Humans, like many other mammals, are awake through the daytime hours and sleep during the night. In some people, this normal sleep-wake rhythm, so taken for granted by most of us, can become chronically impaired, leading to a group of disorders called circadian rhythm sleep disorders (CRSDs). CRSDs are characterized by a misalignment between the timing of the individual’s sleep-wake rhythm and the 24-h social and physical environment. In patients with CRSDs, sleep episodes occur at inappropriate times, often causing waking periods to occur at undesired times. Consequently, the patient complains of insomnia or excessive daytime sleepiness and impairment in various areas of functioning.

The second edition of the International Classification of Sleep Disorders (ICSD-2) divides disorders of sleep-wake schedule into three major categories: CRSDs of primary origin, behaviorally induced CRSDs, and CRSDs due to a substance. Behaviorally induced CRSDs can emerge as a consequence of the individual’s voluntary choice to create a temporal mismatch between his or her sleep-wake cycle and environmental conditions, as happens in shift work and jet lag. This review will focus on primary CRSDs and behavioral and psychiatric consequences of these disorders. Alterations of the sleep-wake schedule following treatment with psychoactive medications will also be described in some detail.

Four types of primary CRSD are listed in the ICSD-2:

- Delayed sleep phase type, also known as delayed sleep phase syndrome (DSPS), which is characterized by habitual sleep-wake times that are delayed usually more than 2 h relative to conventional or socially acceptable times (Figure 1A). When forced to follow an environmentally imposed schedule, these patients...
will complain of difficulties falling asleep and waking up in the morning, and feel sleepy during the day.

- **Advanced sleep phase type**, also known as **advanced sleep phase syndrome (ASPS)**, which is characterized by habitual sleep onset and wake-up times that are several hours earlier than desired or socially accepted (Figure 1B). This pattern results in symptoms of compelling evening sleepiness, early sleep onset, and awakening that is earlier than desired.

- **Free-running type**, also known as nonentrained type or non–24-h sleep-wake syndrome, can be described by a sleep-wake cycle that is usually longer than the 24-h period. Sleep and wake episodes are delayed each day to later hours, thus alternating between synchrony and complete asynchrony with the environmental schedule (Figure 1C).

- **Irregular sleep-wake type**, also known as irregular or disorganized sleep-wake pattern, is characterized by lack of clearly defined circadian sleep-wake rhythm. Sleep and wake episodes are temporally disorganized and variable throughout the 24-h period (Figure 1D). These patients are likely to manifest inability to initiate and maintain sleep at night, frequent daytime napping, and excessive daytime sleepiness.¹

In a study of clinical characteristics of patients with CRSDs in Israel,² the vast majority of patients received the diagnosis of DSPS (83.5%), 12.3% had non–24-h sleep-wake syndrome, while only a handful of patients suffered from an irregular sleep-wake pattern (1.9%) or ASPS (1.3%). A similar distribution of frequencies was reported in a sleep clinic in Japan.³ Limited data are available regarding the prevalence of CRSDs in the general population. It appears that DSPS is more common among adolescents living in Western countries (7.3%)¹ than among adults, where the estimated prevalence ranges from 0.13% in Japan¹ to 0.17% in Norway.⁴ ASPS was estimated to occur in 1% of middle-aged and older adults.⁵ The prevalence of non–24-h sleep-wake syndrome and irregular sleep-wake pattern in the general population is unknown. The majority of patients with CRSDs (89.6%) report that the disorder typically begins in early childhood or adolescence.⁶ There are no known gender differences.

### Pathophysiology

It is currently believed that CRSDs result from an abnormality of circadian timing system, which regulates the diurnal rhythms of an organism. The core component of this system is the suprachiasmatic nucleus (SCN) of the hypothalamus. This internal biological clock has self-generated, endogenous near-circadian rhythmicity, which it conveys through direct and indirect pathways to a widely spread network of subcortical and cortical sites. Thus, many physiological functions, such as hormonal secretion and body temperature, as well as cognitive performance and emotional state, fluctuate according to the time of day.⁶⁻¹¹

Regulation of the circadian rhythm of sleep-wake cycle involves secretion of the hormone melatonin by the pineal gland, one of the central target sites of the SCN.¹² The endogenous biological clock is synchronized or entrained with the environment through time cues, such as light.¹³

What abnormality in the complex mechanisms of the circadian timing system gives rise to CRSDs is still a matter of debate. Among the four disorders of the sleep-wake schedule, DSPS has been the subject of most scientific research. In addition to sleep, circadian rhythms of melatonin and core body temperature¹⁴,¹⁵ were observed to be delayed in this disorder. Further, the phase angle between sleep timing, core body temperature rhythm, and melatonin rhythm was noted to be altered in patients with DSPS.¹⁴⁻¹⁶ Whereas exposure to bright light at night acutely reduces melatonin concentration in subjects with typical sleep-wake rhythm, this effect is even greater in patients with DSPS.¹⁷ Several hypotheses have been proposed to explain how these characteristics produce DSPS, none of which has yet been confirmed or refuted. Some findings demonstrate that a genetic origin might be present in CRSDs. In as many as 44% of patients with CRSDs, there is evidence that other family members have similar sleep-wake patterns as the patient.² In the pedigree of one family with DSPS, the trait was found to segregate with either an autosomal dominant mode of heritance with incomplete penetrance or a multifactorial mode of inheritance.¹⁸ Structural polymorphisms on one of the haplotypes of the human period3 gene (hper3) were implicated as contributors to increased susceptibility to DSPS.¹⁹
Several pedigrees of familial ASPS were reported, in which the ASPS trait segregated as an autosomal-dominant mode of inheritance.20,21 Although a mutation of human period2 (hper2) gene was identified in a large family with ASPS,22 other findings indicate genetic heterogeneity in this disorder.23 The exact mechanisms by which mutations in clock genes produce the physiological and behavioral phenotypes of CRSDs remain to be elaborated.

**Figure 1.** Actigrams of patients with disordered sleep-wake schedules. Sleep episodes are represented by white areas, wake episodes by black areas. The 24-h period is double-plotted in a raster format. A. Delayed sleep phase syndrome. B. Advanced sleep phase syndrome. C. Non–24-h sleep-wake syndrome. D. Irregular sleep-wake pattern.
**Diagnosis**

Diagnosis of CRSDs involves two complementary procedures. A clinical interview should evaluate the patient’s sleep-wake habits and presence of sleep complaints (such as insomnia and daytime sleepiness). Several additional characteristics might be sought for more accurate diagnosis of CRSDs, such as (i) impairment in different areas of functioning: these patients are frequently unable to keep a steady job, follow a school timetable, and maintain a normal social life; (ii) rigidity of sleep-wake patterns: it is extremely difficult for patients with CRSDs to adjust to new sleep-wake routines; (iii) hereditary trends: as shown above, other family members, such as parents, siblings, offspring, aunts, and uncles, are likely to have similar sleep-wake schedules to the patient; (iv) history of head injury or brain tumors: previous findings indicate that CRSDs can emerge as a secondary disorder associated with these conditions; (v) drug intake: as will be described below, CRSDs can also appear as a side effect of psychoactive medications. If DSPS is suspected, it might also be helpful to question the patient about his or her preferences in regard to mealtimes and hours of alertness. Patients with a delayed sleep-wake schedule usually report lack of appetite in the morning and choose evening hours as the best time for activities involving alertness and concentration.

The second procedure is the confirmation of information collected in the clinical interview by 7 to 14 days of sleep logs and/or actigraphic monitoring. The actigraph is a watch-sized device worn on the wrist sampling hand motion. A computerized algorithm can provide highly reliable data on sleep and wake periods of the patient. The documentation of sleep-wake cycles requires monitoring for at least several days; therefore, actigraphy is the most appropriate objective tool for diagnosing CRSDs, and in most cases polysomnography is not necessary. Importantly, actigraphic monitoring must be conducted in free conditions, since sleep-wake schedule obtained under forced conditions can mask the pattern of the schedule, thus misleading the diagnosis.

**Treatment**

At present, bright-light therapy and melatonin treatment, or a combination of the two, have proved to be the most effective treatment modalities for patients with CRSDs. These techniques aim to reset the sleep-wake cycle of the patients to match the external 24-h schedule.

Bright light is one of the most powerful time cues for the internal circadian timing system. Light exposure at specific times of the 24-h period can result in a phase-shift in the endogenous circadian rhythms of a variety of functions, such as melatonin secretion, body temperature, and sleep propensity. These time-dependent effects of light were described by phase-response curves (PRCs). In general, morning bright-light exposure induces a phase advance, whereas evening bright light exposure induces phase delay.

Using the entraining properties of light to synchronize sleep-wake schedule of patients with CRSDs has become an increasingly popular therapy. Artificial bright light applied by light devices at the intensities of 2000 to 4000 lux has been successfully used to realign the circadian phase of patients with DSPS and ASPS, and some evidence supports its effectiveness in treatment of non-entrained type sleep disorders, jet lag, shift work, and dementia. The American Academy of Sleep Medicine has provided the recommended intensities and time limits for phototherapy in the treatment of these disorders. Endogenous melatonin secreted by the pineal gland is another potent regulator of the sleep-wake cycle. It is thought that the nighttime increase in melatonin concentration reduces body temperature, which promotes the onset of sleep. Previous findings have demonstrated that pharmacological preparations of melatonin mimic the effects of endogenous melatonin, which are time-dependent: phase advance is produced by melatonin administered in the evening, whereas melatonin administration in the morning induces phase delays. Thus, the PRC to melatonin is about 12 h out of phase with the PRC to light. Administration of melatonin might be a preferable therapeutic strategy for many patients, who find phototherapy too demanding, leading to decreased compliance. The beneficial effects of 0.5 to 5 mg/day melatonin have been demonstrated in several types of CRSDs. Importantly, treatment with melatonin not only synchronizes the sleep-wake cycle of patients with CRSDs, but also significantly and clinically meaningfully improves several dimensions of their daytime functioning. Although some recent well-designed studies indicate that even relatively large doses of melatonin (10 mg/day for a month) have no toxicological effects, its long-term effects remain to be fully researched and resolved.
In patients for whom all of these treatment modalities fail to help, a rehabilitative approach is recommended. The patients should be guided to accept that their condition is permanent, and should be encouraged to consider changes in lifestyle that will be congruent with their sleep-wake cycle.49

CRSDs in psychiatry

As was described in several recent reviews,50-52 chrono-biological disturbances may play a crucial role in the pathogenesis of major psychiatric disorders, such as unipolar and bipolar depression, seasonal affective disorder, schizophrenia, and neurodegenerative illnesses. In the present review, we will specifically focus on cases where psychiatric practice might encounter disorders of the sleep-wake schedule.

CRSDs and personality disorders

In a large sample of 322 patients with CRSDs who attended a sleep clinic, 72 patients (22.4%) were diagnosed with personality disorders based on clinical interview.7 To confirm this preliminary finding a controlled study was conducted, in which the incidence of personality disorders was examined in a group of 50 patients with DSPS or free-running pattern in comparison with 56 healthy controls.53 Personality disorders in both groups were assessed using the Millon Clinical Multiaxial Inventory54 and Personality Diagnostic Questionnaire-Revised.55 The major finding of this study was that patients with CRSDs suffer more frequently from personality disorders than do normal controls.53 No specific pattern or profile of personality disorders could be clearly detected over and above the existence of general personality pathology.53

In a complementary study, the sleep-wake habits of 63 adolescents hospitalized in psychiatric wards were examined.56 None of the patients had any diagnosed medical disorders, and all received psychoactive medications. The patients suffered from a variety of psychiatric disorders, including schizophrenia and other psychotic disorders; mood disorders; personality disorders; disorders usually first diagnosed in infancy, childhood, and adolescence; anxiety disorders; and substance-related disorders. Sixteen percent of the adolescents were diagnosed as having DSPS. As predicted, the probability of comorbid DSPS among patients with personality disorders was significantly higher than among patients with any other psychiatric disorder. Further, all of the patients with DSPS suffered from disorders characterized by affective lability, namely bipolar disorder, schizoaffective disorder classified as mainly affective, and borderline personality disorder.56 These findings have led the authors to suggest that there may be an interrelationship between CRSDs and personality disorders. It is noticeable that both disorders are defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)57 as primarily involving a mismatch between the expectations of the society in which the individual lives and his or her own behavioral pattern. The direction of causality is difficult to determine. It might be that personality disorders are characterized by a deviant sleep-wake pattern as one expression of the general deviation from the expectations of society. On the other hand, peculiarities of the biological clock might lead to emotional, social, and functional difficulties that subsequently escalate into a personality disorder. According to this latter hypothesis, a deviant sleep-wake schedule frequently emerges early in life, possibly harming the mother and the child’s mutual ability to adapt to each other. The mother, required to adjust to a biological clock of her infant that differs markedly from her own, becomes tired, frustrated, and angry, causing the infant to respond accordingly. The resulting emotional burden, carried by both parties, might jeopardize the attachment processes, thus affecting future prospects of personal and social relationships of the child. At later stages of life, such a child has difficulties following the school timetable of activities, fails to obtain a sufficient amount of sleep at night, loses concentration during the morning and early afternoon hours, and, eventually, falls behind other children in school. Frequently, the abnormal sleep-wake cycle of individuals with CRSDs and the accompanying dysfunction at school or work are misattributed by parents, educators, psychologists, and other health care professionals to psychological rather than biological factors, such as laziness and low motivation. This attitude toward individuals with CRSDs, to which they are subjected since the early childhood or adolescence, adds psychological distress to the practical difficulties of coping with life and contributes to the development of personality disorders.23,56

CRSDs and psychoactive medication

Several cases of disrupted sleep-wake schedule as an iatrogenic effect of psychoactive drugs have been documented in the literature. Treatment with a typical neuroleptic,
Clinical research

haloperidol, in a patient with chronic schizophrenia was associated with an irregular sleep-wake cycle. Switching treatment to the atypical neuroleptic clozapine established a more organized and stable sleep-wake pattern and improved the clinical state of the patient. To further explore the relationship between type of drug and rest-activity patterns, seven additional patients with schizophrenia were studied. Four of these patients received typical neuroleptics (flupentixol or haloperidol) and showed a variety of abnormalities in the daily rest-activity rhythm, eg, delayed circadian phase syndrome, free-running sleep-wake syndrome, and irregular sleep-wake pattern with a circadian component (approximately 48 h). On the other hand, rest-activity cycles of those patients treated with atypical neuroleptic clozapine (three patients) were highly organized and synchronized with the environmental schedule.

Similar effects were observed in a female patient with early-onset Alzheimer’s disease: when treated with haloperidol, her rest-activity patterns became completely arrhythmic; this was accompanied by marked worsening of the cognitive state. When haloperidol was replaced by clozapine, rapid normalization of the sleep-wake cycle occurred and cognitive functioning improved. Additional evidence arises from a case study describing a male patient with Gilles de la Tourette syndrome, who was successfully treated with haloperidol. Prior to haloperidol treatment, the patient reported having a normal sleep-wake schedule. Two years after commencing the treatment, he exhibited an irregular sleep-wake cycle with a dominant 48-h circadian component. When therapy with haloperidol was changed to atypical neuroleptic risperidone, the timing and duration of sleep episodes became more organized, although his sleep-wake schedule still remained somewhat disturbed. Addition of melatonin as a secondary therapy fully recovered the patient’s sleep-wake circadian rhythm. This was accompanied by improvement in his quality of life, social interactions, and employment status. These findings support the proposition that whereas atypical neuroleptics like clozapine and risperidone enhance the congruity of the individual’s sleep-wake cycle with the environment, typical neuroleptics like haloperidol and flupentixol might alter the circadian sleep-wake rhythm. Since this effect was evident in several medical disorders, eg, schizophrenia, Alzheimer’s disease, and Tourette syndrome, it was argued that CRSDs are side effects of typical neuroleptics, rather than an illness-related phenomenon. The exact mechanisms through which typical and atypical neuroleptics exert their differential effects on sleep-wake cycle remain to be elucidated.

Clinical evidence indicates that apart from neuroleptics other psychoactive drugs, such as specific selective serotonin inhibitors (SSRIs), can trigger the emergence of CRSDs as a side effect. Hermesh et al described 10 patients with obsessive-compulsive disorder who developed DSPS during fluvoxamine treatment. It was postulated that delayed sleep-wake schedule in this case series was iatrogenic to fluvoxamine based on the following observations: (i) all patients received no other medications except fluvoxamine prior to the onset of DSPS; (ii) in all patients, DSPS first occurred following fluvoxamine initiation; (iii) when fluvoxamine was withdrawn or the dose considerably reduced, the sleep-wake cycle returned to normal; and (iv) with reexposure to fluvoxamine, DSPS recurred. Interestingly, emergence of DSPS was quite specific to fluvoxamine; treatment with two other SSRIs (clomipramine and fluoxetine) has not been associated with any adverse effects on sleep-wake cycle of these patients. The authors hypothesized that the alteration of sleep-wake schedule or the lack of it by different SSRI agents might depend on the differential effects of these drugs on serum melatonin levels. To summarize, the above cases indicate that certain psychoactive medications might have adverse effects on the circadian rhythm of the sleep-wake cycle. To date, we have clinical evidence of such effects for haloperidol, flupentixol, and fluvoxamine. Whether there are additional psychotropics associated with disruptions of the sleep-wake schedule, whether the response is dose- and time-dependent, and what the characteristics are of the particular patients who might develop CRSDs while on these drugs, remain questions for future research. At this stage, however, sleep-related complaints of patients treated with psychoactive drugs, especially haloperidol, flupentixol, and fluvoxamine, should not always be regarded as drug-induced insomnia or daytime somnolence. As the findings demonstrate, in some cases CRSDs might be taken into consideration as a possible side effect. When iatrogenic CRSD is suspected, changing therapy and/or adding melatonin might be initiated.

CRSDs and psychiatric misdiagnosis

Difficulties in daytime functioning are one of the prominent characteristics of CRSDs. Individuals with CRSDs frequently fail to adjust to the activity hours accepted in
most social, occupational, and academic settings, due to incompatibility of their internal biological rhythms with the environmental timetable. Consider, for example, a patient with DSPS who is expected to arrive at his workplace by 8 or 9 AM. In order to fulfill this requirement, this individual is forced to wake up at what might be the middle of his internal night. It is not surprising, therefore, that he will be frequently late and/or absent, a pattern that will most likely subject him to disciplinary actions up to dismissal. If, however, he manages to meet the attendance standards, his performance will be liable to the detrimental effects of sleep loss and time of day. In childhood and adolescence, when CRSDs usually emerge, the impairment of daytime functioning can be even more remarkable than in adults. Unlike adults, who can at times choose a lifestyle that corresponds to their sleep-wake cycle, the activity hours of persons of younger age are constrained by a strictly predetermined school timetable. The inability to adjust to this timetable may be associated with deteriorated school performance. In a recent study, we found that the vast majority of young patients with DSPS complained of frequent late arrivals and absences at school, underachievement, and behavioral/social difficulties. Importantly, treatment with melatonin significantly reduced the number of children and adolescents complaining of malfunctioning at school.63

In some cases, the daytime functional difficulties might be severe enough to be mistakenly interpreted as symptoms of psychiatric disorders. A case of a 14-year-old boy provides a dramatic illustration of such a scenario.64 During the 4 years prior to his referral to our sleep clinic, the patient suffered from major functioning difficulties, including conflicts with teachers, parents, and peers. At the age of 12, the patient dropped out of school and was sent to an inpatient child-psychiatry center. Three months of psychiatric evaluation yielded diagnoses of atypical depressive disorder with possible schizotypal personality disorder. Due to excessive daytime sleepiness, he was referred to our sleep clinic for assessment of a potential sleep disorder. A thorough sleep study revealed that the patient had a 26-h sleep-wake schedule and dissociation between oral temperature and salivary melatonin rhythms. He was diagnosed with non-24-h sleep-wake pattern. Treatment with oral melatonin normalized the sleep-wake schedule within a month, and follow-up actigraphy after 6 months of melatonin treatment revealed a full entrainment to a 24-h day. The patient returned to school after a year of absence and succeeded in filling the gaps of missing studies. At the end of the first semester, his school report showed excellent results. His parents also reported an improvement in the patient’s relationship with his family and peers. In a repeated psychiatric evaluation by licensed psychiatrists, none of the previously described severe diagnoses were present, and the boy showed no evidence of psychopathology, as was previously thought.64 Over the years of treating patients with CRSDs, we evidenced a considerable amount of similar case histories, some of which were previously documented.49

In this context, the association between CRSDs and attention deficit disorder (ADD) and attention deficit/hyperactivity disorder (ADHD) should also be mentioned. A relatively high prevalence (19.3%) of these disorders was reported in a large sample of patients with CRSDs attending a sleep clinic.2 In a recent retrospective study of 45 children and adolescents with DSPS (aged 6 to 18) who were treated with melatonin, almost half of the sample had a comorbid diagnosis of ADD or ADHD pretreatment.63 The treatment advanced the sleep-wake cycle of these patients and improved their daytime functioning in educational settings. Interestingly, many of them were able to reduce or discontinue psychotherapy and/or stimulant medication during melatonin therapy. This finding indicates that, at least in some cases, CRSD-related dysfunctional behaviors might be erroneously interpreted as symptoms of ADD/ADHD.

**Conclusion**

CRSDs are sleep pathologies associated with multilevel disturbances in daily functioning. These disorders can be relatively easily diagnosed and treated with several available treatment modalities. Yet many cases of CRSDs are underrecognized and misdiagnosed as psychiatric disorders or psychophysiological insomnia. Consequently, these patients receive inappropriate treatment, such as hypnotics, which can enhance the psychological distress and add to the adjustment difficulties that accompany CRSDs. It is of great importance to raise the awareness of these disorders on the part of pediatricians, physicians, neurologists, psychiatrists, and psychologists.
Consecuencias conductuales y psiquiátricas de los trastornos del ciclo sueño-vigilia

Los trastornos del ritmo circadiano de sueño (CRSD) surgen cuando el ritmo sueño-vigilia de un sujeto se desajusta con el ciclo ambiental de 24 horas. Los datos fisiológicos y los estudios genéticos en pacientes con CRSD sugieren que estos trastornos derivan de un funcionamiento anormal del sistema de ritmo circadiano. El diagnóstico involucra el reconocimiento de las características del CRSD, el cual se puede obtener a través de la entrevista clínica y del registro actigráfico de los patrones de reposo-actividad. La terapia de luz brillante y la administración de melatonina han demostrado ser las modalidades terapéuticas más efectivas para los CRSD. En la práctica psiquiátrica los CRSD se pueden encontrar en varias ocasiones. Existe alguna evidencia que indica que una desviación del ciclo sueño-vigilia puede ser un factor de predisposición para los trastornos de la personalidad. Los CRSD pueden aparecer como un efecto iatrogénico de ciertos psicofármacos como haloperidol y fluvoxamina. No es infrecuente que las dificultades funcionales que acompañan a los CRSD durante el día sean mal interpretadas como síntomas de psicopatología. El conocimiento y la identificación de los CRSD debería prevenir años de diagnósticos y tratamientos erróneos en estos pacientes.

Conséquences psychiatriques et comportementales des troubles du cycle veille-sommeil

Les troubles du rythme circadien du sommeil (TRCS) se produisent quand le rythme veille-sommeil d’un individu perturbe le cycle environnemental de 24 heures. Les données physiologiques et les études génétiques chez les patients ayant des TRCS suggèrent que ces troubles résultent d’un fonctionnement anormal du système de la chronologie circadienne. Le diagnostic comporte la reconnaissance des caractéristiques des TRCS, qui peuvent se faire par un interrogatoire clinique et un monitoring actigraphique des schémas repos-activité. Il a été prouvé que le traitement par la lumière brillante et l’administration de mélatonine sont les traitements les plus efficaces des TRCS. En pratique psychiatrique, les TRCS peuvent se rencontrer dans diverses occasions. Nous avons la preuve qu’un schéma veille-sommeil perturbé peut être un facteur prédisposant à des troubles de la personnalité. Les TRCS peuvent survenir en tant qu’effet iatrogène de certains médicaments psychoactifs, tels que l’halopéridol et la fluvoxamine. Il n’est pas rare que les difficultés fonctionnelles de la journée qui accompagnent les TRCS soient faussement interprétées comme des symptômes d’une psychologie pathologique. La reconnaissance et la prise de conscience des TRCS devraient éviter des années de traitement et de diagnostic erronés chez ces patients.

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