad-spectrum light, typically between 2500 to 10,000 lux, to induce phase advancement of circadian rhythms [19-21]. For the treatment of DSPD, exposure to bright light shortly after awakening in the morning (close to but after the nadir of the circadian core body temperature rhythm) will advance the timing of circadian rhythms and improve synchronization with the desired sleep and wake times. For example, bright light (2500 lux) for 2 hours in the morning has shown to successfully phase advance the circadian rhythm of core body temperature in DSPD patients [19].

There is very limited evidence that methylcobalamin (vitamin B12) when combined with bright light in the morning may be effective for the treatment of DSPD [22-25]. Findings that vitamin B12 injected intravenously (0.5 mg/day) at 12:30 pm for 11 days, followed by oral administration (2 mg 3 times per day) for 7 days increased the phase shift induced with a single morning exposure to bright light led to further examination of its effectiveness in treating CRSDs [22]. In an open label study, 28% of patients were effectively treated with either vitamin B12 alone or in combination with bright light [23]. Similar success has been reported in several individual cases [24]. However, administration of 1 mg methylcobalamin 3 times per day after each meal for 4 weeks alone did not show improvements compared to placebo, which suggests that its effects may be dependent on its interaction with light [25]. Therefore, there is insufficient evidence to support vitamin B12 as a treatment for DSPD [10].

Of the pharmacologic approaches for DSPD, exogenous melatonin has been the most studied. The relatively small number of participants and the variability in the dose and timing of melatonin administration have limited most of these studies. Melatonin (5 mg) given 5 hours before sleep onset advanced sleep onset time by about 1.3 hours, wake time by 2 hours [26] and DLMO by 1.5 hours [27], compared with placebo over a 4-6 week

treatment period. In one study, patients also reported feeling more refreshed in the morning with melatonin treatment [27]. However treatment with 5 mg did not change sleep architecture [29]. Timing of melatonin administration can influence the magnitude of the phase shift in patients with DSPD, with earlier times being most effective. Melatonin given 5-6.5 hours prior to the individual DLMO resulted in the largest phase advances of melatonin profiles compared to administration closer (1.5 hours) before the DLMO [27,28]

Long-term effectiveness of melatonin for the treatment of DSPD has also been evaluated. One year after initiating a 6-week treatment with 5 mg melatonin taken daily at 10 pm, participants were surveyed regarding the efficacy of their treatment [30,31]. Almost 97% of patients reported improvement, 80% of whom noted the change within the first 2 weeks. Side effects were usually minor with 57% reporting none at all and 34% noting slight morning fatigue. Of those helped by melatonin, 91% relapsed after treatment discontinued, with almost 30% reporting relapse within first 7 days, 15% within the first month and 42% within 2-6 months after treatment had stopped. Patients that relapsed immediately were found to have more severe symptoms of DSPD based on pretreatment actigraphy measures compared to those with a delayed relapse [30].

Melatonin has also been investigated for the treatment of DSPD in children with attention deficit hyperactivity disorder (ADHD), and has been found to be effective and well tolerated, except for the rare occurrence of new-onset seizures [31]. In an open label study, daily use of melatonin 3 mg at bedtime for 1 week to 3 months significantly shortened sleep onset latency (median=135 min) in children with ADHD [32]. In a larger study, children ages 6-12 years taking either 3 or 6 mg of melatonin at 7 pm daily for 3 weeks were shown to improve sleep onset and advance DLMO by 44 min on average [33]. Improvements of core behavioral problems were also noted. A follow-up study found that approximately 65% of these children were still using melatonin daily and 11% occasionally, with parents reporting its effectiveness in improving sleep onset in 88% of participants [34]. Parents also reported improvements in behavior (71%) and mood (61%) with long-term melatonin treatment [34]. However, recurrence of delayed sleep timing occurred with discontinuation of treatment in most cases [34] similar to previous studies in adults with DSPD [26,30].

Advanced Sleep Phase Disorder

Advanced sleep phase disorder (ASPD) is characterized by a recurrent pattern of early evening sleepiness and early morning awakening. This earlier than desired sleep propensity (7 pm to 9 pm), can interfere with social and work schedules. When trying to maintain a socially desired schedule, and even if sleep onset is delayed, early morning awakening (e.g. before 5 am) still occurs, and results in shortened sleep duration and excessive daytime sleepiness.

Diagnostic criteria for ASPD includes a stable advance in the timing of the major sleep period relative to the desired sleep time in conjunction with an inability to delay sleep onset and remain asleep until the desired conventional clock time [18]. Given the opportunity to sleep at their preferred sleep schedule, patients also display normal sleep duration and quality. Sleep logs or actigraphy monitoring for at least 7 days are recommended to demonstrate a stable advance in the timing of the sleep period [18].

ASPD is thought to be less common than DSPD. ASPD is reported more often among older populations [38]. Etiology remains unclear, although patients with ASPD have an earlier timed temperature and melatonin circadian phase, which may be preventing them from sleeping later [37]. Multiple cases of familial advanced sleep phase pattern have been identified in which the ASPD trait segregates with an autosomal dominant mode of inheritance [35,36,39]. Two gene mutations have been identified, the clock gene *hPer2* in

one family with advanced sleep phase [40], and the *casein kinase 1 delta* gene in another family [38], suggesting that there is heterogeneity of this disorder. Other underlying mechanisms that may be involved include having a short (less than 24 hours) endogenous circadian period [36] or an attenuated ability to phase delay due to a dominant phase advance region of the PRC to light.

Therapeutic Approaches

Treatment approaches for ASPD include chronotherapy, timed light exposure in the evening, and pharmacotherapy with melatonin or hypnotics for sleep maintenance insomnia. However, there is very little evidence of the effectiveness of pharmacological therapy in ASPD. The AASM Practice Parameters recommends prescribed sleep scheduling and timed bright light exposure as treatments for ASPD [10]. Bright light therapy in the evening (between 7-9 pm) is typically used and has been shown to delay the timing of circadian rhythms, improve sleep and daytime performance in older individuals with advanced circadian phase and sleep maintenance insomnia symptoms [45,46], although limited compliance may limit its practicality as a long-term treatment.

Based on the phase response curve to melatonin, early morning administration of melatonin (after the nadir of the core body temperature rhythm) would fall in the curve's advance portion and thus advance the timing of sleep/wake cycle rhythm. However, clinical evidence is lacking regarding its efficacy, and concerns have been raised regarding the safety of taking a potentially sleep promoting agent in the morning [41,42]. Hughes and colleagues [43] evaluated different delivery strategies of melatonin for ASPD in a controlled study. A 2-week administration of immediate release melatonin 0.5 mg, 4 hours after bedtime or controlled release melatonin 0.5 mg, 30 minutes before bedtime did not improve sleep maintenance, but did result in a non-significant phase delay of approximately 27 minutes [43]. Although hypnotics are used in clinical practice to treat the sleep maintenance symptoms of patients with ASPD, their efficacy and safety in this population has not been specifically studied [44].

Free-Running Disorder (Nonentrained Type)

Individuals with free-running disorder (FRD) typically have a longer than 24-hour circadian rhythm, similar to those living in temporal isolation [48]. Because these patients are unable to entrain to the external 24-hour physical, social or activity cycles, sleep and wake periods progressively drift later each day [49]. Although there is an overlap between DSPD and FRD, this inability to stably entrain to a 24-hour sleep-wake cycle is what clinically sets FRD from those with DSPD, who are delayed, but stably entrained [50]. Depending on whether the circadian propensity for sleep and wake fall within the day or night, individuals may present with either insomnia symptoms or excessive sleepiness. These periods of insomnia and sleepiness, usually lasting several days to a few weeks, are intermixed with periods of relatively normal sleep and wake times (when the endogenous circadian rhythm is aligned with the conventional clock times).

Diagnosis of FRD includes complaints of insomnia or excessive sleepiness associated with the misalignment between the endogenous circadian rhythm and the light-dark cycle, that cannot be explained by other causes [18]. Sleep logs or actigraphy monitoring for at least 7 days is recommended for diagnosis, although a longer duration is preferred in order to demonstrate the drift in sleep times from one day to the next [10].

FRD is most common in blind people who lack, or have greatly diminished ability for photic entrainment. It is estimated that approximately 50% of blind persons have non-entrained circadian rhythms [50]. Since light cues are unavailable, sleep disturbances are common

[60]. In fact, the degree of visual loss is related to the occurrence of free-running disorder [51]. The insomnia and daytime sleepiness that occur when the circadian pacemaker is out of phase with the desired sleep time have been noted as being second in debilitation next to the blindness itself [61]. However, a good proportion of blind individuals maintain some light perception and/or are able to entrain to recurring social and activity schedules and thus can maintain entrainment [51]. The disorder is thought to be rare among sighted individuals [53,54]. FRD in sighted individuals is more common in men than in women [52] and onset is typically in adolescence or early-adulthood.

Although the etiology of this disorder is unknown, it has been hypothesized that sighted FRD patients may have a blunted response to light or have a limited ability to phase advance, but has yet to be tested [53,55]. Patients have reported symptoms consistent with DSPD prior to the onset of FRD, a development that may occur during failed treatment attempts similar in nature to chronotherapy [55]. The development of FRD after traumatic brain injury has also been noted [56].

Therapeutic Approaches

Both behavioral and pharmacological options are available for the treatment of FRD, depending on whether the patient is sighted or blind. For sighted patients, the AASM Practice Parameters recommend planned sleep schedules, timed bright light exposure, and melatonin administration as treatment options, and timed melatonin administration for treating FRD in blind individuals [10]. There was insufficient evidence for using vitamin B12 for the therapy of sighted patients with FRD [10].

Due to the rarity of the disorder in sighted individuals, most published treatments have been case reports. Exposure to bright light during the day and maintaining a regular sleep, wake and work schedules can increase the strength of entrainment, and thus should be the basic approach for all sighted patients. In addition, administration of timed melatonin in the evening has been shown to be beneficial. For example, low dose exogenous melatonin (0.5 mg) taken at 9 pm entrained a sighted FRD patient's sleep wake cycle to a 24-hour period [55]. Hayakwa and colleagues [57] described a FRD patient who was able to successfully entrain with light therapy in the morning. However the patient became non-compliant with light therapy and the sleep/wake cycle began to drift. At this point, administration of melatonin 1 mg per day at 9 pm successfully re-entrained his sleep-wake cycle to the 24-hour day. Another FRD patient had long-term success with 3-5 mg melatonin taken between 9 pm -10 pm each night, with continued response to daily treatment at a 15-month follow-up [58]. However, another study using low-dose melatonin (0.3 mg) at 5, 3, and 1 hour before habitual sleep-onset time demonstrated only limited effectiveness [59].

In blind people with FRD, timed exposure to non-photic entraining agents such as planned social and physical activities and melatonin are the primary therapies. There is strong evidence for the effectiveness of melatonin for the treatment of FRD in the blind. However, the appropriate timing and dosage of melatonin is especially important for determining its effectiveness and avoidance of side effects, such as daytime sleepiness [62]. For optimal effectiveness, the initial time of melatonin administration should be adjusted so that it occurs a few hours before the predicted endogenous melatonin onset (DLMO) [63]. This methodology was used to entrain blind patients using melatonin 10 mg, 1 hour before their preferred bedtime over 3-9 weeks [64,65]. Once entrained to the 10 mg dose, patients maintained entrainment for 4 months with daily administration with 0.5 mg. Patients had less wake after sleep onset (WASO) and great sleep efficiency after melatonin compared to placebo. However, after just several days to one month after discontinuation of this lower dose, there was a recurrence of a free-running rhythm.

Alternatively, treatment may be initiated with lower doses. For example, a patient with an unusually long circadian period (24.6) was unable to entrain with a 10 mg dose of melatonin [65], but was able to successfully entrain for 161 days with a daily dose of 0.5 mg administered before bedtime [66]. Entrainment to a 24-hour period occurred by day 47 of this low dose. Before trying this lower dosage, investigators attempted a treatment of 20 mg melatonin for 60 days, which also failed to entrain this patient. It has been postulated that the higher dose may spillover into the delay phase of PRC, which would prevent entrainment. Demonstration of successful entrainment with low doses of melatonin has important clinical implications since chronic treatment with low dose may be better tolerated than high dose [66].

Melatonin treatment for blind patients with FRD typically is considered a long-term therapy because phase drifts typically occur not long after melatonin is discontinued. Since higher doses of melatonin have been associated with sleepiness, determining the lowest effective dose is important. Utilizing a step down method to find the lowest effective melatonin dose in series of physiological doses, entrainment to a normal circadian phase occurred on varying doses between 20-300 μg. [67]. In fact, there appeared to be a linear relationship between the lowest entraining dose and the length of the patients' circadian period (tau) beyond 24 hours (tau minus 24 hours). For example, a patient with tau=24.15 entrained at the lowest dose of 20 μg, whereas someone with a tau=24.55 responded best to a dose of 200 μg melatonin.

Irregular Sleep-Wake Rhythm

Irregular sleep-wake rhythm (ISWR) is a circadian rhythm disorder characterized by the absence of a clear sleep-wake pattern. Patients with ISWR present with symptoms of insomnia, excessive daytime sleepiness, fragmented sleep, and frequent napping, depending on the timing of the sleep wake episode. Total sleep time within a 24-hour period is typically normal, but may consist of several sleep bouts without one primary nocturnal sleep period. ISWR is most common among older adults, especially those in nursing home or care facilities, and is associated with neurological disorders such as dementia, mental retardation, and brain injury [68,70].

An ISWR diagnosis requires chronic complaints of insomnia and/or excessive sleepiness, the total time slept in a 24-hour period to be of normal duration for age and for symptoms to be unexplained by another sleep disorder, medication use or medical condition [18]. Sleep logs or actigraphic monitoring for at least 7 days is recommended to reveal 3 or more irregular sleep bouts during a 24-hour period, although actigraphy may be a useful option in situations when sleep log documentation may be unreliable. Individuals who voluntarily maintain an irregular sleep schedule, perhaps due to rotating work shifts, and engage in poor sleep hygiene may report similar sleep-wake irregularities as those with ISWR, but do not meet criteria for diagnosis [18].

Multiple factors, from a lack of exposure to structured social and physical activities and bright light [68,71] to degeneration of the central circadian clock regulation have been proposed to be involved in the development of irregular sleep-wake rhythms. Compared to age matched controls, there is evidence of increased loss of SCN neurons in patients with Alzheimer's disease (AD) [69,72]. Findings that nursing home residents who slept during the day were also found to engage in less physical and social activities, less light exposure, more disturbed nighttime sleep, and decreased amplitude of circadian rhythms, demonstrate the importance of zeitgebers in regulating the endogenous rhythms and sleep-wake cycle [68]. Although there are no direct findings for a genetic role in ISWR, evidence demonstrates that the variance associated with longitudinal sleep disturbances in patients with AD are related

to “trait”-like characteristics more so than “state” components [73], suggesting that more genetic research is needed to determine a genetic role in the development of ISWR.

Therapeutic Approaches

The overall goals of treatment of ISWR are to increase the duration of consolidated sleep periods during the night and improve daytime function. A multi-therapeutic approach combining bright light exposure, physical activity and other behavioral modifications are indicated as effective treatments for both young and older patients with ISWR [10]. Encouraging good sleep habits and increasing the strength of circadian synchronizers, such as bright light, are basic approaches. Appropriately timed bright light therapy alone has been shown to strengthen circadian rhythms and improve sleep in patients with dementia [76-78]. In addition, behavioral strategies including structured social and physical activities and decreasing nocturnal noise in nursing homes can help improve sleep in institutionalized older adults.

Although melatonin is indicated for children with ISWR or those with psychomotor retardation, it is not recommended for older adults with dementia [10]. The efficacy of melatonin for improving sleep disturbances in patients with AD has yielded inconsistent effects, and thus, was not recommend in the recent AASM Practice Parameters [10]. In a randomized multicenter clinical trial, patients with AD were assigned to take either 2.5 mg sustained release (SR), 10 mg immediate release melatonin, or placebo for 8 weeks about 1 hour before habitual bedtime [74]. A non-significant trend toward increases in nocturnal sleep duration was found in the melatonin groups compared to placebo. However, another more recent study using either melatonin alone, bright light alone or combined treatment of bright light (>1000 lux) and melatonin (2.5 mg) in elderly residents of group care facilities for a mean of 15 months showed improvements in sleep efficiency with the combined treatment, decreased sleep latency with melatonin and increased sleep duration in both individual therapies [75]. Interestingly, treatment with only melatonin adversely affected mood. These results suggest that in an older population, a combined approach using low dose melatonin and bright light may be the most efficacious for improving sleep and daytime function [75].

The use of melatonin to treat circadian rhythm disorders in children with developmental disorders has shown more consistent results than in elderly nursing home patients. However, most of the evidence is derived from case reports or case control studies. Early case reports described the successful treatment of 15 multiply disabled children with melatonin therapy ranging in duration from 3 months to 1 year [79]. Doses of 2.5-5 mg melatonin administered at bedtime were found to induce and improve sleep, increase daytime alertness, decrease behavioral problems and oftentimes alleviate other symptoms (e.g. seizures) without any adverse effects. The 6:30 pm administration of 3 mg melatonin in children with psychomotor retardation for 4 weeks nightly improved sleep-wake patterns by increasing nocturnal sleep duration and quality, while decreasing daytime sleep [80]. Comparisons of fast-release (FR) and controlled release (CR) forms of melatonin in this population administered at bedtime for 22 days revealed that FR was better at initiating sleep, while CR helped improve sleep maintenance, early morning awakenings, and fragmentation [81]. The most effective average dose for both forms was slightly higher than that required in adults (CR mean=5.7 mg; FR mean=7 mg).

Jet Lag Disorder

Travel across multiple time zones can lead to jet lag, which is characterized by symptoms such as sleepiness, insomnia, fatigue and even gastrointestinal problems [82]. Jet lag is caused by the misalignment of the endogenous circadian rhythm to the destination clock

time. For example, if individuals travel from New York to London across 5 time zones, they will need to phase shift advance about 5 hours to be fully entrained to the destination time. The more time zones crossed, the longer it takes to re-entrain the circadian rhythm [83]. Symptoms typically are transient and improve after several days at the destination location. Diagnosis of jet lag disorder requires a complaint of insomnia or excessive daytime sleepiness, as well as daytime functioning impairment or general illness linked with travel across more than 2 time zones that cannot be attributed to other causes [18]. Due to the longer than 24 hour circadian period in humans, phase delays are typically easier to achieve [47]; thus adjustments to westward travel occur more rapidly than eastward travel.

Therapeutic Approaches

Treatments for jet lag disorder are focused on adjustment of the endogenous circadian rhythm to the destination time zone, as well as strategies aimed at improving sleep and daytime alertness. Non-pharmaceutical treatments such as good sleep hygiene, adjusting the sleep schedule prior to travel (when possible) and appropriately timed exposure to light have also been shown to accelerate circadian adjustment and to decrease symptoms of jet lag [83]. Appropriately timed bright light exposure and avoidance of light at the wrong time of the day have been shown to be effective strategies to accelerate entrainment of circadian rhythms. The timing of light exposure depends on the direction of travel and the number of time zones crossed. For example, on an eastward flight from New York to London, when arriving in the early morning, one should avoid bright light, but get as much light as possible in the late morning to early afternoon [84]. In summary, strategic exposure to light appears to be a safe and potentially beneficial therapy for air travelers who suffer from jet lag [85,86].

Pharmacologic approaches include melatonin and hypnotic medications. Data support the use of melatonin to minimize jet lag, although it is not FDA approved for the treatment of jet lag disorder. The general recommendation is melatonin 2-5 mg be taken before bedtime upon arrival and dosing may be repeated for up to four days as needed [84,87]. Potential adverse effects such as headaches, nausea and exacerbation of cardiovascular disease in patients at risk should be considered. Subjects who took 5 mg melatonin for 3 days pre-flight at 6 pm and for 4 days at bedtime after eastward travel subjectively rated their jet lag symptoms as less severe compared to the placebo group [88]. Melatonin treatment with 5 mg administered 3 days before departure (between 10:00 am -12:00 pm) and while at the destination time zone (between 10 pm-midnight) on both outbound (eastward) and inbound (westward) flights across 12 time zones decreased jet lag symptoms compared to placebo [89]. A comparison of 0.5 mg FR, 5 mg FR, 2 mg CR melatonin and placebo administered at bedtime for 4 days after the flight was conducted on individuals traveling eastward across 6-8 time zones [90]. The 5 mg FR group had significantly improved sleep quality, shortened sleep latency, and decreased wake during the night by day 2 of the treatment, and continued to increase sleep duration compared to the other groups. All doses of melatonin made it easier to get up in the morning, and patients felt more rested and improved mood versus placebo [90]. Beaumont and colleagues [91] showed that 5 mg melatonin taken at bedtime improved measures of sleep and subjective sleepiness following an eastbound flight across 7 time zones and 300 mg of slow-release caffeine taken at 8 am reduced self-rated sleepiness, but negatively affected sleep maintenance. These results suggest that slow release caffeine and melatonin may be of value for alleviating some symptoms of jet lag.

The use of hypnotic medications specifically focused on promoting nocturnal sleep at the new destination has also been studied. Benzodiazepines and newer non-benzodiazepines, typically used to treat insomnia, were examined to determine their efficacy in the treatment of jet lag. In a simulation study, the short-acting benzodiazepine triazolam was administered 3 hours before bedtime for 5 days after the 8-hour delayed shift (westbound travel across 8

time zones) [92]. Administration of 0.5 mg triazolam at bedtime the first 4 nights significantly improved circadian adaptation compared to placebo, with triazolam inducing an additional shift delay of over 2 hours by day 3. In contrast, 10 mg of the benzodiazepine temazepam at bedtime for 3 nights after a 5-hour westbound flight revealed no improvements of jet lag symptoms compared to placebo [93]. In an operational setting, both 5 mg zopiclone and 2 mg melatonin single doses taken near bedtime equally facilitated sleep after an eastbound flight across 5 time zones [94]. Participants had longer sleep duration, shorter sleep latency, less time awake, and reported an overall better quality of sleep after both treatments versus placebo. Zopiclone (7.5 mg) administered at bedtime for 4 nights diminished jet lag related sleep disturbances following transatlantic westward flights including increased sleep duration, reduced sleep fragmentation and improved sleep quality compared to placebo [95]. The rest/activity cycle and core body temperature rhythm synchronized and adapted to the destination clock time more rapidly after zopiclone compared to placebo, even though jet lag ratings did not differ between groups. Zolpidem (10 mg) taken at bedtime for 3 nights increased sleep duration, decreased nocturnal awakenings and improved sleep quality compared to placebo during the first 2 nights taken after transatlantic eastward travel (5-9 time zones) [96]. Subjective ratings of mood and alertness did not differ between the 2 groups, suggesting that the effects of circadian misalignment involved with jet lag were still apparent, even though sleep itself had improved. A recent study of ramelteon, a melatonin receptor agonist, showed an improvement in the latency to persistent sleep with a 1 mg dose administered prior to bedtime for 4 nights after eastward travel [90].

Pycnogenol, an extract from the bark of the French maritime pine has been shown to help prevent edema associated with long flights [97]. Recent preliminary results showed that administration of 50 mg of oral pycnogenol 3 times daily commencing 2 days before the 7-9 hour flight significantly decreased the severity and duration of jet lag symptoms (fatigue, sleep disturbance and short term memory) [98]. In addition, CT scans performed within 28 hours post-flight revealed less brain edema in the pycnogenol group.

Based on the evidence, the AASM Practice Parameters recommends timed melatonin administration to reduce jet lag symptoms [10]. Other treatment options indicated include maintaining home-based sleep hours for brief travel, short-term hypnotic use for insomnia and caffeine to counteract sleepiness. For eastward travel, the combination of shifting sleep schedule an hour earlier for 3 days prior to travel and morning light exposure is also suggested to improve symptoms [10,99].

Shift Work Disorder

Many American workers have jobs requiring evening, night or rotation work schedules. Approximately 30% of this population [100] complain for at least 1 month of excessive sleepiness and insomnia in relation to a work schedule falling during the time of habitual sleep, which are the symptoms that characterize shift work disorder (SWD) [18]. Sleep logs or actigraphy monitoring for at least 7 days is recommended for diagnosis of SWD other sleep disorders and conditions should be ruled out [18]. This disorder has also been associated with poor performance, cardiovascular, gastrointestinal and reproductive problems, accidents, illness, and depression [100,101]. These issues occur because the endogenous circadian rhythms are not synchronized with the altered sleep-wake cycle due to shift work.

Typically, sleep is curtailed by 1-4 hours in patients with SWD, with most complaints associated with night and early morning work. These sleep problems may be misinterpreted as either sleep initiation or maintenance issues, as the individual is attempting to sleep at a

clock time misaligned with the endogenous rhythm. Also, reports of excessive sleepiness occur during their work shift when they are awake, but sleep propensity is high. Symptoms may persist during days off due to the circadian rhythm disruption, often resulting in reverting back to a normal schedule of sleeping at night when not working.

Therapeutic Approaches

Clinical Management of SWSD is aimed at re-aligning circadian rhythms with the sleep and work schedules, as well as improving sleep, alertness and safety. Although early morning and rotational shifts are commonly associated with shift work disorder, most of the strategies developed for adjustment to shift work have focused on the night shift worker. Non-pharmacological treatments are basic to the management of SWSD. Family and social factors that disturb sleep can impair adjustment to shift work. Optimizing the sleep environment, adherence to healthy sleep habits and planned naps, when possible, should be encouraged for all patients [102].

Similar to jet lag, appropriately timed bright light therapy and avoidance of light at the wrong time of the day can help accelerate and maintain entrainment to the shift schedule. For night workers, circadian rhythms need to be delayed, so that the highest sleep propensity occurs during the day, rather than at night. Most studies used light intensities between 1200 lux and 10,000 lux for a period of 3-6 hours during the night shift [103]. Intermittent bright light exposure (~20 minutes/hour blocks) has also being shown to accelerate circadian adaptation to night shift work [104,121]. In addition to its circadian phase re-setting effects, light has acute alerting effects which can be useful during the work period [105]. Another complementary strategy is to avoid exposure to morning bright light during the morning commute home [106,121]. Recently in a simulated shift work paradigm, a combination of enforced sleep/wake schedule and intermittent bright light exposure during the night shift was used to achieve a compromised phase position, including on the days off. Under these conditions, there was improvement in performance [107]. A compromise phase position has the potential to improve performance and sleep on work days as well as on days off.

Studies on the effectiveness of melatonin for the treatment of SWD have been mixed [108-114] and may be limited by use of different doses and formulations. For example, melatonin (6 mg) taken before daytime sleep after 4-6 consecutive nights of shift work was ineffective [108], whereas other studies showed increased alertness during the subsequent night shift after taking 10 mg in the morning prior to bedtime for 2-5 days [110], and overall improvement in sleep quality when treated with 5 mg in the morning for 6 consecutive days [111]. In addition, the administration of 1.8 mg CR melatonin after 2 consecutive night shifts before daytime sleep increased sleep duration and sleep quality after the first administration, but not after the second [112]. Although it appears that when taken at bedtime after the night shift, melatonin can improve daytime sleep, it may have limited effects on alertness at work [103]. Melatonin is not approved by the FDA for the treatment of SWD, and one should also be aware of potential side effects such as headaches, vivid dreams, nausea and cardiovascular effects.

Other pharmaceuticals often used for the treatment of sleep disturbance and excessive sleepiness in shift workers includes: hypnotics for sleep and stimulants for maintaining alertness. However, these approaches do not specifically address the issue of circadian misalignment, and thus should be used in concert with behavioral strategies as discussed above. Several studies have used benzodiazepine receptor agonist hypnotics. For example, treatment with temazepam (20 mg) single dose administered at bedtime, increased daytime sleep duration, but did not improve nighttime sleepiness [115], and zopiclone (7.5 mg), taken 30 minutes before bedtime, increased sleep quality in shift workers without negatively impacting night work performance [116].

Stimulants such as caffeine can be used to help manage sleepiness. The combination of napping and caffeine alleviated negative symptoms associated with shift work [117]. Naps of 2-2.5 hours in the evening before the first 2 of 4 consecutive simulated nights in addition to 4 mg/kg (lab study) or 300 mg (field study) caffeine administered 30 minutes prior to each night shift was more effective at improving alertness and performance compared to caffeine or naps alone.

Therapy with wake promoting agents such as modafinil and armodafinil reduced sleepiness associated with night shift work. Administration of 200 mg of modafinil before commencing a simulated night shift was shown to increase alertness, and maintain levels of vigilance and cognitive function, without disruptions to daytime sleep compared with placebo [118] and in a multicenter field study modafinil (200 mg) reduced sleepiness and increased alertness in patients with SWD [119]. Recent studies with armodafinil (an isomer of modafinil) 150 mg before the night shift reduced sleepiness into the morning, improved cognitive performance at night, and diminished severity of SWD symptoms [120]. Both modafinil and armodafinil have been approved by the FDA for the treatment of excessive sleepiness associated with SWD.

A combination of optimizing the sleep environment, planned naps, timed bright light exposure at work, avoiding bright light exposure in the early morning (for night shift workers) and melatonin prior to bedtime can both facilitate circadian adaptation and improve symptoms of SWSD. However, when excessive sleepiness persists, the use of wake promoting agents, such as modafinil or armodafinil is indicated. Based on the evidence, practice parameters set forth by the AASM indicate planned napping before or during a work shift, timed light exposure, and stimulants such as caffeine of modafinil during the night shift to improve alertness [10].

Summary and Future Directions

The impact of circadian rhythm sleep disorders is likely greater than estimated in terms of limited recognition, misdiagnoses and health consequences. This may in part be due to a combination of a lack of practical tools to measure circadian rhythms and that most therapies, including light and melatonin have not been rigorously tested in multicenter randomized clinical trials. Therefore, with the exception of modafinil and armodafinil for the treatment of excessive sleepiness associated with shift work disorder, there are no other FDA approved therapies for the treatment of CRSDs.

Of the pharmacological approaches, melatonin has shown the most success for improving the alignment or amplitude of circadian rhythms, including the sleep-wake cycle, especially in patients with DSPD, FRD, children with ISWR and jet lag disorder. In addition, hypnotic and wake promoting agents have been used for the symptomatic management of insomnia symptoms and excessive sleepiness associated with various CRSDs, particularly SWD and jet lag. Despite its potential, the pharmacotherapy of CRSD using melatonin has been limited by the inconsistent dose, timing of administration and differences in formulations used in the various studies. There is also limited data of its effectiveness and long-term safety from randomized large scale clinical trials.

New formulations, including sustained release and transdermal delivery, have shown clinical potential. Furthermore, recent data demonstrating the ability of selective melatonin receptor agonists such as ramelteon, tasimelteon and agomelatine to induce phase shifts of the circadian clock has prompted investigation of their usefulness in the treatment of several CRSDs. Clearly there is a need for clinically definitive randomized clinical trials in patient populations with CRSDs to determine the efficacy and safety of behavioral and pharmacological therapies, either alone or in combination.

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Figure 1.
Schematic illustration of the human phase response curve (PRC) to melatonin and light. The black circles along the PRC indicate exposure to stimuli (e.g. light or melatonin). The position during which the stimulus occurs indicates whether the effect would result in a phase delay or advance of the circadian rhythm. Melatonin administration in the evening induces a phase advance, whereas given in the morning causes a phase delay. Morning light exposure results in a phase advance, while light exposure in the evening elicits a phase delay.

Table 1

Circadian Rhythm Sleep Disorders-Essential Features, Diagnostic Assessment and Treatment [10,18]

Type	Essential Features	Diagnostic Assessment	Treatment
Delayed Sleep Phase Disorder	-Delayed sleep onset and wake times in relation to desired sleep schedule -Inability to sleep at conventional sleep times -Most common onset in childhood or adolescence	-Sleep log and/or actigraphy monitoring for a minimum of 7 days	-Melatonin administration before desired bedtime -Timed bright light exposure in the morning -Chronotherapy
Advanced Sleep Phase Disorder	-Advanced sleep onset and wake times in relation to desired sleep schedule -Inability to sleep at conventional sleep times -Rare occurrence, typically in elderly	-Sleep log and/or actigraphy monitoring for a minimum of 7 days	-Timed bright light exposure in the evening -Prescribed sleep schedule -Appropriately timed melatonin administration*
Free-Running Disorder	-Sleep onset and wake times are progressively delayed 1-2 hours each day -Complaints of insomnia or excessive sleepiness -More common in blind, rare in sighted individuals	-Sleep diary and/or actigraphy monitoring for a minimum of 7 days; longer monitoring is best to document drift in sleep pattern -Circadian phase markers are also an option for confirming diagnosis	-Timed bright light exposure in the morning, prescribed sleep schedule (sighted only) -Melatonin administration several hours before desired bedtime
Irregular Sleep-Wake Rhythm	-Complaints of insomnia and/or excessive sleepiness -Multiple sleep bouts within 24-hour period -Common in individuals with neurological impairment	-Sleep diary and/or actigraphy monitoring for a minimum of 7 days -At least 3 sleep episodes during 24-hour period -Total sleep time in 24-hour period is normal for age	-Timed daytime bright light exposure -Melatonin administered before desired bedtime (in populations other than elderly demented patients) -Multimodal approach combining bright light exposure, physical activity and behavior modification
Jet Lag Disorder	-Complaints of insomnia and daytime impairment and sleepiness associated with travel across time zones -Symptoms occur 1-2 days after travel across at least 2 time zones	-Diagnostic assessment usually not indicated	-Keep home-based sleep schedule for short trips -Melatonin or hypnotic administered before desired bedtime -Timed bright light exposure -Caffeine
Shift Work Disorder	-Complaints of insomnia or excessive sleepiness associated with work schedule that overlaps usual sleep period -Symptoms occur with shift work schedule occurring at least 1 month	-Sleep diary and/or actigraphy monitoring for a minimum of 7 days	-Planned napping before shift, minimize morning light exposure -Caffeine or modafinil during night shift -Melatonin or hypnotic administered before daytime sleep -Timed bright light during shift

* Theoretical rationale, no reported clinical evidence to support this treatment