Chapter 12
Circadian Rhythm Disorders in Childhood

Silvia Miano

Abstract Chronobiology is a science that studies the physiology and pathology of circadian phenomena. In the last 50 years, numerous studies have been published on sleep changes during puberty and adolescence, which largely consist of delays in the timing of sleep. The most notable consequence of these shifts is a sleep debt due to a forced early wake-up during school days, despite no change in sleep requirements (around 9 h), and diurnal hypersomnolence. All these changes explain why teenagers are particularly vulnerable to delayed sleep phase syndrome, which is known to peak during adolescence (prevalence ranging from 7 % to 16 % compared with 0.15 % during adulthood). Advanced sleep phase disorder (ASPD), delayed sleep-wake phase disorder (DSWPD), irregular sleep-wake rhythm (ISWR), and the non-24-h sleep-wake syndrome or free-running disorder (non-entrained type) are referred to as "endogenous" circadian rhythm sleep disorders. The clinical features of each sleep circadian disorder are discussed together with the recommended treatment. Pediatric categories of subjects that are at risk of developing circadian disorders, such as those with a developmental disability, autism, attention-deficit hyperactivity disorders, and mood disorders, are investigated. Lastly, two case reports that provide examples of clinical practice are also presented.

Keywords Circadian sleep disorders • Sleep • Delayed sleep-wake phase disorder • Children • Adolescents • Melatonin • Light

S. Miano
Civic Hospital of Lugano, Neurocenter of Italian Switzerland, Sleep and Epilepsy Center, Lugano, Switzerland
e-mail: silvia.miano@eoc.ch; silvia.miano@gmail.com

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Introduction

The Circadian Biology and Physiology

Chronobiology is a science that studies the physiology and pathology of circadian phenomena. The circadian system provides temporal organization of sleep-wake cycles, feeding, and reproduction. Many fundamental biological events are characterized by a regular interval and duration, with the cycle being referred to as circadian if they occur periodically 24 h, ultradian if the periods are shorter than 24 h, and infradian if longer. Evolution has selected species whose physiological rhythm corresponds approximately to the time it takes the Earth to rotate once. Circadian oscillations are genetically determined, their occurrence being controlled by endogenous and exogenous stimuli that act as an orchestra. The suprachiasmatic nucleus (SCN) is considered the endogenous master circadian pacemaker brain clock, which comprises a feed-forward circuit of similar cells that can auto-depolarize and that produce a coherent circadian rhythm output for the rest of the body, whereas the light-dark (LD) alternation is considered the most significant endogenous factor that influences circadian biological rhythms [1]. The majority of human cells display the same molecular clockwork and are synchronized to one another via redundant systemic signals that create an accurate correspondence with the environment. These cues originate mostly from the SCN either through autonomous nervous control of hormones, such as glucocorticoids, or through direct innervation of other brain regions. The SCN is synchronized with light via the retino-hypothalamic tract, the result being a flexible system of clocks, each of which has an intrinsic duration of about 1 day that is constantly readjusted to the timing of environmental light [2]. This synchronization is largely due to the light activation of retina photoreceptors, which are not linked to visual function. Light activation stimulates the retino-hypothalamic tract, which terminates in the SCN, as well as the genicolohypothalamic tract, which terminates in the thalamus. Retinal rod and cone cells are not required for photo-entrainment, but a subset of retinal cells containing a light-sensing pigment, melanopsin, which is involved in circadian photo-entrainment does exist [3].

Light is not the only exogenous entrainment of the circadian rhythm, though it is the strongest. Many social cues, and other biological factors such as food intake and locomotor activity, may influence and reset circadian physiological phenomena, especially in humans: the rhythmic control of the digestive function and detoxication can be synchronized with rhythmic food intake by sleep-wakefulness alternation and diurnal cardiac function control changes in energy needs on a systemic level, while mitochondrial cells optimize the regulation of circadian energy production on a cellular level [2]. The oscillatory property of SCN cells persists even when they are isolated from all exogenous factors, in both in vivo and in vitro experiments, maintaining their oscillatory capacity for approximately 24 h (free-running rhythm), which may be prolonged up to 25.5 h [4, 5]. The free-running period (τ) differs according to race, with African Americans displaying a shorter τ than

Caucasians [6]. When the free-running period is forced for an extended period of time, some circadian functions, such as body temperature, cortisol secretion, and REM sleep, become desynchronized, whereas others, such as food intake and locomotor activity, do not, thereby suggesting that other endogenous pacemakers exist [1]. It should be borne in mind that the SNC is a very small hypothalamic nucleus that executes a single function, and if damaged, its function cannot be executed by any other tissue [7]. An orderly and reproducible spatiotemporal pattern of oscillatory gene expression that requires the integrity of the ventrolateral core region has been demonstrated in the SCN. When this core region is absent, the behavioral rhythm is abolished in vivo, although a low-amplitude rhythm can be detected in SCN slices in vitro [7]. These oscillatory genes are called "clock" genes and are a family of loci involved in circadian physiology and pathology, with a clear circadian rhythm of transcription [8]. Some cells within the SCN rhythmically express "clock" genes, whereas others express these genes upon exposure to light [8]. The clock genes are also considered tumor suppressor genes because they regulate cell division and cell differentiation by segregating DNA replication from periods of maximum respiration and by optimizing the time available for the DNA repair process. The direct consequences of in vitro abolition of SCN is tumor growth that is two to three times faster, while mice without the circadian clock genes develop a range of pathologies, including diabetes, arthritis, and cancer [2]. Most of these circadian clock gene functions are unexpressed during embryogenetic life, possibly owing to the rapid rate of cell division, which disrupts the circadian regulation [2].

In humans sleep occurs during darkness, usually 2 h before the melatonin (MLT) peak and 4 h before the temperature nadir. The MLT and body temperature are commonly used as markers of the master pacemaker, since it is impossible to measure SCN activity in vivo [1]. The MLT, which is produced by the pineal gland, controls circadian physiology, seasonal reproductive function, and stimulation of amphibian skin melanophores. Its role in regulating the immune system, gastrointestinal, retina, antioxidant, and antiaging functions is still debated [1]. It is also involved in the early development of neurons and glia and in the ontogenetic establishment of diurnal rhythms [9]. It regulates sleep states through the activation of two receptors: MT2 during NREM sleep and MT1 receptors during REM sleep [10]. The secretion of serum MLT concentrations starts at 3 months of age, reaches its highest nocturnal levels at 1–3 years of age, and steadily declines thereafter by 80 % to attain adult levels at puberty; levels remain stable during adulthood before decreasing in elderly age depending on a general increase in body size as opposed to decreasing pineal secretion (decreasing from 210 pg/ml in preschoolers to 130 pg/ml in school-aged children and to 50 pg/ml in young adults) [11, 12]. One study identified two patterns of early secretion in infants: one mature, with dim light melatonin onset (DLMO) in the evening, and one immature, with a flat distribution or rise in the morning, associated with early sleep problems [13]. Another study demonstrated that MLT levels at 16 weeks of age are significantly lower in infants with abnormal development than in those with normal development at 3 and 6 months of age [14]. The synthesis of MLT involves the pathway of serotonin anabolism, which is acetylated by arylalkylamine (AANAT), and methylated to MLT by the acetylserotonin O-methyltransferase

(ASMT) enzyme. MLT has a short half-life, lasting approximately 30 min, and is first metabolized in the liver by cytochrome P450 1A2 (CYP1A2) and then degraded by cytochrome 450 in the liver, sulfonated, and secreted by the kidney in the urine [15]. Secretion of MLT, which occurs prevalently during the night, is controlled by the SCN and in particular by the retino-hypothalamic-pineal tracts. Output from the pineal gland includes MLT receptors in non-neuronal tissues (gut, ovaries and vessels, among others) and neuronal tissue, where their concentration is highest, with MLT2 in particular having been implicated in phase shift mechanisms and being widespread throughout retina and brain cells. MLT synthesis is strongly inhibited by light and dopamine, whereas MLT inhibits dopamine secretion [1]. A widely used technique to determine the circadian phase is the assessment of the secretory pattern of MLT, according to which circulating MLT is normally low during the daytime, increases abruptly close to bedtime, and once again drops to daytime levels close to wake-up time. Since light suppresses MLT secretion, it is measured in dim light conditions, when the dim light onset of MLT is usually identified (DLMO) [16]. Simultaneous salivary and plasma MLT concentrations have shown that the saliva concentration of MLT corresponds to 40 % of that in the plasma. Thus, if the plasma level threshold for MLT is 10 pg mL^{-1}, the saliva level threshold is considered to be 4 pg mL^{-1} [16].

Desynchronized and disorganized mammalian sleep persists after SCN ablation because another mechanism controls sleep: the homeostatic process S, which reflects sleep pressure, i.e., the buildup during wakefulness and dissipation during sleep [17]. Sleep propensity increases in a nonlinear fashion during the day; sleep deprivation increases sleep pressure, thereby inducing sleep even during the circadian window, which does not usually allow sleep, and overcoming the circadian drive. Both the circadian and homeostatic processes (the so-called C and S processes, respectively) interact to modulate the intensity and the possibility to sleep [1]. In addition, the thalamus synchronizes and transfers the summation of the oscillatory cortical signals via the intergeniculate leaflets to the hypothalamus. Here, the release of neuropeptide y results in several non-photic inputs that regulate sleep. The afferent and efferent projections of the SCN and of the intergeniculate leaflets are widespread [18]. Lastly, the SCN is a nonhomogeneous structure made up of various types of neurons, one of which responds to photic inputs, one to non-photic stimuli, and another to MLT feedback, whereas only some cells exhibit intrinsic rhythmicity [18].

Changes in the Circadian and Homeostatic Processes During Adolescence

Adolescents start going to bed later as they get older. In the last 50 years, numerous studies have been published on sleep changes that occur during puberty and adolescence, which largely consist of delays in the timing of sleep. The most notable consequence of these shifts is a sleep debt due to a forced early wake-up during

school days, despite no change in sleep requirements (around 9 h), together with diurnal hypersomnolence. Studies from several countries have reported similar trends [19]. Adolescents consistently report going to bed later on weekend nights than on school nights and being forced to rise early during schooldays [19]. This shift has been attributed to either psychosocial exogenous factors, such as peer culture, family environment, academic demands, new jobs, and enjoying late-night activities (e.g., television or the Internet) or to changes in endogenous circadian clocks. The intrinsic circadian change, supported by data demonstrating a cross-cultural sleep phase delay during adolescence, may increase the capacity of adolescents to participate in evening activities, thereby reinforcing the changes in sleep timing. A National Sleep Foundation poll in the United States found that 45 % of adolescents report inadequate sleep [20]. A recent cross-sectional survey of adolescents in the United States conducted from 1991 to 2012 indicates that adolescent sleep generally declined over 20 years; the biggest change occurred in the years 1991–1995 and 1996–2000 [21].

Numerous papers have been published on this issue by Carskadon M. and coworkers during the so-called Stanford Summer Camps. The researchers hypothesize that human adolescence is associated with a physiological phase delay and a reduction in sleep pressure drive (around puberty) [22]. The authors found that the timing of MLT secretion was progressively shifted according to the pubertal stage, which is correlated with the circadian phase as defined by the timing of the MLT secretion: more mature children display a later MLT secretion offset phase [22]. A possible explanation for this finding is a longer τ during adolescence, which facilitates the delay in the circadian phase. Alternative explanations for the delayed sleep phase during puberty are an increased sensitivity and response to evening light and a reduced sensitivity to morning light [23]. One of the first studies conducted was designed to determine whether the typical daytime sleepiness reported by adolescents even occurs in the absence of sleep deprivation [24]. The authors found that total sleep time and REM sleep time during the night were stable across the Tanner stages, under controlled conditions in which sleep deprivation was absent (according to the pubertal development rating and secondary sexual characteristics) [26], while slow-wave sleep time declined, with a 40 % reduction from prepuberty to maturity, and daytime sleepiness increased [25]. Sleep timing, as explained above, is derived from the interaction between the circadian system and homeostatic process. The delay in pubertal sleep might also be caused by sleep pressure changes. The marker of sleep pressure changes is widely considered to be slow-wave activity (SWA, electroencephalogram, spectral power frequency range of 0.75–4.5 Hz), which is high during the first cycle of non-rapid eye movement (NREM) sleep, but declines progressively during the night in parallel with the drop in sleep pressure. A spectral analysis of a scalp sleep electroencephalogram (EEG) during adolescence conducted to compare the nocturnal dynamics of SWA in prepubertal and mature adolescents demonstrated a 40.1 % reduction in slow-wave sleep associated with a greater degree of sleep stage 2 NREM in mature adolescents compared with prepubertal adolescents. NREM sleep EEG power was lower in the frequency ranges <7 Hz, 11.8–12.6 Hz, and 16.2–16.8 Hz

in mature adolescents. The dynamics of SWA were identical within the NREM sleep episodes and across the night in both developmental groups, indicating that the homeostatic recuperative drive during sleep remains unchanged across puberty and that the decline in slow-wave sleep during adolescence may reflect developmental changes within the brain rather than changes in sleep regulatory processes [25]. Similar results were obtained when regional sleep EEG power was analyzed in adolescents: the sleep-state-independent reduction in EEG power over almost the entire frequency range was greater in more mature though not in prepubertal adolescents, whereas the decay rate of the sleep homeostatic process did not differ between the two groups [27]. Another study demonstrated that, following 36 h of forced sleep deprivation, the buildup of homeostatic sleep pressure during wakefulness was slower in mature than in prepubertal adolescents, whereas the decline in the homeostatic process remained similar in both groups [28]. In addition, sleep tendency (assessed by measuring latency to sleep onset) was examined during extended waking in prepubertal and mature adolescents to determine whether sleep pressure was lower near bedtime in the latter group, with saliva samples of MTL also being obtained. The saliva sample DLMO was earlier in Tanner 1 group (mean clock time around 20:33 h) than in Tanner 5 group (mean clock time around 21:29 h), and sleep latencies were shorter in Tanner 1 group at 22:30 h, 00:30 h, and 02:30 h [29]. This study indicates that adolescents display a delayed circadian (or internal clock) phase, assessed according to daily endocrine rhythms, even several weeks following the introduction of regulated schedules that allow for sufficient sleep and are maintained under controlled laboratory conditions in which social influences are reduced to a minimum, and correlates with secondary-sex development [29]. Pubertal humans may have a blunted phase advance response to light exposure in the morning and an exaggerated phase delay response to light exposure in the evening [30]. Although girls start displaying a sleep delay 1 year earlier than boys, paralleling their younger pubertal onset [30], the magnitude of the delay is greater in boy than girls, as has been demonstrated by a large epidemiological study performed in Germany and Switzerland [31]. A recent review designed to analyze cross-culture differences found that Asian adolescents' bedtimes were later than those of peers from North America and Europe, while weekend sleep data were generally consistent worldwide, with bedtimes 2+ hours later. The magnitude of the school night-to-weekend discrepancy is associated to problematic outcomes, including impaired school performance and depressed mood. The authors noted a worldwide delayed sleep-wake behavior pattern that was consistent with symptoms of delayed sleep phase disorder, which may be exacerbated by cultural factors [32]. In addition, the delayed timing of sleep during human adolescence is likely to represent a developmental change shared by mammalian species [29]. All these changes explain why teenagers are particularly vulnerable to delayed sleep phase syndrome, which is known to peak during adolescence (a prevalence ranging from 7 to 16 % compared with 0.15 % during adulthood) [28]. The Carskadon laboratory developed a model of delayed sleep phase during adolescence that takes into account developmental changes in homeostatic drive and

circadian timing: human adolescents become resistant to sleep pressure, allowing them to stay up later. At the same time, their circadian phase is delayed somewhat, which gives them the drive to stay awake later in the evening and to sleep later in the morning [33]. These findings should be borne in mind when measures need to be taken to avoid the negative effects of sleep deprivation on grades, the risk of car accidents, and mood [31]. A number of school districts have postponed middle and high school starting times in an attempt to reduce teenage sleep deprivation [34]. Teaching sleep and circadian principles in middle and high school health education is fundamental, instructing adolescents to minimize exposure to light at night and to reduce computer or TV usage immediately before bedtime, adding an outdoor morning activity into a teenage schedule [30] and reducing consumption of common beverages that contain caffeine in view of the long-lasting psychoactive effects of caffeine [35]. Consumption of common beverages that contain caffeine is known to have increased in childhood and adolescence. One recent cross-sectional study conducted on 4243 school-aged children found a twofold increased risk of sleep disturbances in school-aged and adolescent children who drank either coffee or soft drinks [36]. Children are very often unaware of the caffeine content in common drinks. Sodas are a common source of caffeine among adolescents and are associated with daytime sleepiness, insufficient sleep, and poorer sleep quality [36]. Environmental factors (such as decreased parental monitoring) and psychosocial factors (such as increased use of electronic media) exert a considerable influence on the amount of time adolescents sleep, despite reports in the press and information given by clinicians on the negative impact of electronic media on sleep [37]. Media use might impact sleep quality and quantity because it directly displaces not only sleep but even other activities related to good sleep hygiene (such as physical activity). Media use in the evenings may cause children to become physiologically aroused, making it more difficult for them to relax before they go to bed. In addition, evening exposure to bright light from television or computer screens, as well as electromagnetic radiation from mobile telephones, may suppress MLT secretion and consequently delay the circadian rhythm [37]. Almost all American adolescents (97 %) were found to have at least one electronic media device in their bedroom, consisting of music players (90 %), televisions (57 %), video game consoles (43 %), mobile (42 %) or fixed-line telephones (34 %), computers (28 %), and Internet access (21 %). Older adolescents had more media devices in their bedrooms than younger adolescents [37]. Television viewing among children and adolescents should be limited, especially in the evenings, with a recommended maximum of 2 h per day, and televisions should be kept out of bedrooms [38]. Children using electronic media as a sleep aid to relax at night have been reported to have later weekday bedtimes, experience fewer hours of sleep per week, and complain more of daytime sleepiness [39]. Time spent playing computer or electronic games should be restricted both during the day and in the evening for school-aged children and adolescents, with a viewing limit of 2 h per day, though a distinction may need to be made between violent and nonviolent games as playing nonviolent games in the evening appears to have positive effects on sleep [38].

Circadian Rhythm Sleep-Wake Disorders (CRSWDs)

The International Classification of Sleep Disorder – third edition [40] classifies CRSD as dyssomnias, with six subtypes: advanced sleep-wake phase disorder, delayed sleep phase disorder, irregular sleep-wake disorder, non-24-h sleep-wake rhythm disorder, jet lag disorder, and shift work disorder. The primary clinical characteristic of all CRSDs is an inability to fall asleep and wake at the desired time, caused by a problem with the internal biological clock (circadian timing system) and/or misalignment between the circadian timing system and the external 24-h environment, such as timing of patient's school, work, or social activities. A number of tools are available to assess sleep-wake patterns: sleep log and actigraphy are recommended to evaluate CRSWDs and should be conducted for at least 7 days, preferably for 14 days; circadian chronotype (Morningness-Eveningness Questionnaires) and physiological measures of endogenous circadian timing (salivary or plasma DLMO and urinary 6-sulfatoxymelatonin) are considered optional, though significant, additional tools when making a diagnosis. The most common presenting symptoms are difficulty in initiating and maintaining sleep and excessive sleepiness associated with significant impairments in important areas of functioning [40]. Advanced sleep-wake phase disorder (ASWPD), delayed sleep-wake phase disorder (DSWPD), irregular sleep-wake rhythm (ISWR), and the non-24-h sleep-wake syndrome or free-running disorder (non-entrained type, N24SWD) are considered the "endogenous" circadian rhythm sleep disorders, whereas jet lag disorder and shift work disorder are considered the "exogenous" circadian rhythm sleep disorders. The endogenous and exogenous factors in each disorder are, however, always combined to some extent [41]. Jet lag disorder and shift work disorder will not be discussed here because they are typical of adulthood and not adolescence. According to the practice parameters for the clinical evaluation and treatment of CRSWDs drawn up by the American Academy of Sleep Medicine [41], polysomnography is not routinely recommended to diagnose CRSWDs (standard), specific questionnaires such as the Morningness-Eveningness Questionnaire cannot be recommended because evidence pointing to their usefulness is insufficient, and circadian phase markers are indicated to diagnose non-24-h sleep-wake rhythm disorder (option), though not other circadian disorders because evidence of their usefulness is insufficient in this case as well. Actigraphy is recommended for the diagnosis of advanced and delayed sleep phase disorders (guidelines), as well as of non-24-h sleep-wake rhythm disorder and irregular sleep-wake rhythm (option), while sleep log or diary is recommended (guideline) to diagnose all endogenous circadian sleep disorders and actigraphy (guideline) to monitor the response to therapy in these disorders [41].

These following criteria must be met [40]:

1. Features:
   (a) DSWPD: significant delay in the phase of main sleep (habitual sleep-wake timing delayed ≥2 h, relative to conventional or socially acceptable timing, excessive morning sleep inertia, increased rates of psychiatric disturbances. An overlap with non-24-h sleep-wake disorder is possible).

(b) ASWPD: advance (early timing) in the phase of main sleep. Complaints of early morning or maintenance insomnia and excessive evening sleepiness, and chronic sleep debt.
(c) N24SWD: there is a history of insomnia, excessive daytime sleepiness, or both, which alternate with asymptomatic episodes, due to misalignment between the 24-h light-dark cycle and the endogenous sleep-wake circadian rhythm. The magnitude of the daily delay may range from <30 min (period is close to 24 h) to >1 h (period is longer than 25 h). The symptomatic episode will typically begin with a gradual increase in sleep latency and delayed sleep onset. Most individuals are totally blind. In sighted people, social and behavioral factors and psychiatric disorders play an important role. Occasionally, the disorder is associated with developmental intellectual disability or dementia. In sighted patients with N24SWD, the circadian period is about 25 h or longer; in totally blind patients, it is closer to 24 h and may rarely be shorter.
(d) ISWR: chronic or recurrent pattern of irregular sleep and wake episodes throughout the 24-h period, characterized by symptoms of insomnia during the scheduled sleep period, excessive sleepiness (napping) during the day, or both. The chronic or recurring sleep-wake pattern is temporally disorganized; sleep and wake episodes are variable throughout the 24-h cycle. It is more commonly observed in neurodegenerative disorders, such as dementia, and in children with developmental disorders. Total sleep time across the 24 h may be normal for age.

2. The symptoms are present for ≥3 months.
3. Sleep quality and duration improve when sleep schedule can be chosen.
4. Sleep log and actigraphy monitoring demonstrate a delay in the habitual sleep period. Both work/school days and days off must be included.
5. The sleep disturbance is not better explained by another current sleep, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Additional Pediatric Features of CRSWDs

Validated instruments are available for assessing phase preference in pediatric populations, including the Children's Chronotype Questionnaire (CCTQ) (parent report), the Morningness-Eveningness Scale for Children (self-report), and the Morningness-Eveningness Questionnaire for Children and Adolescents [40].

Delayed Sleep-Wake Phase Disorder

Weitzman and colleagues [42] first described delayed sleep phase insomnia, which is characterized by a cluster of features, including a chronic inability to fall asleep and wake at a desired clock time, and consequently locks patients into

a sleep schedule that is out of phase with normal activities. Although it is prevalent above all among adolescents and young adults, onset in early childhood has been described, especially in familial cases. In younger children, DSWPD may present primarily as bedtime resistance, as caregivers attempt to establish bedtimes in conflict with the child's circadian time for sleep. A long history of repeated school absences, chronic tardiness, and/or school failure, rather than sleep complaints per se, is usually reported. Children and adolescents with DSWPD display higher rates of behavioral/emotional problems, including depression and suicidality, academic problems, and a higher likelihood of substance abuse. School avoidance, social maladjustment, and family dysfunction are contributing factors. Motivated DSWPD is a subtype belonging to adolescence, with little intrinsic motivation to successfully complete treatment to obtain a normal lifestyle, which is usually associated with a history of mood or anxiety disorder (school phobia and separation and social anxiety) or learning disorders. DSWPD is commonly associated with specific categories: mood disorders, severe obsessive-compulsive disorder, attention-deficit hyperactivity disorder, and autistic spectrum disorders [40]. Ill-defined medical issues may occasionally be a trigger or may complicate the course of DSWPD. This disorder is more common in the United States, a finding that may be due to the fact that school starting times in other countries, such as those in Europe, are later (08:00–08:30 h) and may thus be more suited to the delaying patterns of adolescence [19]. In adolescents and young adults, prevalence is of 7–16 %; 40 % of subjects have a family history, as an autosomal dominant trait. It is a chronic condition that may last into late life; the recurrence is high, despite appropriate treatments, with a higher risk of substance abuse disorder, increased risk of motor vehicle accidents, and chronic insomnia [40].

The endogenous circadian temperature length (τ) has been found to be longer in young adults with SDWPD than in good sleepers (>25 min). An abnormally long τ would generate a strong and continual tendency to delay the circadian system as well as the sleep-wake cycle and may account for the high relapse rate following treatment for this condition [43]. Moreover, suppression of MLT to light exposure in SDWPD is reported to be greater in adolescents than in controls, which suggests that hypersensitivity to evening light may be a precipitating or maintaining factor for the phase delay [44]. Another study demonstrated sleep deprivation and reduced sleep time in this disorder, thus suggesting such individuals have a scarce ability to compensate for lost sleep [45]. A recent paper confirmed that the timing of sleep in adolescents with SDWPD is delayed when compared with normal controls, though no group differences in sleep parameters emerged once sleep was initiated [46]. Recordings of sleep logs and actigraphy show sleep onset delayed until 1:00–6:00 am (may be earlier depending on age and developmental status), and wake time occurs in the late morning or afternoon. Unlike chronic insomnia disorder, sleep initiation and maintenance are improved when the patient is allowed to sleep on the preferred schedule; inadequate sleep hygiene and insufficient sleep syndrome must also be considered as differential diagnosis [40].

Advanced Sleep-Wake Phase Disorder

ASWPD has been reported in children with neurodevelopmental disorders, while in normal subjects, the typical onset is in elderly, with a prevalence of 1 %. Familial cases may be characterized by an earlier onset [40]. In particular, studies on children with autism spectrum disorders and Smith-Magenis syndrome have displayed marked alterations in MLT secretion profiles, which may become manifest as a phase advance characterized by very early morning waking. In some cases children develop this disorder because they are encouraged to wake up earlier than they wish to as a result of parental attention or by the opportunity they are offered to watch television or use other media upon waking [40]. Genetic analyses reveal a missense mutation in a casein kinase (CK1ε) binding region of a Period gene (hPer2). Recordings of sleep logs and actigraphy demonstrate an advance (typically ≥2 h) in the timing of circadian rhythms [40]. Poor sleep hygiene practices, particularly evening napping, and irregularity of the sleep-wake schedule, "free-running" (non-entrained) circadian rhythm, major depressive disorder that is a common cause of early awakening, must be considered as differential diagnosis [40].

Non-24-h Sleep-Wake Rhythm Disorder (N24SWD) and Irregular Sleep-Wake Rhythm Disorder (ISWRD)

N24SWD is extremely rare in normally developing or sighted children, but has been reported in children with intellectual disabilities and blindness. In congenitally blind children, onset can occur at birth or during infancy. Children with optic nerve hypoplasia due to a variety of causes, especially in children with a hypoplastic corpus callosum and comorbid severe intellectual and visual impairments, display N24SWD features. It has also been described in Rett syndrome and autism spectrum disorders. The underlying mechanism is postulated to be lack of entrainment to the 24-h day, with a failure to perceive and/or attend to social/environmental zeitgebers. Normal-sighted children or adolescents with N24SWD are likely to have psychiatric disorders that predispose them to social interaction avoidance. Children with chronic neurological conditions, such as blindness or neurodevelopmental disabilities, may have a more intractable pattern than children with more self-limited conditions [40]. Caregivers sometimes report that a child with ISWRD sleeps too much, too little, or at inappropriate times. The lack of prolonged consolidated sleep periods and the random distribution of sleep periods, with a marked day-to-day and week-to-week variability, are distinctive features that have a significant impact on caregivers. As occurs in N24SWD, children with developmental disorders, such as autism and Asperger syndrome, have an increased risk of ISWRD. Both non-24-h sleep-wake rhythm disorder and ISWRD are also common in children with Angelman syndrome or with Williams syndrome. In this regard, marked alterations in MLT secretion profiles due to polymorphisms in melatonin enzyme synthesis or variants in genes coding for melatonin receptors have been described in children and adults with autism spectrum disorders as well as in children with Smith-Magenis

syndrome. Other postulated mechanisms include clock gene polymorphisms and decreased levels of entrainment by social/environmental zeitgebers. Traumatic brain injury and chronic fatigue syndrome may be other predisposing factors for both disorders. Brain tumor survivors, especially those in whom the hypothalamic-pituitary axis has been disrupted, may have an increased prevalence of circadian rhythm disorders, including ISWRD. The prevalence of ISWRD increases with advancing age, but it is likely that the age-related increase in neurodegenerative disorders, rather than aging per se, is responsible for this increase [40]. Recording of sleep log and actigraphy over prolonged periods (ideally ≥14 day in blind individuals) demonstrate the lack of a stable relationship between the timing of sleep and the 24-h day, in subjects with N24SWD. When sleep schedules follow the endogenous propensity, sleep onset and wake times are delayed each day. Sleep log and actigraphy reveal an irregular sleep-wake pattern, which is defined as having multiple sleep bouts (typically 2–4 h) during a 24-h period; the pattern may vary from day to day, among individuals with ISWRD.

Insufficient Sleep Syndrome

An inadequate amount of sleep time should always be taken into account when making a diagnosis of circadian sleep disorders, and the normative data for sleep duration should be borne in mind before diagnosing a DSWPD in all patients except long sleepers. Sleep duration recommendations were recently published by the National Sleep Foundation of the United States of America [47]. Chronic sleep loss is a characteristic of modern society, with large numbers of people stating that they are chronically sleeping significantly less, which in turn induces or exacerbates a sleep phase delay [48].

Insufficient sleep syndrome may be more frequent in adolescence, when the need to sleep is greater, but social pressure and a tendency to delay sleep often lead to chronic restricted sleep. The evening preference chronotype predisposes to insufficient sleep. It should be differentiated from delayed sleep phase disorder (in some complex cases in which there is an overlap by measuring circadian biological markers), from the effects of recreational drug use and from school avoidance behavior. Increased predisposition to substance abuse and accidents in teens may be consequent to insufficient sleep. Excessive diurnal somnolence or daytime lapses into sleep, or behavioral abnormalities attributable to sleepiness in prepubertal children, are common complaints. Sleep time, as established by history, sleep logs, or actigraphy, is usually shorter than that expected for age, though it tends to be markedly extended on weekend nights. In this disorder, the reduction in sleep duration is present most days for at least 3 months, and sleep paralysis and hypnagogic hallucinations may occur. Secondary symptoms such as irritability, concentration and attention deficits, reduced vigilance, distractibility, reduced motivation, anergia, dysphoria, fatigue, restlessness, uncoordination, malaise, and depression may, by becoming the patient's main focus, obscure the primary cause of the difficulties. The correct diagnosis of insufficient

sleep syndrome may be particularly challenging in subjects who have a physiological need for unusually large amounts of sleep. Sleepiness and the other complaints can be successfully addressed in such patients by increasing total sleep time, whereas they cannot be in subjects with DSWPD [40].

Treatment of Circadian Rhythm Sleep-Wake Disorders (See Table 12.1)

The timing of treatment is crucial because unless therapy is started at the appropriate circadian time, the patients are likely to get worse. Morning exposure to light will facilitate entrainment in humans who have an intrinsic period that exceeds 24 h, whereas evening light exposure will entrain individuals with an intrinsic period that is shorter than 24 h [19]. The treatment options in clinical practice for circadian rhythm sleep disorders comprise bright light treatment and exogenous MLT administration. Although chronotherapy has been used, the data available documenting its efficacy are still insufficient [49]. Chronotherapy, which has proved to some extent successful in DSWPD, consists in delaying the sleep period by 2–3 h every day until the preferred target sleep time is achieved [40]. In order to administer the treatment correctly, it is essential to identify the circadian phase, i.e., the nadir of the core

Table 12.1 Recommendations for prescribing melatonin in children with circadian sleep disorder of sleep-onset insomnia

Time of administration in children	If used as chronobiotic, administer 2–3 h before dim light melatonin onset or administer melatonin 3–4 h before actual sleep-onset time
Dosage	Start with a low dose of 0.2–0.5-mg fast-release melatonin; increase by 0.2–0.5 mg every week until effect appears; if there is no response after 1 week, increase dose by 1 mg every week until effect appears. When 1 mg is effective: try lower dose; if there are sleep maintenance problems, start after melatonin treatment; melatonin dose is probably too high
	Maximum dose: <40 Kg, 3 mg; >40 Kg, 5 mg
Treatment duration	It should be no less than 1 month. It can be withdrawn just before puberty or shortly after puberty. Stop melatonin treatment once a year for 1 week (preferably in summer) after a normal sleep cycle has been established
When melatonin treatment is no longer effective:	Check timing of administration. In some cases dose reduction is warranted instead of dose escalation, because loss of efficacy of melatonin treatment is most likely caused by slow melatonin metabolism. Metabolism slower, oral contraceptives, cimetidine, fluvoxamine; metabolism faster, carbamazepine, esomeprazole, omeprazole
	Reconsider diagnosis: look for neuropsychiatric comorbidity. For very severe delayed sleep-wake rhythm, consider chronotherapy

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body temperature rhythm or the endogenous MLT rhythm. The core body temperature usually peaks in the late afternoon or evening and reaches its lowest point, i.e., nadir, in the early morning, with sleep normally ending approximately 2 h following the nadir. MLT secretion increases soon after the onset of darkness, peaks in the middle of the night, and gradually falls during the second half of the night [49]. The protocol followed to estimate the nadir of the core body temperature requires that the patient be placed in a semirecumbent position in a laboratory environment for a number of consecutive hours (often 26), with a light intensity of less than 50 lx; the patient receives a 100-kcal meal every hour [49]. The DLMO measurement is based on several samples of MLT (normally with a 30- or 60-min interval) of saliva, urine, or plasma. The level of illumination currently recommended for sampling is 10 lx [50]. While the samples are being collected, subjects should avoid drinks with artificial colorants, alcohol, or caffeine as well as teeth-brushing, lipstick/lip gloss, chewing gum, lemons, and bananas, as well as avoid eating, drinking, or using tobacco for 30 min prior to sampling [46]. In cases in which the sleep phase disorder is severely delayed or advanced, saliva should, if possible, be collected at later or earlier times or hourly for 24 h [51]. A simple way to assess the nadir is to instruct the patient to sleep until he/she wakes up spontaneously (i.e., without an alarm clock) – it is reasonable to assume that the nadir will be approximately 2 h before the subject awakens. The body temperature nadir usually coincides with the moment in which the greatest difficulty in staying awake is encountered, which is worth bearing in mind when the nadir in jet lag disorder and night workers needs to be calculated. Short wavelengths (blue light) have a stronger MLT-suppressing effect and a stronger phase-shifting effect on the human circadian rhythm. Light exposure before the nadir of the core body temperature rhythm causes a phase delay, whereas light administered after the nadir causes a phase advance. Bright light is typically administered by portable units yielding about 10,000 lx, with an exposure time of approximately 30–45 min per day being required to advance sleep, and units yielding about 4000 lx for 2 h being required to delay sleep. The patient is instructed to keep his gaze directed at the light source, but not continuously. Whenever outdoor light of a sufficient intensity is available, it is preferable to be outdoors than sit in front of a light box [49]. Some rare cases of mania as a side effect of phototherapy have been reported [52]. Compliance may be increased in some patients by using a light visor. Blue light-blocking glasses may be useful in adolescents as a countermeasure for alerting effects induced by light exposure through light-emitting diode screens [53], while a prototype light mask using narrow-band "green" light to deliver light through closed eyelids suppresses MLT by 40 % through the closed eyelid without disrupting sleep [54]. In ASWPD, the subject should be exposed to bright light as close to bedtime as possible. The effects of bright light may not be as clear in ASWPD as in DSWPD because exposure to light in the former occurs many hours before the nadir, and waking up the patients in the middle of the night (i.e., just before the nadir) is normally not considered acceptable. In sighted individuals with a free-running disorder, exposure to bright light may be tried before administration of MLT, when the rhythm is in phase with the environment [49].

Exogenously administered MLT has phase-shifting properties, with the effect following a phase response curve (PRC) that is about 12 h out of phase with the PRC of light. MLT administered in the afternoon or early evening will phase advance the circadian rhythm, whereas when it is administered in the morning, it will phase delay the circadian rhythm, with maximal phase shifts occurring when melatonin is scheduled around dusk or dawn. The doses used in most studies range from 0.5 to 5 mg, though it is not clear whether the effects of MLT are dose-related [49]. The recommendations of a European consensus conference held in Rome in 2014 that was aimed at assessing the current role of melatonin in childhood sleep disturbances were recently published [51] (see Table 12.1, modified version of these recommendations). MLT displays its maximum phase-advancing effect 3–5 h before the DLMO, whereas when it is administered 2–3 h after the DLMO, it may have either no effect or a reversal effect in DSWPD [51]. There is no evidence that slow-release MLT is preferable to the fast-acting MLT [51]. Possible side effects include increased blood pressure, headache, dizziness, nausea, and drowsiness [55]. Bright light has been recommended as the first treatment approach to SDWPD; if the response is not satisfactory, MLT is added, usually 12 h before exposure to light [49]. MLT is administered 12 h after the last awakening in blind patients with free-running disorders. In conclusion, the most important practical points to bear in mind when treating CRSWDs are do not start bright light treatment for SDWPD in the early morning but wait until the patient wakes up spontaneously (without an alarm clock); bright light is subsequently administered 1 h earlier every day until entrainment. Appropriate timing of melatonin administration is approximately 12 h after bright light treatment [49].

Subjects with Neurodevelopmental Disorders Have Increased Risk of CRSWDs

Autism Spectrum Disorders (ASD)

Sleep problems are particularly common in children with ASD, with prevalence rates ranging from 50 to 80 % compared with 9–50 % in age-matched, normally developing children. Such problems tend to increase with age, rather than disappear [56, 57]. The most common sleep problem reported by caregivers is insomnia, whose pathogenesis is multifactorial and includes disruption of circadian rhythms and MLT dysregulation. It has recently been hypothesized that the increased use of media combined with the bright screen of the media devices may contribute to the alterations in MLT secretion in ASD [58]. An overresponse to sensory input at bedtime associated with increased precognitive arousal has been observed in such children [59]. Furthermore, the relationship between sleep problems and ASD is complex because circadian abnormalities and epilepsy are both strong, bidirectional contributors [60, 61]. The multifactorial factor that is

implicated in ASD may explain the marked night-to-night variability of the sleep-wake cycle and the fragmented irregular sleep-wake patterns, including the inconsistent sleep onset and rise time, free-running sleep-wake rhythm, sleep onset delay, and early morning awakening [62, 63]. Significantly lower levels of nocturnal and daytime blood melatonin levels, as well as lower levels of its primary metabolite 6-sulfoxymelatonin, have been observed in many individuals with ASD when compared with normally developing controls [64, 65]. A disruption of the serotonin pathway, associated with high whole-blood serotonin levels and reduced plasma MLT, was also reported in one study on 278 ASD subjects [61]. Most of the studies that have investigated MLT-related genes in ASD focused on the ASMT gene, with reports indicating that a decreased expression of the ASMT transcript is correlated with decreased MLT blood levels in ASD patients and their relatives [65]. The few studies that analyzed genome-wide gene expression found 15 circadian rhythm regulatory or responsive genes that are differentially expressed in the most severe ASD subgroup though not in the mild or savant subgroups, thereby pointing to a link between circadian rhythm dysregulation and the severity of language impairment. In particular, the presence of the gene encoding AANAT was reported to be significantly reduced [66, 67]. Many polymorphisms within the CYP1A2 gene that alter MLT degradation and are predictive of slow metabolizing alleles have been implicated in the pathogenesis of ASD and sleep problems, accompanied by a loss of efficacy of MLT supplementation after 1 or 2 months [68]. It has been hypothesized that normal nocturnal blood values of MLT in some children with ASD may be caused by a combination of lower MLT production levels and the slow metabolic activity of CZP1A2 [68]. CRSWDs in children with ASD have been investigated above all by means of sleep questionnaires and actigraphic recordings (usually associated with sleep logs), while the detection of plasma, urine, or salivary MLT secretions continues to be used as a diagnostic tool for research purposes [56]. Basic principles of sleep hygiene, including the selection of an appropriate bedtime and establishment of a positive bedtime routine aimed at reducing emotional and/or behavioral stimulation at night and thus at minimizing television viewing and playing computer or video games, may represent an important means of improving sleep [58]. A parent group program of intervention may help to manage insomnia in ASD [69]. Supplemental MLT in ASD may go beyond the treatment of a deficiency state alone; for example, melatonin, which acts as a hypnotic when used independently of a deficiency state (in ASD children with normal endogenous MLT levels), also has antianxiolytic effects that may mitigate hyperarousal-related insomnia [68]. Moreover, some trials and meta-analysis studies in which MLT has been used to treat ASD highlighted the efficacy of MLT in this disorder (with varying dosages of up to 6 mg administered under both immediate- and controlled-release conditions, 5–6 h before the desired bedtime) [70, 71]. In one randomized placebo-controlled study, controlled-release melatonin treatment combined with behavioral interventions in 134 children with autism and long-lasting sleep problems proved to be highly effective [72].

Neurodevelopmental Disabilities (NDD)

The most common sleep disturbances in NDD are delayed sleep onset, frequent awakenings during sleep, lasting minutes or hours, and early morning awakenings. Day-night reversals, advanced sleep onset, and free-running sleep-wake rhythm disorders are much less common. Since individuals affected by NDD cannot sleep when sleep is desired, needed, or expected, most of the sleep disturbances belong to the diagnostic category of CRSWDs [73]. CRSWDs in children with NDD tend to be misunderstood and underdiagnosed. Light/darkness influences brain functions, including cognition, via pathways other than the monosynaptic retinal-hypothalamic tracts [74]. The prevalence of CRSWDs is increasing among normally developing and healthy children owing to a combination of lifestyle changes and increased exposure to light. This change also applies to children with NDD, 70 % of whom are affected by CRSWDs, especially those with moderate-severe NDD, i.e., with bilateral and extensive brain lesions. Persistent early morning awakenings are common in children with NDD and fulfill the criteria of CRSWDs because such children are unable to sleep when sleep is desired, needed, or expected. Delayed sleep-onset disorders in children with severe NDD are associated with a marked variability in the timing of sleep onset and frequency of a delay, with the total sleep time per 24 h not being age appropriate, but frequently reduced [75]. A good response to melatonin administered at bedtime has been reported in such cases [76]. It is important to bear in mind that restless legs syndrome, with or without periodic limb movement, may also cause delayed sleep onset. The prevalence of this syndrome is likely to be underestimated because of the difficulties encountered in diagnosing it in children with NDD [73]. Free-running sleep-wake rhythms with no other sleep disturbances are generally observed in neurologically healthy children who have total ocular blindness, though this condition is rare because total ocular visual loss is now uncommon as a result of improved ophthalmological care. By contrast, children with loss of visual acuity due to occipital lobe visual impairment do not exhibit free-running sleep-wake disturbances because the monosynaptic retinal-hypothalamic pathways to the SCN remain intact. Since children with NDD have altered cortical connectivity, they may not be able to properly perceive the environmental cues required to develop the sleep-wake rhythm, which results in inadequate thalamic signals to the hypothalamus and, ultimately, in CRSWDs [73]. A recent EEG study on children with extensive brain damage and profound developmental disabilities showed that up to 100 % of them had persistent, severely impaired sleep-wake patterns, though very few had ocular lesions, thus demonstrating that the cerebral structures play a major role in sleep-wake regulation [77]. Cerebral palsy (CP) is defined as a group of nonprogressive disorders of movement and posture resulting in activity limitations that occur in the developing fetal or infant brain and affect 1.5–2.5 children per 1000 live births. About 20–50 % of children with CP have a cortical visual impairment, resulting in a free-running circadian rhythm [78]. Smith-Magenis syndrome (SMS) is a rare multisystemic disorder that occurs in 1:25,000 births. It is caused by a mutation or small deletion in a transcriptional regulator gene of the mammalian circadian

clock, i.e., RAI1 (retinoic acid induced) on chromosome 17p11.258, and is characterized by intellectual disability of varying degrees, short stature, a deep hoarse voice, obesity, scoliosis, distinctive facies (deep, close-set eyes, midfacial hypoplasia, and broad, square-shaped face), and peripheral neuropathy [79]. Maladaptive and disruptive behavior is typical of this syndrome and is associated with 24-h sleep disorder. Actigraphic data have revealed a total sleep time that is 1 or 2 h shorter than that in normal healthy controls and fragmented sleep starting from as early as 6 months and persisting throughout school age [80]. Many studies have found that an alteration in the circadian clock gene action results in inverted endogenous melatonin secretion, which thus peaks during daytime, in the vast majority of children with SMS [81]. Oral acebutolol administered alone in the early morning and combined with MLT in the evening has been used in an attempt to improve the sleep-wake rhythm in patients with SMS [82]. Angelman syndrome (AS) is a neurodevelopmental disorder that is characterized by mental retardation, seizures, gait ataxia, speech impairment, epilepsy, craniofacial abnormalities, and easily provoked laughter and is due to abnormalities in chromosome 15q11–q13. The prevalence of sleep problems associated with this syndrome is usually very high, with up to 90% subjects being affected [83]. Sleep problems mainly consist of difficulties in falling asleep and multiple awakenings. A lower level of MLT and a high prevalence of CRSWDs (irregular, free-running, and sleep phase delayed disorders) have been reported in AS, though open-label and placebo-controlled trials have shown that treatment with MLT supplementation yields a good response [84–86]. A possible explanation for this positive response is the lack of ubiquitin protein ligase E3A gene expression on the maternal chromosome 15q11–q13, which is reported in AS and is known to be implicated in the control and development of circadian rhythm [87]. This hypothesis is supported by another study in which a patient with Rett syndrome, an abnormality that affects the ubiquitin protein ligase E3A gene, N24SWD, markedly improved following MLT oral supplementation [88].

Although genetic and/or epigenetic abnormalities in sleep-wake circadian regulation may predispose children with NDD to CRSWDs, poor sleep hygiene, negative associations, and the lack of restrictions all contribute to the maintenance of sleep problems. The active collaboration of caregivers is essential to be able to adopt behavioral treatment strategies, such as creating a dark, quiet, non-stimulating environment and reducing the number of stimuli (such as electronic devices) [71]. A recent large clinical trial confirmed the efficacy of MLT as a means of treating sleep problems in children with NDDs, using doses ranging from 0.5 to 12 mg, which were found to reduce sleep latency and increase total sleep time [89].

Attention-Deficit Hyperactivity Disorders (ADHD)

About 25–50% of children and adolescents with attention-deficit hyperactivity disorder (ADHD) experience sleep problems, with objective data based on actigraphic recordings demonstrating an increase in sleep-onset latency associated with a

decreased amount of time spent asleep in such subjects [90]. According to the data in the literature, five sleep phenotypes may be identified in ADHD: a sleep phenotype characterized mainly by a hypoarousal state, resembling narcolepsy, which may be considered a "primary" form of ADHD; a second phenotype associated with a delayed sleep-onset latency and a higher risk of bipolar disorder; a third phenotype associated with sleep disordered breathing; a fourth phenotype related to restless legs syndrome and/or periodic limb movements, which may further extend the delays in the sleep phase disorder; and, lastly, a fifth phenotype related to epilepsy/or EEG interictal discharges [90]. We will discuss the second phenotype here. Sleep-onset delayed insomnia is the most common sleep disorder in children with ADHD. The onset of sleep delayed phase disorders may occur at as early as 3 years of age, with an accumulation of sleep deprivation over time. Children in this subgroup have a delayed DLMO associated with a significant delay in sleep latency when compared with ADHD children without insomnia [91]. Preliminary evidence from severe mood dysregulation-related disorders indicates that morning light therapy has a positive effect on depressive symptoms, circadian rhythms, inattention, and irritability [92]. It has been suggested that the core endophenotypic characteristic of pediatric bipolar sleep is a phase delayed circadian sleep-wake cycle rather than a reduced need for sleep per se (see below) [93]. Many studies have demonstrated the efficacy and safety of MLT in the treatment of insomnia in children with ADHD, with doses ranging between 3 and 6 mg [94]. MLT may, if required, be combined with light therapy, particularly in children that are at risk of developing bipolar disorder as the use of stimulants remains controversial in such subjects [90]. Stimulant medication does not appear to affect the core symptoms related to a lower vigilance state in children with sleep delayed insomnia. Furthermore, the use of stimulant medications may exacerbate insomnia in children with ADHD, thereby affecting circadian motor activity levels, as has been demonstrated by actigraphic analyses [95]. The authors of this review believe that the administration of long-acting medications may increase the risk of developing or worsening sleep-onset insomnia in children with ADHD [95]. A large placebo-controlled trial on ADHD studied the effects of 4-week MLT therapy on the sleep-onset latency and circadian phase, as assessed by means of the DLMO [96]. The results of that trial did not detect any improvement in ADHD symptoms or cognition at the end of the 4 weeks [96]. A follow-up study revealed that improvements in behavior and mood after long-term treatment (2–3 years) only occurred in those children still using melatonin, while discontinuation of MLT resulted in a relapse of sleep-onset insomnia [97]. In one study on adult ADHD patients [98], treatment with early morning bright light therapy improved ADHD symptoms after 3 weeks, with the positive effects appearing to occur more rapidly than following administration of MLT. Interestingly, the effects of both sensorimotor rhythm (SMR) and slow cortical potential (SCP) neurofeedback treatment of ADHD symptoms last longer than those induced by medication, possibly because they act by increasing sleep spindle density and normalizing sleep-onset insomnia, thereby resulting in vigilance stabilization. Although neurofeedback does not target the circadian phase delay directly, this effect is mediated by subcortical and cortical circuits that regulate sleep spindle production and sleep onset [99].

Mood Disorders

In view of the significant changes in sleep and circadian rhythms that occur during a person's lifespan, age may contribute to the heterogeneity in sleep-wake profiles linked to mood disorders. The severity of depressive symptoms is expected to be associated with a more pronounced phase delay during youth and later diagnosis of bipolar disorder, while a reduced sleep duration and consolidation and disorganization of circadian rhythms is expected in older age [100]. Indeed, it has been suggested that the restoration of normal circadian rhythms contributes to the remission of depression and prevention of relapses in young people with depressive symptoms. Actigraphic monitoring has been used to show that poor sleep is a hallmark of major depression during a stable depressive phase among young people (13–35 years old) [101]. A reduced need for sleep, together with elation, grandiosity, and racing thoughts, distinguishes mania and bipolar disorder from attention-deficit hyperactivity and other childhood psychiatric disorders. Children with manic bipolar I disorder typically experience a decreased need for sleep resembling that of adults, whereas many children who are bipolar, who exhibit part-day manic episodes (pediatric bipolar type IIA and type IIB), or who have chronic mixed conditions (pediatric bipolar type IIIA) do not [93]. Children with bipolar type IIA exhibit prominent diurnal cycles on most days (pediatric bipolar type IIA): initial morning depression and subsequent (typically late afternoon and/or evening) mania. They display disturbed sleep patterns, characterized by an evening acceleration and a significant delay in sleep onset, which may, or may not, be accompanied by a decreased need for sleep and difficulty in awakening for school; moreover, a decreased need for sleep has been observed in subjects with manic cycles lasting days (pediatric bipolar type I) or chronic mania [93]. It has been suggested that the main bipolar sleep defect is a heritable phase delay in the sleep-wake cycle resulting from mutations in SCN circadian clock genes, which interact with, but are independent of, evening or ongoing manic psychomotor accelerations [93]. Several clock genes, such as CRY1 and NPAS2, have been associated with affective disorders, with CLOCK and VIP being specifically linked to the mania-hypomania phenotype [102]. This hypothesis predicts (i) that most bipolar children and adolescents, whose afternoon and/or evening manic acceleration typically terminates overnight, with ultradian cycling (pediatric bipolar types IIA and IIB), will display delayed sleep onset but a low prevalence of decreased need for sleep; (ii) that the intrinsic sleep-onset phase delay, when coupled with bedtime and early morning manic psychomotor acceleration (hedonic or dysphoric), reduces the need for sleep; and (iii) that the reduced need for sleep is greatest among individuals whose manic cycles last longer than 1 day (pediatric bipolar type I) or among those with chronic mania (pediatric bipolar type IIIA). An increase in tobacco use was recently found among depressed young people with a delayed sleep phase and

short sleep duration [103]. To sum up, sleep-onset phase delays and delayed sleep phase syndromes that occur during euthymic or depressed states may be trait markers of bipolar spectrum illness [93].

Case Reports

Case Report 1: SDWPD

A female adolescent aged 17.5 years came to the sleep disorder outpatient service of the Neurocenter of Italian Switzerland because she had been suffering from sleep-onset difficulties since she was 3 years old. Her bedtime had become increasingly delayed in the last 3 years (sleep time: from 01.30 am to 7 am), and she complained of excessive daytime sleepiness, requiring a 3-h nap, and of school difficulties. She also reported fear and strong nausea at bedtime and usually fell asleep at around 5 am. At weekends she tended to sleep for more than 12 h. She suffered from lypothymic attacks and dizziness during daytime, which made her feel more irritable. DSWPD was confirmed by means of the MLT salivary test (DLMO after 00.30 am) and actigraphic recording (see Fig. 12.1). She was placed on therapy with long-acting MLT 2 mg at 8 pm, which led to the complete disappearance of the anxiety, lipothymic attacks, and dizziness; restored healthy sleep, from 9:30 pm to 9 am; and eliminated the diurnal hypersomnolence or napping. She now feels happy.

Case Report 2: Sleep-Onset Insomnia (First Suspected Diagnosis of SDWPD)

A male 14-year-old adolescent came to the sleep disorder outpatient service of the Neurocenter of Italian Switzerland because he had been suffering from sleep-onset difficulties for many years. His sleep problems had got worse in the last months after he had started therapy with long-acting methylphenidate following a diagnosis of ADHD, learning disabilities, anxiety disorder, and suspected mood disorders (pediatric bipolar disorders type IIA). His anxiety increased in the afternoon and evening after the onset of treatment. He reported that his bedtime was 10.00 pm. Sleep onset occurred 30 min later, though sometimes even after midnight, and he woke up at 7.00 am. He said he had difficulties in waking up in the morning. He had a history of motor tics, tonsillitis, and respiratory allergy, as well as familiarity for somnambulism and ADHD. A video-polysomnographic recoding revealed a very mild mixed-sleep apnea disorder, some periodic leg movements during sleep, and

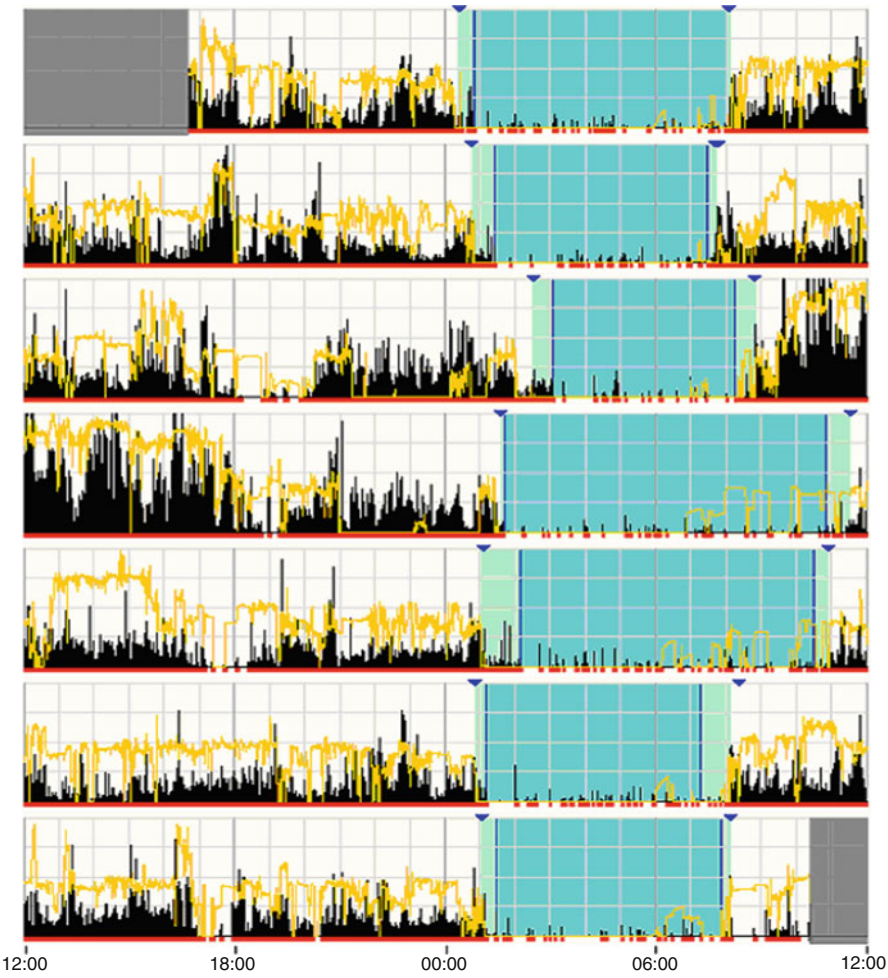

Fig. 12.1 Actigraphic recording of case report 2 (weekend fourth and fifth days)

increased sleep latency. A 1-week actigraphic recording demonstrated a tendency to fall asleep late (around 23:00 pm, with a mean sleep latency of one and a half hours), with no sleep fragmentations or diurnal nap (see Fig. 12.2). Blood examinations revealed a ferritin level of 54 mcgr/l. He was placed on therapy with long-acting MLT at 19.30, 2 mg, for 3 months, though with no benefit. The final diagnosis was sleep-onset insomnia with anxiety disorder exacerbated by stimulant therapy, which was subsequently replaced by a more appropriate therapy containing a mood stabilizer.

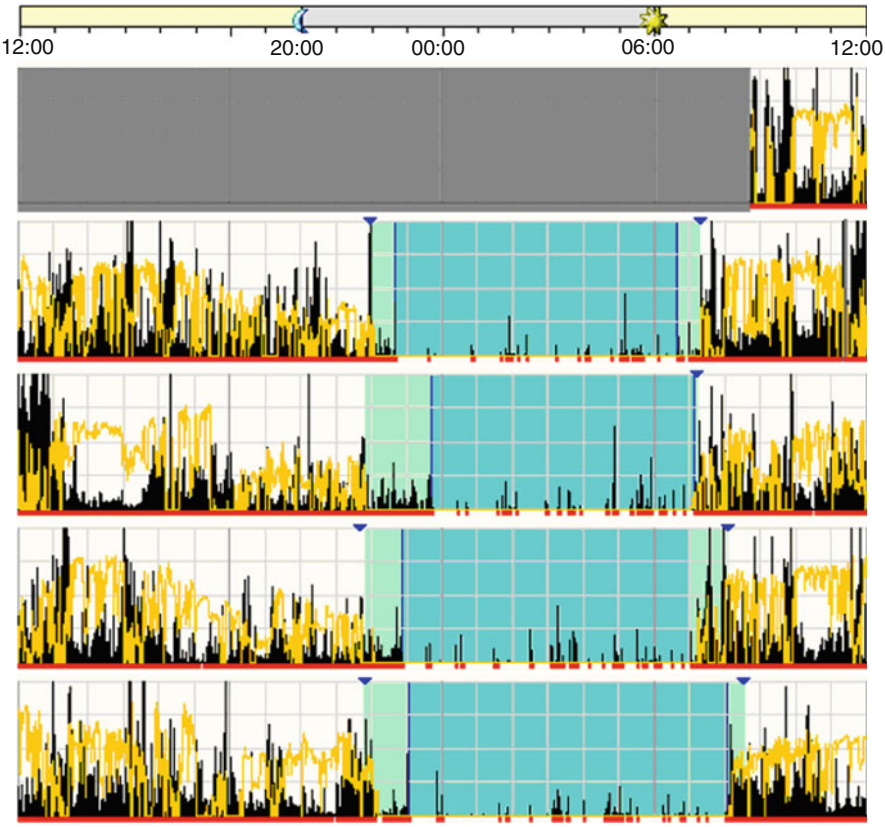

Fig. 12.2 An example of 4 days of actigraphic recording of case report 2

Conclusions

CRSWDs are an unrecognized cause of sleep loss in children that tend to persist over time unless adequately treated, particularly in view of ongoing changes in lifestyle and an increase in exposure to artificial light. The adverse effects of chronic sleep disorders on brain development in children often escape detection, with long-lasting sleep loss during critical developmental periods proving particularly harmful because it deprives young children of the environmental exposure required for healthy cognitive and motor development and consequently prevents them from achieving their full developmental potential. Persistent sleep difficulties may be associated with a number of health, economic, and emotional difficulties and raise the risk of suicide in sleep-deprived teenagers. Moreover, CRSWDs might contribute to the increased prevalence of cancer and cardiac and metabolic diseases that have been observed in recent times [2].

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