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Circadian Rhythm Sleep Disorders

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Abstract

Objective—To review circadian rhythm sleep disorders, including underlying causes, diagnostic considerations, and typical treatments.

Methods—Literature review and discussion of specific cases.

Results—Survey studies [1,2] suggest that up to 3% of the adult population suffers from a circadian rhythm sleep disorder (CRSD). However, these sleep disorders are often confused with insomnia, and an estimated 10% of adult and 16% of adolescent sleep disorders patients may have a CRSD [3-6]. While some CRSD (such as jet lag) can be self-limiting, others when untreated can lead to adverse medical, psychological, and social consequences. The International Classification of Sleep Disorders classifies CRSD as dyssomnias, with six subtypes: Advanced Sleep Phase Type, Delayed Sleep Phase Type, Irregular Sleep Wake Type, Free Running Type, Jet Lag Type, and Shift Work Type. The primary clinical characteristic of all CRSD is an inability to fall asleep and wake at the desired time. It is believed that CRSD arise from a problem with the internal biological clock (circadian timing system) and/or misalignment between the circadian timing system and the external 24-hour environment. This misalignment can be the result of biological and/or behavioral factors. CRSD can be confused with other sleep or medical disorders.

Conclusions—Circadian rhythm sleep disorders are a distinct class of sleep disorders characterized by a mismatch between the desired timing of sleep and the ability to fall asleep and remain asleep. If untreated, CRSD can lead to insomnia and excessive daytime sleepiness, with negative medical, psychological, and social consequences. It is important for physicians to recognize potential circadian rhythm sleep disorders so that appropriate diagnosis, treatment, and referral can be made.

Introduction

Humans, like most other organisms, have near-24-hour rhythms in many aspects of physiology and behavior, including the daily cycle of sleep and wakefulness. These circadian rhythms are not a simple response to environmental changes associated with day

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and night, but are intrinsic to the organism. While there are circadian rhythms present in individual cells, overall coordination of the circadian system is driven by the suprachiasmatic nuclei in the hypothalamus [7-13].

As the term “circadian” implies (circa=approximately, dies=day), these rhythms are near 24 hours in length, but in most individuals the circadian period (cycle length) is not exactly 24 hours. In specialized laboratory studies designed to measure circadian period in humans, the range is reported to be from about 23.5 to 24.5 hours in sighted individuals [14-20]. These near-24-hour rhythms are entrained (synchronized) to the 24-hour day by regular exposure to light during the daytime and darkness at night. This is achieved because the circadian timing system responds to light in a phase-dependent manner. This means that the same light experienced at one time of day does not have the same effect on the circadian system as the exact same light (intensity, duration, wavelength) experienced at a different time of day. Light exposure in the late biological night and early biological morning (the hours surrounding typical wake time for the individual) produces phase advance shifts (shifts of the circadian system to an earlier hour), light exposure in the middle of the biological day produces no or very small phase shifts, and light exposure in the late biological evening and early biological night (the hours surrounding typical bed time for the individual) produces phase delay shifts (shifts in the timing of rhythms to a later hour) [21-26]. When stably entrained, the individual's underlying circadian rhythm in light sensitivity will be aligned such that it produces a daily phase shift to light exposure that equals the difference in period between the individual's circadian period and 24 hours. Therefore, an individual with a 24.2-hour circadian period will be aligned such that they achieve an average daily phase advance shift of 0.2 hours from light exposure in the morning, allowing them to remain stably entrained [15].

One of the many daily rhythms generated by the circadian timing system includes a rhythm in sleep-wake propensity [27-30]. This rhythm is timed such that the greatest drive for wakefulness occurs just before usual bedtime, and the greatest drive for sleep occurs in the latter part of the night, around the time of usual awakening [29, 30]. This circadian rhythm in sleep-wake propensity interacts with a sleep-wake homeostatic process, a process that reflects recent sleep-wake history and produces greater sleep drive with longer wake durations [31]. When these two sleep regulatory systems are in balance, they allow for a consolidated sleep episode at night and a long and consolidated wake episode during the day, something routinely experienced by adult humans but rare in most other species [32]. However, alterations to either one of these processes, or to the interaction between them, can result in a sleep disorder.

The circadian rhythm sleep disorders (CRSD) arise when the desired timing of sleep does not match the underlying circadian rhythm in sleep propensity. Thus, the individual is attempting to sleep when sleep is difficult or impossible, resulting in a persistent or recurrent pattern of sleep disturbance [33]. The underlying cause of this mis-match may be due to biological or behavioral reasons. For example, some feature of the circadian system itself may predispose the individual to a circadian rhythm sleep disorder. A circadian period that is much shorter or longer than usual is one example where a biological cause can lead to a circadian rhythm disorder. In such cases, the period difference between the underlying

circadian system and the 24-hour world in which the patient lives may be so large that it is difficult to achieve the daily circadian phase resetting required to remain synchronized. An altered circadian response to entraining signals from the environment (such as light) that normally synchronizes the circadian system to the 24-hour solar day may also lead to a circadian rhythm disorder. For example, a reduced responsiveness to light may produce daily phase resetting that is of insufficient magnitude to allow for stable entrainment [34-37].

Because many behaviors can influence the circadian timing system, they can contribute to mis-matches between sleep timing and the rhythm in sleep propensity. The most likely of these behaviors to have a strong impact on the circadian system is the exposure to light and darkness. As noted above, the timing of light exposure is critical to the impact of that light on the circadian system, and the overall pattern of daily exposure to light and darkness (including the intensity and wavelength of light exposure) can determine whether stable entrainment is achieved, or instead whether the light-dark exposure works against stable entrainment and contributes to difficulty sleeping when desired. For example, most individuals have a circadian period longer than 24 hours, and require morning light exposure to achieve a daily phase advance shift in order to remain entrained to the 24-hour day [15]. If sufficient (in terms of intensity and/or duration) morning or daytime light exposure is not obtained on a regular basis, the circadian system may begin to drift out of synch with clock time, leading to a circadian rhythm disorder [38, 39]. Similarly, excessive evening light exposure on a regular basis may cause shifts of the circadian system to a later time, and these shifts may then not be counteracted with sufficient shifts to an earlier hour from morning light exposure, leading the circadian system to become out of synch with clock time [40-43].

Issues related to poor sleep hygiene can also contribute to the development of a CRSD. For example, an irregular sleep-wake schedule (bedtimes and wake times varying by hours from one day to another) typically is also associated with irregular light-dark exposure. Without regular light exposure to entrain the circadian system, a circadian rhythm sleep disorder may develop. Individuals with flexible schedules who have an opportunity to nap during the day and opportunities to “sleep in” may also be prone to developing CRSD, due to their greater opportunity to pursue poor sleep hygiene practices.

Circadian rhythm sleep disorders can also arise when the circadian system has a normal period and entrainment response, but the individual abruptly changes their sleep timing. This occurs in shift workers when they change shift timing (and therefore must also change their sleep timing), and also occurs when an individual travels rapidly across multiple time zones. In both cases, the circadian timing system cannot adapt quickly to the new schedule, resulting in a CRSD that may be transient or persistent.

Circadian Rhythm Sleep Disorder Types

The International Classification of Sleep Disorders (ICSD-2) suggests classification of CRSD into six distinct types (see Table 1). These include: 1) delayed sleep phase type, 2) advanced sleep phase type, 3) irregular sleep wake phase type, 4) free-running type, 5) jet lag type, and 6) shift work type.[33] The term, ‘type’ in this classification is used

interchangeably with the earlier terms ‘syndrome’ or ‘disorder’. A brief description of each of these six types follows.

Individuals with Delayed Sleep Phase Type [or delayed sleep phase syndrome, herein called DSPS] are characterized by sleep onset and offset several hours later than desired and also later compared to normal individuals. Individuals with DSPS have a very prolonged sleep latency when they attempt to fall asleep at a conventional time, and similarly have great difficulty to arise when they try to get up at a conventional time. When allowed to sleep unconstrained by social requirements, they show normal sleep architecture and sleep duration. DSPS is the most frequent type of CRSD seen by the clinician, and often first occurs in adolescence or young adulthood [44]. Individuals with DSPS often have difficulty with school or employment, because they have difficulty falling asleep at an early enough time to be able to obtain sufficient sleep. These individuals often remain awake until very late at night, and consequently have difficulty waking up in the morning. This leads to tardiness and/or to poor performance and even falling asleep at work or school due to daytime sleepiness. In some cases, patients whose DSPS remains untreated or fails to respond to treatment may develop other psychological disorders [45].

Advanced Sleep Phase Type (ASPS) individuals experience problems opposite to those of DSPS individuals. They have regular sleep-wake patterns but with much earlier than desired (or conventional) sleep onset and offset times, but with normal sleep durations. These individuals typically do not have the same occupational consequences that DSPS patients do, and thus are less likely to be seen by physicians. In extreme cases, patients with ASPS may seek help when they have difficulty remaining awake in the evening for social events or to spend time with family. ASPS is more likely to be observed in the elderly than in young adults [3, 46].

The CRSD Irregular Sleep Wake Phase Type is characterized by a normal 24-hour sleep duration, but disruption and fragmentation of the sleep-wake cycle. These individuals suffer from disorganized and fragmented sleep. This type is most frequently seen in institutionalized patients, who may spend many hours per day in bed and who are not exposed to a strong light-dark cycle.

Free-Running Type, also known as non-24-hour sleep-wake syndrome, hypernychthemeral syndrome, or non-entrained type, is characterized by a gradual delay of sleep onset time from one day to the next, so that sleep begins to occur during the daytime hours and then eventually drifts back into the night (and around to the day again). Patients with DSPS may transition to this type if untreated. In rarer cases, the sleep onset time moves earlier from one day to the next (an extension of ASPS rather than DSPS). By definition, patients with Free-Running Type have experienced a failure or lack of ability of their circadian system to be entrained to the 24-hour day. This syndrome occurs in many totally blind people whose neural light entrainment structures are damaged [34, 47], but occurs in sighted individuals as well.

Individuals who cross multiple time-zones may experience Jet Lag Type, which occurs because the circadian timing system is set to the home time zone and cannot reset to the new

time zone quickly upon arrival. The greater the difference from the home time zone, the more likely there will be jet lag, and the longer it will take to fully adjust. In many cases, jet lag is exacerbated by the effects of sleep loss that often accompany long-distance travel. For most people this is a self-resolving problem. However, for individuals who must travel frequently for work, jet lag can be a more persistent problem. In such cases, the daytime sleepiness, gastrointestinal symptoms, and sleep loss associated with jet lag [48] can lead to short-term (safety issues associated with daytime sleepiness, neurocognitive deficits associated with sleep loss and attempting to be awake at a biologically inappropriate times) [49, 50] problems, and there is even evidence that there are long-term health consequence of repeated jet lag in airline flight crews [51, 52].

Shift work disorder is experienced by many of the estimated 9% of Americans (12.5 million) who work on the night shift or on irregular/rotating shift schedules that include overnight work hours [53-55]. In such cases, the circadian system of the worker does not adjust to the work schedule, leading to drowsiness during night work and difficulty attempting to sleep during the day. Night shift workers have shorter sleep durations on average than day or evening shift workers because they are attempting to sleep at a biologically inappropriate time, and as a consequence are unable to remain asleep. They also typically attempt to sleep following work (as opposed to just before starting work as most day workers do), and thus begin each night of work after insufficient sleep and many hours of wakefulness. Because of this, night work is associated with an increased risk of occupational [56-63] and motor vehicle accidents (especially on the way home from work) [59, 60, 63-72]. Shift work disorder is typically relieved after the patient resumes a day-work, night-sleep schedule, but for patients who work regular night shifts, or who work rotating shifts, the symptoms persist. Shift work disorder can also impact individuals with early shift start times because many such individuals find it difficult to go to bed early enough to obtain sufficient sleep. Chronic shift work increases the risk of myocardial infarction [73], cardiovascular disease [73-77], GI disorders [63, 78, 79], metabolic syndrome [80-87], and cancers [88-96].

If untreated, CRSD can lead to physical, psychological and social stresses. Insufficient sleep, a consequence of many CRSD, is recognized as a contributing factor to a number of heath problems, including obesity, cardiovascular disease [97], altered glucose metabolism [98-102], and immune dysfunction [103-108]. CRSD may also lead to greater accident risk, due to daytime drowsiness and/or attempting to perform at an adverse biological time. Thus, while most of the CRSD do not impact large numbers of patients, they can have long-lasting and serious impacts for the patients who are affected.

Clinical Approach to CRSD

Many patients with sleep problems complain of daytime sleepiness, fatigue, or other symptoms consistent with insomnia. These symptoms are also common in a variety of other medical and psychiatric disorders. Therefore, a systematic approach to determining the cause of the excessive daytime sleepiness or the sleep disruption is needed. Kales et al. suggested six important principles when taking a sleep-wake history: 1) define the specific sleep problem; 2) assess the clinical course; 3) differentiate between various sleep disorders; 4) evaluate sleep/wakefulness patterns; 5) question the bed partner; and 6) evaluate the

impact of the disorder on the patient [109]. These principles apply for all causes of daytime sleepiness or sleep disruption, not only CRSD. In their 2011 review, Salas and Gamaldo [110] summarized a series of key questions to ask of patients when evaluating sleep disorders (see Table 2), and these are useful in evaluation patients for CRSD as well. In fact, it is important to rule out other conditions that can affect the sleep-wake cycle in ways that can mimic CRSDs. Those conditions include poor sleep hygiene, depressive mood, temporary physical or psychological changes, and even medication side effects.

Sleep History Assessment

Because CRSD are defined as a misalignment between the timing of sleep and the timing of circadian rhythms, an evaluation of the patient's sleep-wake pattern across days or weeks (rather than a “snapshot” on a single night) is an important first step in making an accurate diagnosis. Evaluating the sleep-wake pattern can be done using standardized questionnaires that query the patient about habitual time to bed, time to fall asleep (sleep latency), usual waking time, frequency and duration of nighttime awakening, napping (including frequency, duration, and timing), and regularity of sleep and waking time (see below). This retrospective evaluation should then be supplemented with a prospective sleep log (and in some cases actigraphy) to confirm the diagnosis, as recommended by the American Academy of Sleep Medicine [111]. In general, a polysomnogram is not necessary for CRSD diagnosis unless there is a suspicion of another sleep disorder as the cause of sleep disruption and/or daytime sleepiness [111].

In addition to the sleep-wake pattern, information about other factors that may influence sleep is an important part of the sleep history. Co-morbid conditions such as psychiatric disorders can make the diagnostic approach to symptoms of excessive daytime sleepiness or nighttime sleep disruption difficult. Medications for psychiatric diseases often have nighttime sleep or daytime sleepiness side effects. Most tricyclic antidepressants (TCAs), selective serotonin receptor inhibitors (SSRIs), and some monoamine oxidase inhibitors (MAOIs) show sedative side effects [112]. Some studies suggest that there is a higher prevalence of CRSD in patients who have psychiatric problems like schizophrenia, but antipsychotic use in these patients may confound this observation because of the well-known sleep impacts of both first generation and second generation antipsychotics [113, 114].

Medications (not only psychiatric medications) with sleep disrupting and/or daytime drowsiness side effects can alter the sleep-wake homeostatic process, thus leading to problems sleeping at the desired time. Excessive stimulant use (including caffeine) and using stimulants too close to bedtime can make it difficult to fall asleep and delay normal sleep onset. In addition, many individuals with sleep difficulties will use over-the-counter remedies, herbal supplements, or alcohol to help them sleep. Thus, a thorough evaluation of all of the substances the patient is using, with attention to the time of day at which they are used, is important for evaluating the cause of the sleep difficulty and/or daytime sleepiness.

Evaluation of other behaviors that may influence sleep or daytime sleepiness is also a key component of the CRSD diagnostic process. Timing of exercise, typical evening activities, recent travel across time zones, work schedules, etc. should all be included in the patient history.

The impact of the sleep concern on the patient's well-being and daytime functioning is an important part of evaluating the patient for CRSD. There are several standard questionnaires that may be helpful in evaluating these impacts on the patient (see below).

Finally, evaluation of the timing of circadian rhythms in patients with suspected CRSD, while not currently supported by the American Academy of Sleep Medicine for CRSD evaluation other than Free-Running Type [111], can not only help to confirm the diagnosis, it can provide important insight into the underlying mechanism causing the CRSD, and/or can help to optimize treatment timing [115-118].

Questionnaires

There are several questionnaires that can be useful in evaluating patients with possible CRSD. The Morningness-Eveningness Questionnaire (MEQ) [119] is a questionnaire designed by Horne and Östberg to rate an individual's propensity for morning or evening activity. It consists of 19 questions asking the patient about preferred timing of various daily activities, and scores can range from 16-86. The score places the individual into one of five morningness-eveningness categories, “definitely evening type”, “moderately evening type”, “neither type”, “moderately morning type”, and “definitely morning type”. More recently, Roenneberg and colleagues have developed the Munich Chronotype Questionnaire (MCTQ) to assess the individual's relative morningness or eveningness, and actual sleep timing on weekdays and weekends [120]. Mid-sleep time on free days (days without school or work obligations) is considered to represent the individual's relative type. A major difference between the MEQ and the MCTQ is that the MEQ asks about preferred times of daily activities (including sleep and wake), while the MCTQ asks about actual sleep and wake timing.

There are also questionnaires that can be used to determine the degree of sleep problem or complaint experienced by the patient, as well as the degree of waking dysfunction. While these questionnaires have been developed for use in general sleep disorders populations, they may be of use to determine the extent of the problem experienced by the patient, and/or to re-assess the patient after initiating treatment to determine treatment efficacy. The Pittsburgh Sleep Quality Index (PSQI) consists of 19 questions about the patient's sleep over the past month [121]. Four ask for specific information about bedtime, wake time, sleep latency, and sleep duration. The remaining questions ask the patient to rate on a 4-point scale how often they have experienced specific problems with their sleep, taken medications for sleep, experienced daytime sleepiness, etc. Of particular usefulness for evaluating patients with potential CRSD are questions about prolonged sleep latency and waking up too early. Responses are used to calculate seven component scores, and these are tallied for a global score, and the patient can then be placed into a category that indicates the severity of his/her sleep disruption. The Insomnia Severity Index (ISI) is a brief questionnaire containing seven questions. The patient is asked to rate aspects of his/her sleep on 5-point scales, with questions about the severity of sleep problems in the past two weeks and impact on waking functioning and other aspects of their life. Of particular usefulness in evaluating patients with possible CRSD, the initial question focuses on the severity of problems with

falling asleep, staying asleep, or waking too early. The overall ISI score can be used to place the patient into an insomnia severity category.

The Functional Outcomes of Sleep Questionnaire (FOSQ) consists of 35 questions about the difficulty level experienced by the patient when performing various daily activities within four domains of waking function [122]. Each question is rated on a 4-point scale, and there are sub-scale scores (within the four domains of waking function) as well as a global score designed to indicate the impact of excessive sleepiness on activities of daily living. The Epworth Sleepiness Scale (ESS) asks the patient about their likelihood of dozing or falling asleep in eight different situations, with four possible choices ranging from never to a high chance of dozing [123]. A total score is then compiled and the patient placed into a daytime sleepiness category ranging from low, moderate, to high daytime sleepiness.

Treatments for Circadian Rhythm Sleep Disorders

There are several treatment modalities specifically for CRSD that are designed to address the underlying mismatch between the desired timing of sleep and the ability to fall asleep and remain asleep that characterizes CRSD, including chronotherapy, phototherapy, and melatonin administration. In addition to these CRSD-specific treatments, other treatments used for typical sleep initiation or sleep maintenance insomnias such as hypnotic medications or cognitive behavioral therapy (CBT), and treatments for excessive daytime sleepiness such as stimulants, can be used in CRSD. A detailed description of the evidence in support of each of the treatments for each CRSD type, and current practice parameters, is reviewed in a recent American Academy of Sleep Medicine Task Force report [111, 126, 127].

Chronotherapy

Chronotherapy involves modifying the scheduling of sleep to resynchronizing the underlying circadian rhythm so that it is at a normally entrained clock time [128]. Chronotherapy attempts to gradually adjust the timing of the biological clock by delaying (for DSPS) or advancing (for ASPS) sleep and light-dark exposure times. This method works with the patient's underlying tendency for later (or earlier) bedtimes, and avoids abrupt changes in sleep times that can result in sleep deprivation. There are not many large trials of chronotherapy vs. other treatments, and there is one case report of a DSPS patient in whom chronotherapy resulted not in treatment but in Free-Running Disorder [129]. In spite of these limitations, there are numerous small reports of successful chronotherapy, and it is typically well-tolerated by patients [45, 128, 130]. In Free-Running Type and Irregular Sleep-Wake Type, there are few reports of the success of chronotherapy.

Timed Light Exposure (Phototherapy)

As described above, light is the most effective environmental cue for circadian entrainment, and the time of day at which light is received determines the amount and direction of circadian rhythm adjustment in response to that light exposure. Phototherapy takes an advantage of this by timing bright light exposure at strategic times designed to advance (in the case of DSPS) or delay (in the case of ASPS) the circadian system to a time that will allow sleep to occur at the desired time. In DSPS, morning exposure to bright light is used to

advance circadian rhythmicity and sleep time while in ASPS, conversely, evening exposure to bright light is used to delay circadian rhythmicity and sleep time. Typically, a commercially-available light box is used to deliver the light, which is brighter than standard indoor light sources (typically up to 2,500 lux). The patient is instructed to sit in front of the light box for 1 hour or more each morning (for DSPS) after arising at their desired wake time (or in evening prior to their desired bed time for ASPS). Studies of both sleep timing and the timing of biological rhythms have demonstrated that phototherapy can be effective for both DSPS and ASPS [111, 131-135]. There are also case reports showing that morning phototherapy can produce successful entrainment in patients with Free-Running Type [136-138]. Unfortunately, compliance is an issue with phototherapy for many patients. The initial beneficial effects can take several days to occur during which time the patient often experiences sleep deprivation, and maintenance therapy is typically required once the desired sleep timing is achieved.

Enhancing the overall light-dark cycle (by limiting exposure to light at night and by enhancing the brightness of light exposure during the day) has been shown to improve the sleep-wake fragmentation of older institutionalized patients with Irregular Sleep-Wake Type [139]. Phototherapy has also been demonstrated to be beneficial as a pre-treatment for jet lag, although it may not be practical for the occasional traveler. There is evidence that phototherapy can aid in the adjustment of shift workers to night shifts or to a change in work schedule, although in such cases the phototherapy is typically delivered during the work hours and thus may not be practical in all work settings [111, 140-149]. In addition, the adjustment process takes several days, and thus for workers who rotate shifts on a weekly basis phototherapy alone will be insufficient to alleviate their shift work disorder. In the case of permanent night workers, they often adapt a night-sleep, day-wake schedule on weekends or days off for family and social reasons, and thus most never full adapt to the night work schedule [150, 151], and may not even wish to be fully adjusted to their night work schedule. For these reasons, partial adjustment via a “compromise” phase position has been advocated, as it improves sleep and on-shift alertness during night work but allows adoption of a more conventional schedule on days off [152-155]. Alternatives to bright light boxes to achieve the goals of phototherapy for shift workers, including reducing light exposure in the morning using dark glasses, increasing light exposure in the afternoon or evening at home using natural or artificial light, and combinations of these, have also been tested.

Timed Melatonin Administration

The hormone melatonin is produced by the pineal gland at night, and its secretion is closely regulated by the circadian timing system. Exogenous melatonin has been shown to have both soporific (especially when administered during the biological daytime when endogenous melatonin is not present) and chronobiotic effects [156-162]. Melatonin administration in the evening has been shown to benefit patients with DSPS by producing advances of circadian rhythms and sleep timing [161, 163-166]. Doses of 0.5-5 mg are administered in the late afternoon or evening (1-6 hours before desired bedtime) for days or weeks, but the optimal dose and administration schedule have not been standardized [111]. There are also case reports that melatonin can be used to entrain sighted patients with Free-Running Type [136, 167 ,168], and melatonin has been used to successfully treat free-running

blind patients [169-173]. There is also evidence for melatonin's use in Jet Lag Type [111, 174-178], although not all studies have found that melatonin improves Jet Lag compared with placebo. This is likely due to the phase-dependent effects of melatonin, and if administered at the incorrect time melatonin may be ineffective or even produce the opposite effect to the desired one [162 ,179, 180]. Melatonin has also been used to treat patients with Shift Work Type, often in combination with phototherapy [141, 142, 177, 181].

Summary and Case Reports

In this brief review, the CRSD, which result from a mismatch between the desired timing of sleep and the circadian rhythm in sleep-wake propensity, are described. The features of the major CRSD, a diagnostic approach for evaluating patients suspected of having a CRSD, and typical treatments for CRSD are outlined. While most CRSD affect very few individuals, as alluded to above it can be difficult to differentiate between a primary CRSD and other sleep-related disorders. Furthermore, poor sleep hygiene can perpetuate or exacerbate a CRSD and make it challenging to treat. While there are several treatments for CRSD, optimal timing of the treatment with respect to the patient's underlying circadian rhythm is critical to a successful outcome, and can present the clinician with significant challenges.

To illustrate the approach to evaluating patients with possible CRSD, we close with presentation of two cases.

Case 1. A 24-year-old man with difficulty initiating sleep

Initial Presentation and Evaluation—Chief complaints: Sleep initiation difficulty, drowsiness in the morning, daytime fatigue. His Epworth Sleepiness Scale score was 10, indicating a moderate level of daytime sleepiness.

1) Sleep /Social History: The patient's usual time into bed is 1:00 am, with a sleep latency of 1 to 2 hours. His usual wake up time is 10 am.

The patient used to have a late sleep and wake typical of DSPS. This was not associated with sleep initiation difficulty (as long as he did not attempt to go to bed early), and he did not experience daytime fatigue. Several months ago, he began trying to wake up much earlier than his habitual wake time (around 5:00 am) in order to go to church, and had been afraid of waking up late. This led to increasing anxiety, and he began to have difficulty falling asleep and staying asleep.

Three years ago, he had depressive symptoms, which made him unable to go to school sometimes. However, he reports not having treatment for the depressive symptoms, which gradually improved after about one year.

2) Medications: None.

3) Other Medical, Psychiatric Conditions: None. No current depressive symptoms. The patient was given the Beck Depression Inventory, and his score was 8.

4) Initial Testing: The patient was asked to keep a sleep diary, which confirmed his late sleep and wake times. The patient was then evaluated with PSG and an evening salivary melatonin profile. His dim light melatonin onset occurred at 00:04 am, significantly later than normal. His night of PSG began at 02:30 am and showed a sleep latency of 8.1 minutes, a lower than usual amount of REM sleep (11%), some snoring but no evidence for sleep apnea (AHI 0), and a final wake time of 08:34 am, but was otherwise not remarkable.

5) Initial Diagnosis and Treatment Plan: The patient met all the clinical requirements to diagnose DSPS by ICSD-2 criteria: A). a delay of the major sleep episode relative to the desired sleep and wake time, as evidenced by a chronic or recurrent complaint of inability to fall asleep at a desired conventional clock time together with the inability to awaken at a desired and socially acceptable time; B). when allowed to choose their preferred schedule, patients will exhibit normal sleep quality and duration for age and maintain a delayed but stable phase of entrainment to the 24-hour sleep-wake pattern; C). sleep- log or actigraphy monitoring (including sleep diary) for at least seven days demonstrates a stable delay in the timing of the habitual sleep period. A delay in the timing of other circadian rhythms, such as the nadir of the core body temperature rhythm or DLMO, is useful for confirmation of the delayed phase. D). The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder. However, in addition to (and because of) the DSPS, the patient had developed anxiety about his ability to fall sleep, obtain sufficient sleep, and wake at the desired time, and so a treatment plan that addressed both issues was indicated.

Morning light therapy was initiated to address his DSPS. The patient was given a light therapy box and instructed to begin a 1-hour light exposure each morning at 08:30 am, and was asked to maintain a daily sleep log. Cognitive behavioral therapy (CBT) for the patient's sleep-related anxiety was also initiated. This included group therapy sessions and sleep restriction.

6) Follow-Up: The patient visited the clinic on a weekly basis to monitor his progress. His sleep logs showed sleep between 02:00 and 09:30 am. The patient attended five group therapy sessions as part of his CBT. His sleep quality improved and his sleep latency became shorter after sleep restriction. His sleep-related anxiety also diminished. At a 7-week follow up visit, his sleep latency was reduced to 30 minutes or less, and his usual wake up time was 7:50 am.

Case 2. A 67-year-old woman with a complaint of early awakening, early sleep onset, and excessive daytime sleepiness

Initial Presentation and Evaluation—Chief complaints: Sleep maintenance difficulty, daytime fatigue.

1) Sleep /Social History: The patient is a 67-year old woman. She reports going to bed and waking earlier than desired on a daily basis for at least the past year. This has caused her to have extreme daytime sleepiness, requiring her to nap each day. She states that “often feel as if I have not had enough sleep”.

The patient reports going to bed around 9 or 10 pm and waking around 4:30 am. This is about 1.5 hours earlier than her desired wake time of 6 am. She reports a sleep latency of 5-20 minutes, and waking once every night to void. Approximately once per week, she wakes around 2 am, thinks about work, gets up to do work until she is sleepy again (usually after about two hours), and then returns to sleep for a few hours, sometimes sleeping as late as 9 am. Her Pittsburgh Sleep Quality Index score is 11, indicating moderate sleep difficulty.

She reports feeling so sleepy during the daytime that she takes an afternoon nap each day, with the nap lasting from 15 minutes to 2 hours. Her Epworth Sleepiness Scale score is 18, indicating severe daytime sleepiness.

The patient reports not snoring, and her BMI is 21.9. Her normal BMI and report of not snoring make it less likely that a cause of her nighttime awakenings and extreme daytime sleepiness is sleep apnea, even though her age and post-menopausal status make her more likely than a younger woman to suffer from this common sleep disorder [182]. However, from the information we have sleep apnea cannot be ruled out as a possible cause of her sleep disruption and excessive daytime sleepiness, given that even normal weight patients and those who do not report snoring may have sleep disordered breathing [183, 184]. She does not report symptoms of Restless Legs Syndrome, and does not report limb movements during the night. Thus, Periodic Limb Movement Disorder or other sleep-related movement disorders are an unlikely cause of her daytime sleepiness. She has not traveled across time zones for more than a year, and does not have a history of night or rotating shift work, both of which could cause a circadian rhythm sleep disorder. She reports drinking 1 cup of decaffeinated coffee daily, an occasional cup of tea, but otherwise no drinks or foods that contain caffeine. She is a non-smoker and drinks 3-4 glasses of wine per week. Her modest use of caffeine, nicotine, and alcohol are unlikely to be the source of her sleep difficulty.

2) Medications: Amlodipine (a calcium channel blocker; 2.5mg daily at bedtime) for the past six months. Alendronate (a bisphosphonate; 70mg weekly) for the past three months. Transdermal estradiol about two times per week for the past four years. A multivitamin, evening primrose, a bone formula supplement, and 2,000mg of vitamin D each day. Ibuprofen or aspirin occasionally for pain. She denies taking any other supplements or medications. Evaluation of the reported side effects of her medications on sleep or daytime sleepiness reveals only that her calcium channel blocker lists drowsiness and tired feeling as a side effect. However, the patient takes this medication at bedtime, so it this and her other medications are unlikely to be the cause of her sleep disruption or daytime sleepiness.

3) Other Medical, Psychiatric Conditions: She reports no history of depression or other psychiatric disorder, and her score on the Beck Depression Inventory was 2, a normal (non-depressed) score. She has well-controlled hypertension [BP 115/73].

The patient had arthroscopic knee surgery five years ago, but reports no ongoing pain associated with this that might disrupt her sleep. She suffered a concussion without loss of consciousness six months ago. She reports that her sleep did not change after the concussion.

4) Initial Impression and Testing: The patient does meet some of the diagnostic criteria for ASPS as outlined in the ICSD-2. These include an advance in the timing of the major sleep period related to desired sleep timing. However, the patient's reported sleep patterns (middle-of-the-night waking on some nights and then return to sleep; wake times varying by several hours; daytime napping of varying durations) make it difficult to evaluate whether the patient's sleep hygiene behaviors may be contributing to subsequent sleep disruption. The patient's history of concussion may be important, but she reports that the sleep problem began before and did not change as a result of the concussion.

The patient was asked to maintain a sleep-wake log for 1-2 weeks, and to document the use and timing of medications, caffeinated drinks, and alcohol, as well as the timing and duration of naps.

5) Initial Follow-up: The patient maintained a detailed sleep log for nine days. During that time, her time into bed varied by nearly two hours (from 9:01 to 10:56 pm), and her final wake time varied by more than an hour (from 4:22 to 5:38 am). Her self-reported sleep latencies were quite short, being less than five minutes on all but one of the nights (when it was 15 minutes). On six of the nights, she woke one or two times during the night, and on five of the nights it was for less than five minutes each time, which is not unusual for someone of her age and is unlikely to be the cause of her daytime sleepiness. On one of the nights she was awake for 30 minutes during the night. Considering her reported bed and wake times, sleep latencies, and nighttime awakenings, her sleep durations ranged from 4.67 to 8.25 hours, and were longer than seven hours on seven of the nine nights. She reported napping on only one of the days, but that nap was four hours long. The day with the long nap preceded the night with the shortest sleep duration.

6) Diagnosis and Treatment Plan: Similar to clinical requirements to diagnose DSPS above, the ICSD-2 criteria for ASPS are: A). an advance of the major sleep episode relative to the desired sleep and wake time, as evidenced by a chronic or recurrent complaint of inability to stay awake until the desired conventional clock time together with the inability to remain asleep until a desired and socially acceptable time; B). when allowed to choose their preferred schedule, patients will exhibit normal sleep quality and duration for age and maintain an advanced but stable phase of entrainment to the 24-hour sleep-wake pattern; C). sleep- log or actigraphy monitoring (including sleep diary) for at least seven days demonstrates a stable advance in the timing of the habitual sleep period. An advance in the timing of other circadian rhythms, such as the nadir of the core body temperature rhythm or DLMO, is useful for confirmation of the advanced phase. D). The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

While the patient meets ASPS criteria A-C, her poor sleep hygiene (very irregular sleep times from night-to-night and daytime napping) is likely contributing to her ongoing sleep difficulty at night, and when this leads her to nights of very short sleep, it may in turn lead to her daytime sleepiness. Thus, a treatment plan to address both her ASPS and her sleep hygiene was indicated.

The patient was counseled about her sleep hygiene, with particular attention to the duration of daytime naps (keeping them to less than 30 minutes), more consistent bedtimes and wake times (getting in to bed and arising at nearly the same time each day, regardless of her sleep quality), and remaining in bed in darkness attempting to return to sleep when she wakes in the middle of the night rather than getting up to do work. In addition, the patient was started on a regimen of evening phototherapy. She was given a light box and instructed to use it for 1-2 hours each evening beginning at 8:00 pm, and was asked to keep a sleep log.

6) Follow-Up: The patient visited the clinic four weeks later to monitor her progress. Her sleep logs showed sleep between 9:30-10:00 pm and rise time on most mornings between 05:00 and 06:00 am. She still felt the need to have daytime naps, but on most days these were limited to less than half an hour. If her daytime sleepiness persists, further follow-up may include an at-home or laboratory sleep evaluation to rule out sleep apnea or periodic limb movements.

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Table 1

International Classification of Sleep Disorders categories of Circadian Rhythm Sleep Disorders with typical clinical features.

Disorder	Clinical features
Delayed sleep phase type	Sleep and wake times are delayed (later) compared to normal individuals and desired times, with striking inability to fall asleep and wake earlier at the desired time
Advanced sleep phase type	Sleep and wake times advanced (earlier) compared to normal individuals and desired times, with striking inability to remain awake and remain asleep until the desired time
Irregular sleep-wake type	Unrecognizable pattern and disorganized sleep and wake times, with insomnia and/or excessive daytime sleepiness
Free running type	Gradually delayed bedtime by 1-2 hours a day with insomnia and inability to wake in the morning
Jet lag type	Inability to fall asleep and wake at times compatible with desired times due to recent travel to new time zone.
Shift work type	Inability to fall sleep (during the day) and remain awake (at night) at times required for work schedule.

Table 2

Components of a sleep history.

1. Define the specific sleep problem
What is the primary complaint?
2. Assess the clinical course
When did the sleep problem begin?
3. Examine recent factors/changes that can affect sleep
Recent medical, psychiatric, and surgical history, recent changes in medications?
*Recent travel history (crossing time-zones), changes in work hours?
4. Evaluate sleep/wakefulness patterns
*When does the patient get into bed, how long does it take them to fall asleep?
*What is the final rising time?
How many times during the night does the patient awaken, for what reasons (to void, environmental, unknown), how long does it take them to fall back asleep?
*Regularity of bedtimes and wake times (including work days vs. days off)?
5. Evaluate sleep hygiene
What is the sleep environment (noise, light, bed partner)?
What is the pre-bedtime routine (including medications)?
What are the current medications that could impact sleep or daytime sleepiness (including caffeine, alcohol, sedatives)
6. Obtain information from the patient or bed partner about signs associated with specific sleep disorders
Is there snoring, gasping, morning headache, limb movements?
7. Evaluate the impact of the disorder on the patient
What is the patient's daytime functioning (daytime sleepiness, napping, job performance)?

*Key questions for CRSD diagnosis.

Table 3
Questionnaires that can be useful in evaluating patients with possible sleep disorders

Questionnaire	Measurement
Morningness-Eveningness Questionnaire [119] and/or Munich Chronotype Questionnaire [120]	The typical or desired timing for activity and sleep across the 24-hour day
Pittsburgh Sleep Quality Index [121]	Quality, timing, duration and disturbance of sleep in the past month
Beck Depression Inventory [124]	Determine co morbid depressive mood disorder
Epworth Sleepiness Scale[123]	Excessive daytime sleepiness
Insomnia Severity Index [125]	Type, severity, and functional consequences of insomnia
Functional Outcomes of Sleep Questionnaire[122]	Difficulty performing daily activity due to sleepiness