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Sleep, circadian rhythms, and delayed phase in adolescence

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Abstract

Sleep/wake timing shifts later in young humans during the second decade of life. In this review we describe sleep/wake patterns, changes in these patterns across adolescence, and evidence for the role of environmental, psychosocial, and biological factors underlying these changes. A two-process model incorporating circadian (Process C) and sleep/wake homeostatic (Process S) components is outlined. This model may help us to understand how developmental changes translate to shifted sleep/wake patterns. Delayed sleep phase syndrome (DSPS), which has a typical onset during the second decade of life, may be an extreme manifestation of homeostatic and circadian changes in adolescence. We describe symptoms, prevalence, and possible etiology of DSPS, as well as treatment approaches in adolescents.
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1. Introduction

This review describes changes to sleep/wake behavior during adolescent development and the contribution of the circadian and sleep/wake homeostatic systems to this changing behavior. We also review delayed sleep phase syndrome (DSPS), which may be an extreme manifestation of these changes or may be a distinct clinical entity. Last, we describe approaches to treat DSPS in adolescents. For the purpose of this review, we consider biological adolescence to span the second decade of life.

2. Developmental changes in sleep/wake (light/dark) patterns

Sleep/wake patterns of developing adolescents are often described in the context of a school year and have

been described separately for school (weekday) and non-school (weekend) days. Sleep timing is often quite different during school vacations. Describing sleep patterns during both school and vacation times provides a more comprehensive account of developmental sleep/wake behavior changes, yet few studies have examined vacation sleep patterns.

Table 1 summarizes adolescent self-reported sleep patterns derived from survey studies that reported weekend and weekday data during the school year. These data show that adolescents report going to bed later as they get older. Studies from such countries as Canada [1], Poland [2], Belgium [3], Australia [4], Finland [5], and Brazil [6] show similar trends. Investigators associate this age-related change in bedtime on school nights with a number of environmental factors, including reduced parental influence on bedtimes [7,8], increased homework [9], and extra-curricular activities, such as sports, musical groups, clubs, and service groups [10], or part-time work [7,10,11]. Other environmental, usually stimulating activities, that often affect bedtime

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Table 1

Mean self-reported school-year weekend and weekday sleep patterns from survey reports in the U.S

Reference	age/school grade	Weekday Bedtime[a]	Weekend Bedtime[a]	Weekday Rise Time[a]	Weekend Risetime[a]
Middle School Years (11-13 years old)					
Carskadon, 1990 [7]	11 years	2130 (2140)	2222 (2250)	0705 (0700)	0825 (0745)
NSF Poll 2006 [8]	Grade 6	2124	2231	0642	0853
Carskadon, 1990 [7]	12 years	2145 (2150)	2255 (2305)	0655 (0705)	0835 (0835)
NSF Poll 2006 [8]	Grade 7	2152	2305	0635	0912
Manber et al., 1995 [9]	middle school	2137	2311	0610	0847
Carskadon, 1990 [7]	13 year	2206 (2228)	2320 (2342)	0650 (0700)	0845 (0845)
NSF Poll 2006 [8]	Grade 8	2153	2326	0636	0921
Wolfson & Carskadon, 1998 [13]	13-14 years	2205	2354	0559	0922
High School Years (14-19 years old)					
O'Brien & Mindell, 2005 [12]	Grade 9	2238	2359		
NSF Poll 2006 [8]	Grade 9	2215	2353	0628	0954
Wolfson et al., 2003 [16]	13.8 - 19.9 years	2246	0017	0620	0940
Carskadon, 1990 [7]	14 years	2210 (2216)	2357 (0006)	0556 (0615)	0914 (0912)
Carskadon, 1990 [7]	15 years	2224 (2243)	0011 (0027)	0605 (0627)	0924 (0925)
Wolfson & Carskadon, 1998 [13]	15 years	2220	0006	0600	0940
O'Brien & Mindell, 2005 [12]	Grade 10	2307	0042		
NSF Poll 2006 [8]	Grade 10	2232	0003	0623	0952
Link & Ancoli-Israel, 1995 [15]	15-18 years	2244	0041	0555	0951
Manber et al., 1995 [9]	high school	2238	2356	0608	0915
Carskadon, 1990 [7]	16 years	2252 (2308)	0028 (0044)	0613 (0638)	0921 (0937)
Wolfson & Carskadon, 1998 [13]	16 years	2237	0030	0605	0946
O'Brien & Mindell, 2005 [12]	Grade 11	2313	0115		
NSF Poll 2006 [8]	Grade 11	2251	0025	0623	1006
Carskadon, 1990 [7]	17 years	2258 (2314)	0039 (0051)	0626 (0645)	0921 (0927)
Wolfson & Carskadon, 1998 [13]	17-19 years	2251	0049	0610	0932
O'Brien & Mindell, 2005 [12]	Grade 12	2324	0124		
NSF Poll 2006 [8]	Grade 12	2302	0045	0631	0951

[a] Values followed by parentheses indicate that authors computed means for boys and girls separately in the original report; the first value = mean time reported by girls; parenthetical value = mean time reported by boys.

include watching TV, playing video games, and using the computer [3,8].

Adolescents consistently report going to bed later on weekend nights compared to school nights (see Table 1). The difference between weekend and school-night bedtimes (*weekend bedtime delay*) in adolescents averages between 1 and 2 h [7–9,12–16], usually greater in the older than the younger adolescents.

Most school systems in the United States are organized so that high school students are required to report to school earlier than middle school students [8]. Rise time on school days reflects this pattern (see Table 1). Several reports note that girls rise significantly earlier than boys on school mornings [7–9,13,15]. Early rising for school is unwelcome and forced for most adolescents. For example, one survey study showed that 61% of a suburban high school student sample reported commonly being "too sleepy to get out of bed in the morning" [17]. A longitudinal study completed in Switzerland reported that about 63% of participants at the average age of 15 and 17 years reported being tired upon awakening [18]. A more recent telephone poll by the U.S. National Sleep Foundation reported that approximately 70% of middle school and high school students required an adult to wake them on school mornings [8].

Another consistent finding is that the reported rise times on weekend mornings are significantly later than those on school mornings, especially for older adolescents (see Table 1). Findings are inconsistent about whether or not boys and girls have different sleep patterns. For example, LaBerge and colleagues found sex difference in a group of 10–13 year olds, with girls sleeping later on weekends compared to boys [1]; however, in another study this difference did not emerge in a group of 13- to 19-year-old adolescents [13]. With an average school-day rise time between 0600 and 0700 h, the difference between weekday and weekend rise time (*weekend rise time delay*) averages about 1.5–3 h in 10–13 year olds and 3–4 h in high school students. One study marks this weekend sleep delay at almost 3 h in adolescents, defined as less than 21 years old [19].

The adolescent's social milieu changes from school months to vacation months. Most adolescents experience less constrained daily schedules during vacation, yet little research has focused on changes to sleep/wake patterns under this more unconstrained schedule.

Hansen and colleagues [20] studied sleep patterns of fourth-year high school students in August (before school started) and again in September (after school started). Sleep diary data showed that weekday bedtimes

in September averaged about 1.5 h earlier than in August. These data suggest that older adolescents report later bedtimes during school vacation compared to the school year.

We compared sleep patterns of a group of adolescents (9–16 years old) on self-selected sleep schedules during the summer ($n = 59$) to other adolescents during the school year ($n = 149$) [21]. Data were derived from daily verbal reports of bedtime and wake-up time via morning telephone messages over a week. Overall, adolescents reported later bedtimes in the summer (means = 2256, standard deviation (SD)=61 min) compared to during the school year (means = 2200, SD = 49 min); however, when subdivided into age groups (9–12 versus 13–16 years), the younger participants showed a 64-min difference between the school and summer vacation bedtimes while older participants showed a 32-min difference. Summer vacation wake-up times were also later (means = 0819, SD = 76 min) compared to school-year times (means = 0703, SD = 32 min). In this case, the average difference between school and summer vacation rise times was 91 min for the older participants and 60 min in the younger participants. (We note that the school year means are weekend and weekday sleep times combined.)

The less restrained daily schedule during vacation likely accounts for later sleep schedules, and changes to parental influence over sleep schedules may also influence these differences. Thus, parents may place less emphasis on a "good night's sleep" during the school vacation because academic performance is not necessarily emphasized. A similar idea has been proposed by Roenneberg and colleagues [19,22], who argue that an individual's chronotype, which is controlled in part by genetic factors, is estimated best using the midphase of sleep on "free" days or days without social constraints. Their data show a progressive delay of midphase of sleep from age 10 to 20 [22]. When schedules are not as constrained during the summer or on free days as during school days, the adolescent may be able to sleep when his or her body feels it needs to, doing so at a relatively late clock time. On the other hand, the summer (or free day) pattern does not necessarily reflect biological factors alone, since environmental and psychosocial factors differ in the summertime and may influence sleep patterns.

In summary, older adolescents tend to have later school-year bedtimes on both school and non-school nights compared to younger adolescents; reported wake-up times are later primarily on weekends for older adolescents compared to younger adolescents. Furthermore, sleep/wake patterns are later during the summer vacation compared to the school year, and the magnitude of the summer delay depends on the youngster's age. Changes in the circadian timing system and the homeostatic sleep system during adolescent develop-

ment provide some insight into these sleep/wake behavioral changes. We provide a general background of both systems and then discuss how these processes appear to change during adolescent development.

3. The circadian timing system

The circadian timing system provides temporal organization for regulatory mechanisms to facilitate adaptive behavior, such as feeding, reproduction, and sleep/wake cycles [23]. These coordinated temporal patterns, or circadian rhythms, are self-sustained and oscillate with a period of about 24 h. The internal mechanism (pacemaker) that organizes these rhythms in mammals has been localized to a small paired nucleus in the hypothalamus, the suprachiasmatic nucleus (SCN; [24]). Biological events or markers associated with these rhythms can be used to estimate circadian time or phase.

Melatonin is a hormone secreted by the human pineal gland that oscillates with a circadian rhythm. Levels of the hormone are nearly absent during the daytime, rise in the evening near one's usual bedtime, stay relatively constant during the nighttime, and decline near one's habitual wake-up time. Melatonin is suppressed by light [25], and recent studies show that even room light levels ($\sim$200–300 lux) can have a suppressive effect on human endogenous melatonin production [26–28]. The onset of melatonin secretion, also called the dim light melatonin onset (DLMO) phase, is a marker of the circadian timing system [29] and can be measured from saliva samples collected at $\sim$30-min intervals in dim light ($<$30 lux) [30]. Research laboratories often define DLMO phase as the time at which melatonin concentration rises above a designated threshold (e.g., 4 pg/mL for saliva and 10 pg/mL for plasma melatonin). The decline of melatonin, also called the dim light melatonin offset (DLMOff) phase, and the midpoint between DLMO and DLMOff are other phase markers of the circadian timing system derived from the melatonin rhythm. Other rhythms such as core body temperature have also been used to mark the circadian system; however, DLMO phase is currently thought to be the most reliable marker of phase [31,32].

The circadian timing system oscillates with an intrinsic period slightly different from 24 h but synchronizes (entrains) to the 24-h day in response to external timegivers, or zeitgebers. The primary synchronizing stimulus for the circadian timing system is the daily variation of daylight and darkness [33]. The circadian system is sensitive to light, especially during the nighttime, which for humans is the usual sleep period. A phase response curve (PRC) describes how light input is able to shift circadian rhythms earlier or later in time. Fig. 1 shows a PRC to light for adult humans, constructed by Khalsa and colleagues (2003) [34]. These researchers measured circadian phase by way of plasma melatonin before
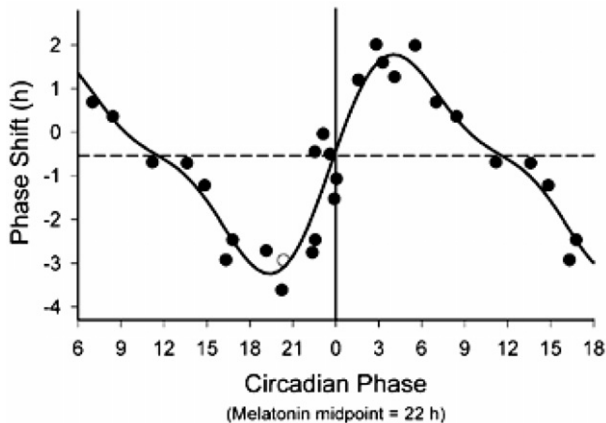
Fig. 1. Figure and figure legend are reprinted with permission from Khalsa et al. (2003) [34]. Phase advances (positive values) and delays (negative values) are plotted against the timing of the centre of the light exposure relative to the melatonin midpoint on the pre-stimulus constant routine (defined to be 22 h), with the core body temperature minimum assumed to occur 2 h later at 0 h. Data points from circadian phases 6–8 are double plotted. The filled circles represent data from plasma melatonin, and the open circle represents data from salivary melatonin in subject 18K8 from whom blood samples were not acquired. The solid curve is a dual harmonic function fitted through all of the data points. The horizontal dashed line represents the anticipated 0.54 h average delay drift of the pacemaker between the pre- and post-stimulus phase assessments.

and after a 6.7-h bright light stimulus (~10,000 lux) timed at various times of day. The x-axis represents the timing of the light stimulus. The melatonin midpoint phase is defined as 22 h and core body temperature minimum phase is estimated at 0 h. (The midpoint of melatonin secretion usually occurs just after the midpoint of a regular sleep episode in adult humans sleeping 8 h [35]). Responses to the bright light stimulus are shown on the y-axis as a phase shift.

In general, the human system responds in a systematic and predictable manner: light during the end of the daytime and beginning of the nighttime (before the estimated core body temperature minimum) shifts circadian rhythms later (phase delay); bright light during the end of the nighttime or at the beginning of the daytime (after the estimated core body temperature minimum) shifts circadian rhythms earlier (phase advance) [34,36]. (It is important to note that a PRC to light for adolescent humans has not yet been described and may differ from the adult PRC.) This flexibility of the system allows animals, including humans, to entrain to the 24-h solar day. The entrainment process differs among individuals because some manifest an oscillatory period shorter than 24 h and some longer than 24 h. The intrinsic period of healthy human adolescents averages 24.27 h [37]. The *majority* of humans entrain by a small phase advance each day and a small-proportion entrain by a small phase delay [38]. According to the adult human light PRC, morning exposure to light will facili-

tate entrainment in humans who have an intrinsic period greater than 24 h, whereas evening light exposure will entrain individuals with an intrinsic period shorter than 24 h.

The circadian clock is one part of the system that coordinates sleep/wake behavior. Homeostatic sleep/wake processes, which are controlled by brain mechanisms that are not entirely understood, also play a role in the regulation of sleep and wake.

4. The homeostatic sleep system

The homeostatic sleep/wake system is thought to be relatively independent of circadian timing. A simple way to characterize the process is that sleep pressure increases the longer one is awake and dissipates as one sleeps. Slow wave sleep (SWS, stages 3 and 4) and electroencephalographic (EEG) slow wave activity (SWA, power in the 0.75–4.5 Hz range) have been used as physiological markers for "sleep pressure." Thus, SWA is high at the beginning of the nocturnal sleep episode when sleep pressure is greatest, and SWA shows an exponential decline across the night's successive non-rapid eye movement (NREM) episodes [39–41]. Furthermore, as wake is extended, SWA increases during subsequent sleep episodes, proportional to prior wake duration [41–43]. The homeostatic process is also reflected in changes in the theta and alpha components of the waking EEG as a function of sleep and wake durations [44].

Models describing the interaction between sleep/wake homeostasis and the circadian timing system are used to describe sleep/wake regulation. Borbély [39] was the first to describe a model to identify the interaction between these two systems in the "Two Process Model of Sleep Regulation," a model that was later refined by Borbély and others [40,45–47]. He called the circadian component Process C and the homeostatic sleep/wake component Process S. A schematic of the two interacting processes is shown in Fig. 2. Sleep occurs when Process S reaches an upper threshold and wake occurs when Process S is below a lower threshold. Process C controls the thresholds and has been termed the "somnostat," drawing an analogy to a thermostat [40]. According to this model, sleep is initiated at one circadian phase and wake is initiated at a different circadian phase. Accordingly, the frequency of the sleep/wake cycle depends on the distance between the two thresholds or phases.

Another variation of the model [48] casts the two systems in opposition to one another for describing sleep/wake regulation. In this model, a circadian (clock-dependent) alerting process opposes a wake-dependent sleep-promoting process to maintain wakefulness across the daytime [48]. Dijk and Czeisler [49] propose a similar opponent process to describe the maintenance
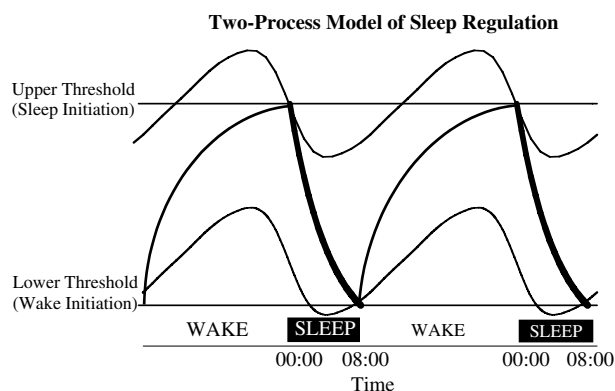
Two-Process Model of Sleep Regulation

Fig. 2. A schematic of the Two-Process Model of Sleep Regulation adapted from Daan and colleagues (1984) [40]. Bold lines represent Process S: sleep pressure accumulates during waking and dissipates during sleep. Process C regulates the timing of sleep so that when sleep pressure surpasses an upper threshold, sleep is initiated and, when sleep pressure falls below a lower threshold, wake is initiated. Process S and Process C align so that sleep is timed from midnight to 0800 h, a typical adult sleep schedule.

of nocturnal sleep in humans. As sleep pressure dissipates across the night, sleep is protected by the circadian timing system, which achieves maximal levels of sleep propensity during the second half of the habitual sleep period.

Our laboratory has used the two-process model as a framework to study adolescent sleep/wake regulation [50,51]. We review studies that have investigated pubertal changes of the circadian and homeostatic sleep systems. These data may provide us with additional insight into the observed sleep/wake behavioral changes of adolescents.

5. Circadian timing and sleep/wake homeostasis during adolescent development

5.1. Process C

The circadian timing system undergoes developmental changes during adolescence. Although sleep/wake patterns have long been known to delay in adolescents, behavioral factors (e.g., social and scholastic obligations) were assumed to be entirely responsible. The notion that circadian timing may change was noted by Carskadon and colleagues in a study of circadian phase preference in young adolescents [52]. Phase preference, or morningness/eveningness is a behavioral construct related to the time of day best suited for waking behavior. Carskadon and colleagues found that phase preference was correlated with self-assessed pubertal development, especially in girls [52]. Subsequent studies confirmed that more mature and older adolescents prefer later timing of activities than younger, less mature adolescents [22,53]. Adolescents with evening and morning phase preference also show differences in patterns of

sleep/wake; those with evening preference report later sleep schedules than those with morning phase preference [52,53]. Adult studies show that the temporal alignment between sleep and circadian timing differs between morning and evening types; morning types sleep at a *later* circadian phase compared to evening types [54,55]. These studies provide some evidence that sleep regulation mechanisms may differ between phase preference types. Furthermore, these studies leave open the possibility that the adolescent phase preference shift toward eveningness is indicative of underlying changes to mechanisms regulating sleep and wake during pubertal development. Indeed, laboratory studies provide evidence to suggest that the circadian timing system changes during puberty: pubertal stage is positively associated with later circadian timing when sleep (dark) is held fixed [51,56].

One of the themes of our laboratory's research program is to understand the factors that contribute to the developmental circadian phase delay during adolescence. We have hypothesized that changes in light sensitivity, the endogenous circadian period, and/or the homeostatic sleep system may play a role in the developmental circadian and sleep behavior changes.

Our studies have investigated these hypotheses by studying adolescents at different levels of maturity, indexed by Tanner stage. Tanner stage is a rating of pubertal development and based on secondary sexual characteristics, including pubic hair growth and distribution, stage of genital development for boys, and stage of breast development for girls [57].

The human light PRC (Fig. 1) predicts the circadian timing system's response to light; however, the amplitude of this response may differ between individuals and during development. One possible explanation for the adolescent phase delay is a change in light sensitivity. Preliminary results do not support this hypothesis; evening (2300–0000 h) light sensitivity and morning (0300–0400 h) light sensitivity do not differ between Tanner 1/2 (pre- to early pubertal) and Tanner 3/4/5 (mid- to post-pubertal) participants. Both early pubertal and mid-/late pubertal youngsters showed similar melatonin suppression responses and, thus, light sensitivity as a result of 150 and 500 lux of white broad spectrum light [37].

Developmental differences may not have manifested because of the amount of variability in the melatonin suppression response. These individual differences may be due to differences in daytime light exposure between individuals. More bright light exposure during the daytime decreases the response to a subsequent light exposure as assessed by melatonin suppression [58]. Furthermore, in this study, time in bed was held fixed to 10 h per night for both Tanner groups, which is another possible explanation for the lack of developmental differences in melatonin suppression. Ten hours is not the typical amount of time spent in bed, especially

for the older group, and recent work shows that less total sleep time may attenuate the phase shifting response [59,60]. In other words, if adolescents are studied on their "natural" schedules, it is possible that older adolescent may show a weaker response to light compared to younger adolescents. Dampening the response to the phase advance portion of the light PRC may hinder synchronization.

Additional research is needed to understand responses to light during adolescent development. Furthermore, given that the circadian timing system is most sensitive to short-wavelength light (~460 nm) [61,62], further investigation of sensitivity to defined light bandwidths may help us understand how the circadian timing system and its sensitivity to external zeitgebers may or may not change during adolescence.

A developmental delay of circadian phase during adolescence may also be related to a lengthening of the intrinsic period of the circadian clock, that is, a longer "internal day length." In a preliminary analysis, Carskadon and colleagues measured period in 27 adolescents aged 9–15 years, showing an average of 24.27 h [63]. The sample size was not adequate to test differences across Tanner stage; however, intrinsic period was significantly longer than the average in adults, as measured by others [51,63–65]. Reports show that entrained circadian phase in young adults was positively associated with circadian period; a later circadian phase was related to a longer period [66,67]. Furthermore, recent work showed that a longer intrinsic period was associated with a circadian timing system that more readily phase delayed in constant conditions [68]. Preliminary data from adolescents and drawing parallels in the adult literature leaves open the potential that a longer period during adolescence could lead to a developmental circadian delay. This hypothesis still needs to be tested with more participants across pubertal development.

5.2. Process S

Recent modeling work of Jenni and colleagues [69] provides data to support developmental changes to Process S. Using model simulation techniques of SWA, results showed a slower accumulation of Process S during wake in mature adolescents (Tanner 5) compared to pre- or early pubertal adolescents (Tanner 1 and 2) under conditions of sleep deprivation. Furthermore, the upper threshold (asymptote) for Tanner 5 participants was higher compared to Tanner 1 and 2 participants; the difference between the thresholds was larger for the Tanner 5 youngsters compared to Tanner 1 and 2. Further support for the slowing of Process S comes from sleep latency data, which shows Tanner 1 participants falling asleep faster in the evening (2230 and 0030 test points) compared to Tanner 5 participants

[70]. In other words, sleep pressure may build at a faster rate for the pre-pubertal adolescent, allowing sleep onset to occur more rapidly than for the mature adolescent. By contrast, the dissipation of Process S during sleep does not differ between pre-/early pubertal and mature adolescents [71–73].

In summary, evidence to date supports hypotheses that circadian mechanisms change across adolescent development, including a change toward evening circadian phase preference and later circadian phase. Furthermore, adolescents may tend to have a longer intrinsic period compared to adults. Slower accumulation of homeostatic sleep pressure during puberty also permits the older adolescent to stay awake longer and, thus, delay the sleep/wake (dark/light) cycle. Therefore, in addition to environmental factors, underlying changes in the circadian and sleep systems accompanying pubertal development may also be associated with later sleep/wake schedules often observed in adolescents. Puberty is associated with enormous change to the neuroendocrine milieu. To date, however, it is unclear how these changes interact with specific sleep regulation mechanisms [74].

6. Delayed sleep phase syndrome (DSPS)

The developmental changes in the circadian and sleep systems we have described may be exaggerated in adolescents who receive a diagnosis of delayed sleep phase syndrome (DSPS). DSPS is a disorder with a typical onset in the second decade of life or earlier [75]. Weitzman, Czeisler, and colleagues [76,77] first described delayed sleep phase insomnia as a distinct syndrome characterized by a cluster of features including a chronic inability to fall asleep and wake at a desired clock time, consistency in reported sleep times at later hours than other individuals, and otherwise normal sleep when measured by all-night polysomnography if the delayed schedule is allowed. An important characteristic of the syndrome is that patients are able to initiate and maintain sleep on their normal delayed schedule; difficulties manifest only when they attempt to synchronize their sleep schedule with requirements of normal everyday schedules of society. As a result, patients with DSPS are locked into a sleep schedule that is out of phase with usual work and school requirements. Other consequences of DSPS include sleep loss, disturbed sleep, excessive daytime sleepiness, and impaired waking function.

The 2005 International Classification of Sleep Disorders (ICSD)-Revised lists DSPS (now called Delayed Sleep Phase Disorder) within a set of Circadian Rhythm Sleep Disorders and provides three general criteria for a circadian rhythm disorder: (1) a persistent or recurrent pattern of sleep disturbances resulting from a misalignment of endogenous rhythm and external factors that

affect the timing or duration of sleep; (2) sleep disruption that leads to insomnia and/or excessive daytime sleepiness; and (3) impaired social, occupational, or other spheres of functioning related to the sleep disturbance. The ICSD notes that objective findings typically show a delay demonstrated by diary and actigraphy of sleep onset until 0100–0600 h, with wake-up time in late morning or early afternoon, especially on weekends and vacations; normal sleep from all-night polysomnography on the delayed schedule and prolonged sleep latency on a conventional schedule; measures of circadian phase (e.g., temperature recording or DLMO) that indicate a phase delay; scores on a morningness/eveningness (phase preference) questionnaire in the definite evening type range. Differential diagnosis issues include the importance of distinguishing DSPS, particularly in adolescents, from ''normal'' sleep patterns where a delayed schedule is maintained without distress or impaired functioning. Social and behavioral factors, such as late evening activities, school avoidance, and social or family dysfunction, may have a role in the development and maintenance of a syndromic delay. In addition, differentiation of DSPS from other insomnias rests on the finding that sleep initiation and maintenance are normal when the patient is allowed to sleep on his or her preferred schedule. Finally, the excessive daytime sleepiness in these patients occurs on mornings on which they must arise earlier than preferred; sleepiness abates if the preferred sleep schedule is allowed.

Prevalence estimates of DSPS range widely. The 1997 edition of the ICSD [78], estimated that 5–10% of patients with insomnia complaints seen in sleep clinics have DSPS. The 2005 ICSD-Revised [79] places this figure at 10%. Other reports based on questionnaires, telephone sampling, or mixed subjective and objective measures estimate the prevalence of DSPS in the general population anywhere between 0.13% and 3.1% [80]. A recent study, based on interviews structured to question Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV) criteria in 1124 European adolescents aged 15–18 years, reported a relatively low rate (0.4%) of adolescents with some circadian disorder [81]. The rate was 0.2% in a companion sample of young adults, ages 19–24 years. The authors noted that a larger number of adolescents reported some indicators of circadian rhythm disorders, such as differences between real and desired sleep schedule, extra sleep on days off, and difficulties getting up in the morning, although they did not report negative daytime consequences requisite for DSPS classification. Furthermore, this study was completed in Europe, where later school start times (0800–0830 h) than in many areas of the United States may better fit the normally delaying patterns of adolescence and involve less distress related to poor sleep. The prevalence rate for at least one symptom of insomnia in the adolescent sample was 30%, and the most commonly reported symptom was non-restorative sleep, followed by difficulties in initiating sleep.

DSPS is associated with a wide range of problems, including inability to work or attend school, which can lead to job loss, truancy, school failure [75,77,82], daytime sleepiness, social difficulties, and depressed mood [75,83]. Thorpy and colleagues [75] reported more than half of adolescent DSPS patients in their study had features of depression as measured by the Beck Depression Index (BDI), Minnesota Multiphasic Personality Inventory (MMPI), or psychological evaluation; 6 of the 22 patients had prior treatment for depression. Ferber [84] suggested that adolescent DSPS patients might include some who are clinically depressed and resistant to treatment and others who are cooperative to treatment and not depressed. The direction of effects for these affective disorders is not clear. Alcohol, drug, and substance use and abuse may also occur.

Original speculations regarding the etiology of DSPS included abnormalities of the circadian timing system, such as long intrinsic period or a weak phase advance portion of the light PRC [76,77]. Subsequent work has expanded possible mechanisms to include the sleep homeostatic system, systems coordinating circadian and sleep processes, behavior, psychological traits and features, genetic processes, and combined effects. In addition to the hallmark delays of sleep onset and offset, patients also manifest delayed timing of melatonin secretory patterns and core body temperature nadir [85,86]. A recent study by Aoki and colleagues [87] reported increased suppression of melatonin to light exposure in DSPS patients versus controls; they suggest that hypersensitivity to evening light may be a precipitating or maintaining factor for the phase delay in DSPS. Ozaki and colleagues [86] reported a longer interval between body temperature nadir and sleep offset in DSPS patients compared to controls as well as longer sleep episodes, findings since replicated in two studies [88,89]. Ozaki and colleagues [86] suggested that the inability of DSPS patients to phase advance normally might result from not being exposed to the advance portion of their light PRC due to their elongated sleep episodes. Of note is that the interval between body temperature nadir and sleep offset is shorter in normal controls with an evening preference [54,55] but longer in DSPS patients, suggesting a discontinuity along the morningness/eveningness dimension. In any case, the interface between circadian and homeostatic processes appears to be disturbed or irregular in DSPS patients.

Another line of experimental investigation implicates deficits in sleep/wake homeostasis in the etiology of DSPS. Uchiyama and colleagues [90], for example, studied DSPS patients and healthy controls using a constant routine followed by an ultra-short sleep/wake protocol. Results showed reduced sleep in patients versus controls following sleep deprivation. These researchers

suggested that DSPS patients may have poor ability to compensate for lost sleep and, thus, have difficulty falling asleep even when they wake early or have shortened sleep. Watanabe and colleagues [89] also reported difference between DSPS patients and controls on several polysomnographic sleep variables, including SWS, further indicating involvement of the homeostatic system.

These findings indicate that DSPS may involve abnormalities of the circadian timing system or the sleep/wake homeostatic process. Circadian period, phase, and entrainment mechanisms, as well as the capacity of the sleep homeostat have all been implicated in the etiology of this disorder. Because this disorder has the highest prevalence during adolescence and school performance is often compromised, the issue of effective treatment takes on added importance.

Three techniques are typically used to treat DSPS: chronotherapy, phototherapy, and exogenous melatonin administration. We note, however, that few studies have tested these treatments for DSPS in adolescents. The first treatment proposed for DSPS was chronotherapy, which requires the patient to delay bedtime and wake-up time by 3 h per day until the desired sleep schedule is reached. At this point, the patient is advised to maintain the desired sleep/wake schedule seven days per week [77].

Bright light therapy, or phototherapy, is another technique used to treat DSPS. Light timed at the end of the patient's night over consecutive days phase advances the circadian timing system. Because the timing of light administration is critical for the efficacy of phototherapy, measuring initial circadian phase in constant conditions is necessary. Using the light PRC as a guide, light is then timed relative to the individual's circadian phase. Light intensity appears to phase advance the circadian timing system in a dose–response manner; thus, brighter light (~9500 lux) induces greater phase shifts in comparison to normal indoor lighting (~180 lux) [91]. Unfortunately, as Wyatt [80] notes, there is no "duration" response curve; the optimal number of hours and consecutive days of light exposure has not been determined.

Exogenous melatonin administration is another proposed treatment for DSPS. Melatonin is thought to have both a chronobiotic (phase shifting) and soporific (sleep-inducing) effect on humans. Melatonin administration must be timed relative to circadian phase as Lewy's [92] melatonin PRC demonstrates; melatonin administered approximately 1–3 h before DLMO phase induces a phase advance shift. Studies show a phase shift in the advance direction in adult DSPS patients using exogenous melatonin administration (0.3–5.0 mg) [93–95].

Sedative effects of exogenous melatonin are reliably observed in adults during the late morning to early evening hours when circulating endogenous melatonin levels are low [96–105]. By contrast, if melatonin is administered when circulating levels of the hormone are above the basal daytime levels, the sleep-promoting influence of the hormone is attenuated or absent [106–109]. Therefore, DSPS patients may benefit from the sedative effects of melatonin administered a few hours before DLMO phase (when circulating melatonin levels are low) when attempting to phase advance the circadian timing system.

7. Conclusions

Developmental delays in sleep/wake behavior across adolescence are associated with extrinsic and intrinsic factors. Investigations of circadian timing mechanisms and homeostatic sleep processes may provide insights into biological underpinnings of behavioral changes. Future research is needed to identify whether DSPS is an exaggeration of a typical developmental delay or whether the pathophysiology of DSPS has other pathways. Furthermore, efficacy studies of chronotherapy, phototherapy, and exogenous melatonin treatments of DSPS in adolescents are needed.

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