Chapter 6
Delayed Sleep Phase Syndrome in Adolescents

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Introduction

Delayed sleep phase syndrome (DSPS) is present to some degree in most if not all adolescents. It is thought to be a normal biological developmental phase. Weitzman et al. first described DSPS in 1981 [1], and Carskadon et al. in 1993 [2] first linked it to the biological process of puberty. Its mean age of onset is 15.4 years [3].

The International Classification of Sleep Disorders describes DSPS as a disorder in which the major sleep episode is delayed in relation to the desired clock time, resulting in complaints of sleep onset insomnia and/or difficulty in awakening at the desired time. Symptoms must be present for at least 1 month, and other explanations to account for excessive daytime sleepiness must be excluded [4]. This chapter will briefly summarize basic science regarding circadian rhythm disorders, review clinical research regarding DSPS, and discuss treatment options as well as hope for future directions.

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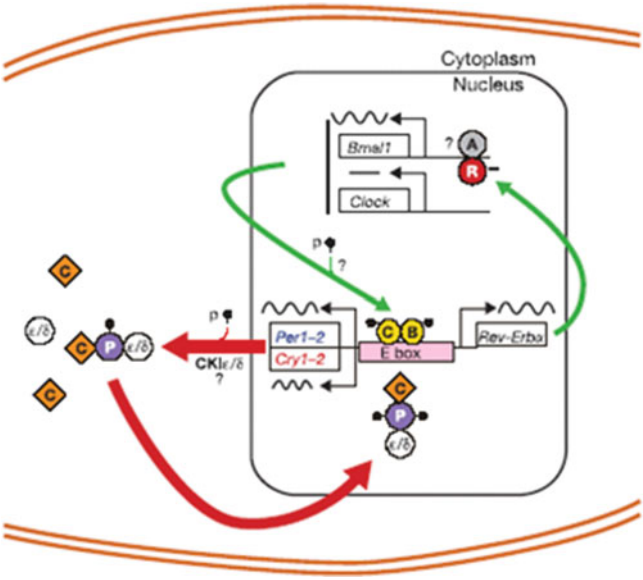

Fig. 6.1 Mammalian circadian clockwork model (Reproduced with permission of Macmillan Publishers Ltd from Reppert SM, Weaver DR. Coordination of circadian timing in mammals. Nature 29 August 2002; 418:035–941)

Review of Basic Science Surrounding Circadian Rhythm Control

Light is the most powerful entraining agent of the circadian system. Retinal ganglion cells mediate the effects of light to the suprachiasmatic nucleus (SCN) in the hypothalamus through the chemical mediator melanopsin. Activated by melanopsin, the SCN increases its uptake of glucose, leading to the expression of genes including *per*, *clock*, and *tim*. Cytochromes in the cells of the SCN also play a role in the expression of *per*, *clock*, and *tim*. Oscillations generated by rhythms in gene and protein expression create long feedback loops (Fig. 6.1). These long feedback loops ultimately regulate the release of hormones such as melatonin in the pineal gland and numerous peripheral circadian rhythms of the body, including thyroid stimulating hormone (TSH) release, cortisol secretion, and core body temperature control [5].

These create the circadian rhythm known as process C. The two-process model proposed by Borbely in 1982 describes a model where process C is affected by sleep homeostasis process, also known as process S [6]. Process S describes the physiology that sleep propensity increases as duration of wakefulness accumulates and dissipates during sleep (Fig. 6.2). Interaction of process S and process C leads to the manifest sleep–wake cycle.

Research regarding sex differences in circadian timing has yielded variable findings. A recent study comparing young adults did show differences between the sexes, with women having earlier timing of the circadian rhythm phases of melatonin secretion and

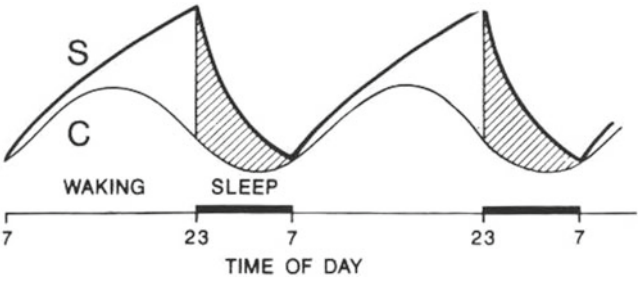

Fig. 6.2 A two-process model of sleep regulation showing that DSPS may involve problems related to the homeostatic regulation of sleep (Reproduced with permission from Borbely AA. A two-process model of sleep regulation. Human Neurobiology 1982 Oct; 9(3):195–204)

core body temperature related to men, despite similar actual sleep–wake times [7]. Further research in this area may help us better understand the pathophysiology of DSPS in adolescent girls.

Delayed Sleep Phase Syndrome

Clinical Research

Teens have an increased incidence of circadian rhythm disorders, particularly DSPS. The incidence of DSPS in teens is 7% [8], ten times greater than that of middle-aged adults [9]. Contrary to popular belief, Carskadon has revealed that there is a physiologic imperative to delayed sleep seen in teens in general, and more strikingly in teens with DSPS. They have delayed release of melatonin, and this biologic imperative seen in DSPS contrasts with conventional wisdom that rationalizes teen sleep patterns as simply the consequence of social pressures [10]. Others have suggested that people with DSPS have an increased sensitivity to evening light, which may also influence their circadian rhythm [11].

Research has also revealed alterations in sleep homeostasis process in teens with DSPS. In one study, patients with DSPS did not exhibit recovery sleep during the subjective day despite sleep deprivation. The authors suggest therefore that DSPS may involve problems related to the homeostatic regulation of sleep after sleep deprivation [12]. Development of DSPS may therefore be an interplay of biological changes to both process C and process S in the adolescent population.

Sequelae of Delayed Sleep Phase Syndrome

Regular sleep deprivation related to the truncation of the normal sleep period is seen frequently in adolescents with DSPS. The impact of this includes daytime

sleepiness, deficits in cognitive functioning, difficulty with mood regulation, and increased propensity for accidents [13]. Tardiness to school and academic difficulties, especially in classes in the early part of the day, are common concerns. Eveningness has also been associated with increased trends toward substance use, which for adolescent girls can also be influenced by age of menarche [14]. These impacts should all be considered in the evaluation and treatment of teens with this disorder.

Clinical Evaluation

Patients with DSPS can often present complaining of an inability to fall asleep. This can be differentiated from sleep onset insomnia by procuring additional history, including whether the patient is able to sleep later in the morning if given the opportunity (uncommon in psychophysiological insomnia), and what the patient's sleep patterns are like on vacation or weekends. DSPS patients generally have less sleepiness if they are allowed to have a delayed schedule (as on vacation), whereas abnormal sleep patterns and fatigue persist with those patients with insomnia. Sleep logs are a useful subjective measure of the overall sleep pattern and can be instructive in demonstrating these patterns to the patient. Actigraphy is an excellent objective measure [15]. Guidelines for the clinical use of actigraphy in evaluation of circadian rhythm disorders including DSPS are available [16]. Actigraphy is especially useful when sleep logs are not completed or unreliable. The morningness eveningness questionnaire (MEQ) measures a person's biologic activity tendencies within the day span, and can be useful as a supportive clinical tool [17].

DSPS Case History

Erica is a 15-year-old female who presents with a several year history of difficulty falling asleep. Her parents complain that they have difficulty walking her in the morning. In fact, over the past 5 months she has missed 35 days of school because her parents were physically unable to help her out of bed. Truancy officers are threatening remedial action. 24-h history reveals that she goes to bed at 11 PM. She often does not fall asleep until between 1 AM and 4 AM (Fig. 6.3). She denies feeling anxious while lying in bed. She does not have leg restlessness nor does she complain of pain anywhere in her body preventing sleep onset. Once asleep she remains so without arousals. Her parents begin calling her at 7 AM. After several calls, they will try and rouse her from bed physically. Often they are unable to awaken her. On weekends, holidays and days she does not go to school, she awakens between noon and 2 PM. During summer vacation when she sleeps ad lib, she does not complain of excessive daytime sleepiness. During the school year, she shares that she falls asleep in her first three classes most days.

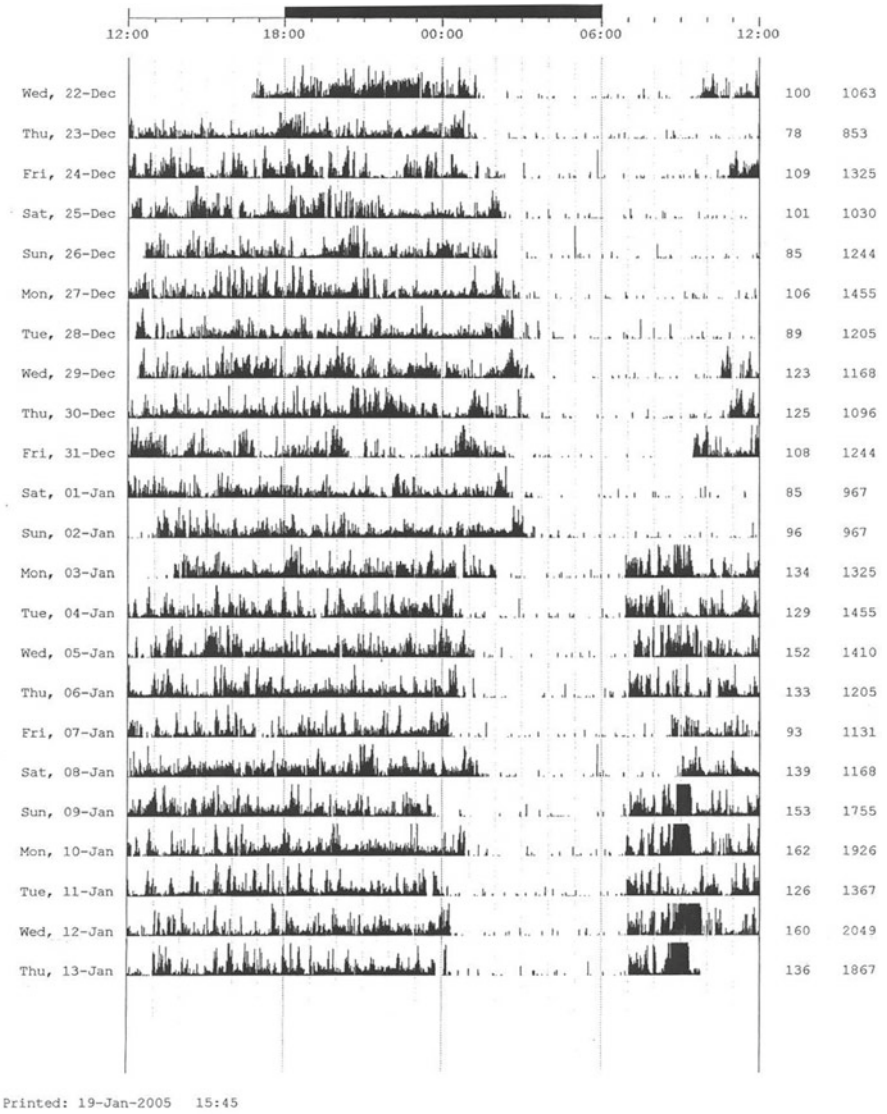

Fig. 6.3 Actigraphy showing the subject's delayed sleep phase

Treatment

Treatment of circadian rhythm disorders falls into three categories: phototherapy, chronotherapy, and pharmacotherapy. The motivation of the teen should be assessed as regular use of the interventions discussed next requires discipline. The teen must be involved in the implementation. If resistance is encountered, searching for an

underlying cause such as depression should be pursued. If depression is present, treating it simultaneously is necessary [18].

Timed light exposure or "phototherapy" involves increasing morning light and decreasing evening light [19]. In North America, increasing morning light may mean using a "light box" 2,500 lx between 6 and 9 AM has been shown to advance sleep as measured by changes in core temperature and improved morning alertness on multiple sleep latency tests. *Ultraviolet* light should be filtered. Patients may also benefit from avoidance of exposure to bright light in the evening [19, 20]. This can include avoidance of artificial sources of light such as television and computer screens.

Rescheduling treatment, known as "chronotherapy," involves the timing of wakefulness and sleep to minimize excessive daytime sleepiness. A general review of sleep hygiene is recommended. Specifically, wake time on the weekends should not be more than 2 h later than wake time during the weekdays. Daytime napping should be avoided.

Standard chronotherapy involves phase advancement. To implement this, the wake time and bedtime are made 15 min earlier each day until the target wake time is achieved [21]. Rarely, physicians promote phase delay [21, 22]. Progressive phase delay involves delaying the bedtime and wake time 2–3 h each 24 h period until the target sleep onset and wake times are achieved. Phase delay is generally reserved for the more severely DSPS patients as it is more difficult to implement with typical daytime responsibilities. Unfortunately, chronotherapy alone often fails [23].

The physician can act as an important advocate for teens with DSPS. Standard high school early morning start times are not in alignment with the physiologic sleep/wake patterns of teens in general and are grossly incompatible and may be academically devastating for teens with DSPS. Writing a letter for a 9 AM school start time is not unreasonable.

Pharmacotherapy is limited to melatonin. Several studies have shown that melatonin advances the sleep phase of patients with DSPS [24–26]. In early studies, 5 mg of melatonin were given 5 h before the mean group sleep onset time. The majority of patients reported a small advance in their sleep phase [27]. Recent studies have revealed that small doses (0.3 mg) of melatonin were as effective as larger doses and timing 6.5 h before dim light melatonin onset (DLMO) provided the best response [28]. The National Sleep Foundation has warned against using melatonin in patients with immune disorders and lymphoproliferative disorders and patients who take corticosteroids or other immunosuppressants [4]. Melatonin is not approved by the Food and Drug Administration (FDA) in the United States [29]. There is not enough evidence to support the use of sedative hypnotics in treatment of DSPS. There is also no evidence to support the use of stimulant medication to promote alertness in patients with DSPS [30]. It must be admitted that many teens are not successful in the implementation of these just described interventions. There is known heterogeneity of genetic mutations manifesting as DSPS. This includes the 4-repeat allele of the per gene3 [31], a gene encoding arylalkylamine (serotonin) N-acetyltransferase (AA-NAT) and HLA-DR1 [32, 33]. It is likely that some mutations are more amenable to treatment than others. Rather than blaming the patient, this should lead the physician to recommend adaptation of the external environment. One strategy is the integration of school

officials and truancy officers in the creation of a plan that helps the teen to graduate. This may mean advocating for evening classes with credits that apply to graduation.

Future Directions

The field needs to improve the objective verification of this diagnosis instead of relying only on self-reported information. This could be done using DLMO serum or salivary assays. This will allow differentiation of circadian rhythm disorders from chronic insomnia [34]. Exogenous melatonin is only effective when given before DLMO. An easy to use assay would make diagnosis more accurate and treatment more effective. Currently, these assays are only available for research purposes in Europe. A clinically available application should be ready within 5 years [35].

Challenges for future research include determining the degree of contribution of homeostatic vs. circadian processes in DSPS. Mary Carskadon is currently studying the homeostatic contribution to DSPS by a method she calls forced desynchrony [36]. Forced desynchrony imposes a 20-h day on individuals involved in the study for 2 weeks. The hypothesis is that the homeostatic process will be revealed as the available sleep time is shifted away from the circadian phase. Finally, conducting treatment research aimed at determining efficacy, effectiveness and mechanism or mechanisms of action is necessary [14]. The field is in need of a more effective chronobiotic agent [30].

References

1. Weitzman ED, Czeisler CA, Coleman RM, et al. Delayed sleep phase syndrome. A chronobiological disorder with sleep-onset insomnia. Arch Gen Psychiatry. 1981;38:737–46.
2. Carskadon MA, Vieira C, Acebo C. Association between puberty and delayed phase preference. Sleep. 1993;6(3):258–62.
3. Schrader H, Bovim G, Sand T. The prevalence of delayed and advanced sleep phase syndromes. J Sleep Res. 1993;2(1):51–5.
4. Touitou Y. Human aging and melatonin: clinical relevance. Exp Gerontol. 2001;36(7):1083–100.
5. Dijk D, Lockley S. Integration of human sleep-wake regulation and circadian rhythmicity. J Appl Physiol. 2002;92:852–62.
6. Borbely A. A two process model of sleep regulation. Hum Neurobiol. 1982;1:195–204.
7. Cain S, Dennison C, Zeitzer J, et al. Sex differences in phase angle of entrainment and melatonin amplitude in humans. J Biol Rhythms. 2010;25:288–96.
8. Pealy R, Thorpy MJ, Bovinski P. Prevalence of delayed sleep phase syndrome among adolescents. Sleep Res. 1998;17:362.
9. Ando K, Kripke DF, Ancoli-Israiel S. Estimated prevalence of delayed and advanced sleep phase syndromes. Sleep Res. 1995;24:509.
10. Shibui K, Uchiyama M, Okawa M. Melatonin rhythms in delayed sleep phase syndrome. J Biol Rhythms. 1999;14(1):72–6.
11. Aoki H, Ozeki Y, Yamada N. Hypersensitivity of melatonin suppression in response to light in patients with delayed sleep phase syndrome. Chronobiol Int. 2001;18:263–71.

12. Uchiyama M, Okawa M, Shibui K, Kim K, Kudo Y, Hayakawa T, et al. Poor recovery sleep after sleep deprivation in delayed sleep phase syndrome. Psychiatry Clin Neurosci. 1999;53(2):195–7.
13. Crowley S, Acebo C, Carskadon MA. Sleep, circadian rhythms, and delayed sleep phase in adolescence. Sleep Med. 2007;8:602–12.
14. Negriff S, Dorn L, Pabst S, Susman E. Morningness/eveningness, pubertal timing, and substance use in adolescent girls. Psychiatry Res. 2011;185:408–13.
15. Morgenthaler T, Alessi C, Friedman L, Owens J, Kapur V, Boehlecke B, et al. Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. Sleep. 2007;30940:519–29.
16. Littner M, Kushida CA, Anderson WM, Bailey D, Berry RB, Davila DG, Hirshkowitz M, Kapen S, Kramer M, Loube D, Wise M, Johnson SF, Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for the role of actigraphy in the study of sleep and circadian rhythms: an update for 2002. [Guideline. Journal Article. Practice Guideline]. Sleep. 2003;26(3):337–41.
17. Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol. 1976;4:97–110.
18. Shirayama M, Shirayama Y, Iida H, Kato M, Kajimura N, Watanabe T, et al. The psychological aspects of patients with delayed sleep phase syndrome (DSPS). Sleep Med. 2003;4(5):427–33.
19. Rosental N, Joseph-Vanderpool J, Levendosky A, Johnston S, et al. Phase-shifting effects of bright morning light as treatment for delayed sleep phase syndrome. J Sleep Res. 1990;13(4):354–61.
20. Wyatt J. Delayed sleep phase syndrome: pathophysiology and treatment options. Sleep. 2004;27(6):1195–203.
21. Czeisler CA, Richardson GS, Coleman RM, Zimmerman JC, Moore-Ede MC, Dement WC, et al. Chronotherapy: resetting the circadian clocks of patients with delayed sleep phase insomnia. Sleep. 1981;4(1):1–21.
22. Weitzman E, Czeisler CA, Coleman RM, Spielman AJ, Zimmerman JC, Dement W, et al. Delayed sleep phase syndrome. A chronobiological disorder with sleep-onset insomnia. Arch Gen Psychiatry. 1981;38(7):737–46.
23. Ito A, Ando K, Hayakawa T, Iwata T, Kayukawa Y, Ohta T, et al. Long-term course of adult patients with delayed sleep phase syndrome. Jpn J Psychiatry Neurol. 1993;47:563–7.
24. Kamei Y, Hayakawa T, Urata J, Uchiyama M, Shibui K, Kim K, et al. Melatonin treatment for circadian rhythm sleep disorders. Psychiatry Clin Neurosci. 2000;54(3):381–2.
25. Smits M, Nagtegaal EE, van der Heijden J, Coenen AM, Kerkhof GA. Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial. J Child Neurol. 2001;16(2):86–92.
26. Dahlitz M, Alvarez B, Parkes J, English J, Arendt J, Vignau J. Delayed sleep phase syndrome response to melatonin. Lancet. 1991;337(8570):1121–4.
27. Dagan Y, Yovel I, Hallis D, Eisenstein M, Raichik I. Evaluating the role of melatonin in the long-term treatment of delayed sleep phase syndrome. Chronobiol Int. 1998;15(2):181–90.
28. Lewy AJ, Ahmed S, Jackson JM, Sack RL. Melatonin shifts human circadian rhythms according to a phase-response curve. Chronobiol Int. 1992;9:380–92.
29. Wagner J, Wagner M, Hening W. Beyond benzodiazepines: alternative pharmacologic agents for the treatment of insomnia. Ann Pharmacother. 1998;32(6):680–91.
30. Sack R, Auckley D, Auger R, Carskadon M, et al. Circadian rhythm sleep disorders: part II: advanced sleep phase disorder, delayed sleep phase disorder, free-running disorder, and irregular sleep-wake rhythm. An American Academy of Sleep Medicine review. Sleep. 2007;30(11):1484–501.
31. Ebisawa T, Uchiyama M, Kajimura N, et al. Association of structural polymorphisms in the human period3 gene with delayed sleep phase syndrome. EMBO Rep. 2001;2:342–6.

32. Hohjoh H, Takasu M, Shishikura K, Takahashi Y, Honda Y, Tokunaga K. Significant association of the arylalkylamine N-acetyltransferase (AA-NAT) gene with delayed sleep phase syndrome. Neurogenetics. 2003;4:151–3.
33. Hohjoh H, Takahashi Y, Hatta Y, et al. Possible association of human leucocyte antigen DR1 with delayed sleep phase syndrome. Psychiatry Clin Neurosci. 1999;53:527–9.
34. Regestein QR, Monk TH. Delayed sleep phase syndrome: a review of its clinical aspects. Am J Psychiatry. 1995;152:602–8.
35. Strollo J. The future of sleep medicine white paper. Darien, CT: American Academy of Sleep Medicine; 2011.
36. Carskadon M. Forced Desynchrony as a means of assessing circadian and sleep/wake homeostasis 2004. www.hhs.gov/ohrp/panels/407-01pnl/grantapp.pdf.