Chapter 8
Advanced Sleep-Wake Rhythm Disorder

Elliott Kyung Lee

Advance-Related Sleep Complaints and Advanced Sleep-Wake Phase Disorder (ASWPD)

The term circadian rhythm sleep-wake disorder (CRSWD) is used to encompass a wide variety of conditions in which there is significant misalignment between the innately preferred sleep/wake schedule and the 24-hour light/dark cycle [1]. This chapter focuses on advance-related sleep complaints, when individuals have habitual sleep onset and/or offset times that are markedly earlier than desired. These patients may present with complaints of early evening sleepiness in conjunction with early-morning awakenings. Alternatively, individuals may be obligated to maintain a relatively delayed/conventional bedtime (or fail to recognize/report inadvertent evening sleep bouts that occur prior to their defined "bedtimes"), but persist with undesirably early rise times, leading to chronic insufficient sleep and daytime sleepiness [2]. Although sleep complaints can be an issue for these persons, some data suggest an advanced sleep phase or morningness traits may be more socially acceptable and possibly confer increased resilience and optimism, which may contribute to these persons not seeking clinical attention.

Advance-Related Sleep Complaints

Table 8.1 identifies criteria for advanced sleep-wake phase disorder (ASWPD), whereby patients identify simultaneous nighttime and morning complaints. The International Classification of Sleep Disorders Third Edition (ICSD-3) states that

E. K. Lee (✉)
Department of Psychiatry, Royal Ottawa Mental Health Center and Institute for Mental Health Research, University of Ottawa, Ottawa, ON, Canada
e-mail: elliott.lee@theroyal.ca

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Table 8.1 Advanced sleep-wake phase disorder diagnostic criteria

Diagnostic criteria	Description (criteria A–E must be met)
A	There is an advance (early timing) in the phase of the major sleep episode in relation to the desired or required sleep time and wake-up time, as evidenced by a chronic or recurrent complaint of difficulty staying awake until the required or desired conventional bedtime, together with an inability to remain asleep until the required or desired time for awakening
B	Symptoms are present for at least 3 months
C	When patients are allowed to sleep in accordance with their internal biological clock, sleep quality and duration are improved with a consistent but advanced timing of the major sleep episode
D	Sleep logs and, whenever possible, actigraphy monitoring for at least 7 days (preferably 14 days) demonstrate a stable advance in the timing of the habitual sleep period. Both workdays/school days and free days must be included within this monitoring
E	The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder

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Alternate names: Advanced sleep phase type, advance sleep phase disorder, advance sleep phase syndrome
Notes
1. Standardized chronotype questionnaires are useful tools to assess the chronotype of eveningness and morningness. Individuals with advanced sleep phase score as morning types
2. Demonstration of an advance (typically greater than 2 hours) in the timing of other circadian rhythms such as dim light melatonin onset (DLMO) or urinary 6-sulfatoxymelatonin is desirable to confirm the advanced circadian phase

such patients will "typically" exhibit sleep onset and offset times between 1800 and 2100 hours and 0200 and 0500 hours, respectively [3]. Accordingly, afflicted patients present with difficulties remaining awake in the late afternoon/early evening, in addition to endorsement of early-morning awakenings. This innate circadian preference makes it difficult or impossible to adhere to a socially desirable sleep/wake schedule [4]. While the ICSD-3 stipulates a 3-month duration criterion, the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) requires only 1 month [2, 5]. There are select physiologic data that demonstrate earlier timing of circadian biomarkers (melatonin, core body temperature) of ASWPD patients (2–4 hours earlier than unaffected subjects) [6].

Clinicians are unlikely to encounter patients meeting strict ICSD-3 criteria for ASWPD, however, in part because the affiliated sleep/wake schedule infrequently presents with marked social or occupational conflicts. Indeed, such behavior is often rewarded in occupational settings. In addition, one can voluntarily delay sleep onset times and/or fail to report inadvertent sleep that occurs out of the bedroom, making it difficult to identify individuals with an early evening sleepiness complaint required for the diagnosis [7]. As such, a broader consideration of advance-related sleep complaints is required, whereby sole sleep maintenance difficulties are inferred to be due to a phase advance in the circadian cycle and, by relation, responsive to circadian interventions [10].

Epidemiology

Prevalence statistics on ASWPD are varied. One large Norwegian study of 7700 individuals using strict ICSD criteria did not identify a single subject meeting diagnostic criteria [11, 12]. Other studies have suggested a population prevalence of 0.5%–1% [11, 13]. A separate study from New Zealand by Paine and colleagues described a prevalence of 0.25%–7.13%, depending upon the definition used, with men and older individuals more likely to be affected [14]. Another study by Ando and colleagues suggested that up to 7.4% of the general population may have advance-related sleep *complaints* [15], based on telephone surveys administered to random participants in San Diego. A 2019 study by Curtis and colleagues evaluated the prevalence of advanced sleep phase (ASP), familial advanced sleep phase (FASP), and ASWPD in 2422 patients seen in a Utah sleep clinic over a span of almost 10 years [8]. Assessments included the Morningness-Eveningness Questionnaire (MEQ), structured clinical interviews and assessments and, when possible, polysomnography, 10-day ambulatory actigraphy, sleep logs, and salivary dim light melatonin onset (DLMO). Their results showed an ASP prevalence of 0.33%, an FASP prevalence of 0.21%, and a ASWPD prevalence of 0.04% in patients referred to a North American sleep clinic for an assessment [8].

Etiology and Risk Factors

Genetics

Advance-related sleep complaints have a strong heritability component. The first familial study was done by Jones et al. in 1999 [6]. In this study, 29 out of 75 evaluated family members of Northern European descent were shown to have significant advanced, or "morning lark" traits, with autosomal dominant transmission and high penetrance. While the youngest of these subjects was 8 years old, most subjects knew by age 30 that they had advanced traits. A 3–4 hour advance in melatonin and body temperature rhythms was documented in comparison to controls. One subject also demonstrated a shorter circadian period (23.3 hours) when evaluated in temporal isolation. Further analysis identified an autosomal dominant inherited missense mutation (serine to glycine substitution at amino acid 662 – S662G) at the Period 2 (h*Per*2) gene located on the short arm of chromosome 2 [16], resulting in decreased phosphorylation of the h*Per*2 protein by casein kinase epsilon (CK1ε). Phosphorylation normally promotes degradation of the Per protein, preventing subsequent dimerization with the Cryptochrome (Cry) protein and leading to moderation of nuclear accumulation. As a result, h*Per*2 degradation is impaired, leading to increased accumulation and positive regulation of BMAL1. The BMAL1/Clock heterodimer normally drives the production of protein products of Per, Cry, and clock-controlled genes (CCGs) (see Fig. 8.1). These processes lead to a secondary increased transcription of BMAL1 and subsequent phase advancement. The mutation is not ubiquitous, however, as another

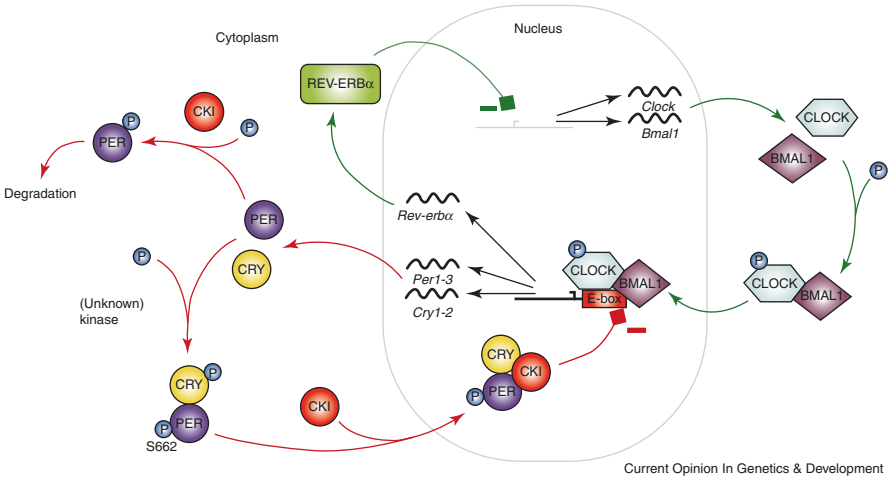

Fig. 8.1 Schematic representation of the basic components of the molecular circadian clock from Tafti et al. (2007) [16]. This molecular clock is based on several interacting positive (shown in green) and negative (shown in red) transcriptional loops, resulting in oscillating RNA and protein levels of key clock components. Transcription factors Clock and BMAL1 heterodimerize and are subsequently phosphorylated and translocated across the nucleus to activate transcription of 3 period genes (*Per*1-3) and two cryptochrome genes (*Cry*1-2). The protein products of the *Per* and *Cry* genes subsequently dimerize outside the nucleus in several combinations, and may undergo phosphorylation by casein kinase I (CKI) and translocate across the nucleus to inhibit the transcriptional activation by the Clock/BMAL1 heterodimer (negative loop, exerting autoregulation of their own transcription). CKI also phosphorylates *Per* proteins tagging them for degradation. Mutations in *Per*2 and *Per*3 result in impairment of phosphorylation by CKI, and have been identified as etiologies for phase advancement. On the other hand, the Clock-BMAL1 heterodimer also activates transcription of REV-ERBα. These proteins then translocate across the nucleus to activate transcription of Clock and BMAL1 proteins (positive feedback). Other genes implicated in phase advancement include Dec2, *Cry*2, and CKIδ (not shown). Per *Per*1-3, Cry *Cry*1-2, CKI CK1ε, and CKIδ. (Reprinted from Tafti et al. [16], with permission from Elsevier)

phenotypically similar Japanese family was identified, that did not exhibit the same mutation [7]. Figure 8.1 provides an example of clock gene mechanics within a cell.

Other studies support genetic heterogeneity of ASWPD. One study highlighted involvement of the Period 3 (Per3) gene, with two rare missense mutations (Per3-P415A/H417R) found in association with a familial advanced sleep phase and seasonal affective disorder, suggesting a genetic pathway for a connection between circadian rhythm and mood regulation [17]. Other implicated mutations have been found in casein kinase I delta (CKIδ), Basic Helix Loop Helix E41 (BHLHE41, i.e., Dec2), and Cryptochrome 2 (Cry2) proteins [13, 18–20]. Advanced sleep-wake phase disorder has also been identified in Smith Magenis syndrome, a congenital condition associated with deletion of chromosome 17 band p11.2, which includes the RAI1 gene [21–23]. In the absence of discretely identified genetic causes, some have speculated that patients with advance-related sleep complaints may have

higher sensitivity and/or exposure to morning light and accompanying advancing effects, or decreased sensitivity and/or exposure to evening light and accompanying delaying effects [24].

Risk Factors

Age

Children born preterm have been found to have an advanced sleep phase during subsequent adolescence [25]. It has been suggested that this is due to increased neonatal stress including hypoxia, nonideal nutrition, and chronic exposure to light (e.g., in an intensive care unit), which may result in compromised development of the suprachiasmatic nucleus [25, 26]. Conversely, older individuals tend to shift toward a morning preference and may be less sensitive to the circadian effects of light compared to younger adults [27–29], although not all studies agree [30]. Increasing age is accompanied by an advance in circadian phase, including peak melatonin concentration and wake time [9, 19, 31, 32]. There has been increasing interest in the potential effect of ethnicity on circadian phase, with some investigators suggesting persons of African American descent are predisposed to an increased sensitivity to the phase-advancing effects of light, and may possess a shorter innate circadian period, leading to a higher risk of having an advanced sleep phase [2, 19, 33].

Diagnosis

A diagnosis of ASWPD or advance-related sleep complaints requires a thorough clinical history, ideally with collateral information [3]. Lack and colleagues described 25 patients with advance-related sleep complaints, categorized with the use of sleep diaries, a sleep questionnaire, and a Beck Depression Inventory (the latter to rule out a depressive disorder). This phenotype was subsequently validated with core body temperature measurements and actigraphy [34]. Further useful assessment tools include validated chronotype questionnaires, such as the Morningness-Eveningness Questionnaire (MEQ) or the Munich Chronotype Questionnaire (MCTQ). The MEQ has been validated against core body temperature minimum (CBT_{min}) [35]. Both the MEQ, midpoint of sleep on work-free days, and sleep corrected score (MSF_{sc}) of the MCTQ have been shown to be correlated with the dim light melatonin onset (DLMO) [36, 37]. Palmer and colleagues recruited 47 patients prescreened for advance-related sleep complaints, 91% of whom confirmed morningness traits on the MEQ, with correlation with urinary 6-sulfatoxymelatonin (aMT6s) levels [38]. In Jones' study of familial ASWPD, MEQ scores of affected probands were dramatically higher (average score 77,

where MEQ scores >59 suggest moderate morning type and scores >69 indicate definite morning type) than unaffected relatives (average score = 48.2, where scores between 42 and 58 indicate intermediate type) [6].

Actigraphy is an additional clinical tool to longitudinally assess the stability of sleep-wake complaints. Data should include at least 7 days (including both "free" and work/school days) and preferably 14 days for adequate interpretation [3, 5, 24]. Other confounding conditions need to be excluded, most notably mood disorders and inadequate sleep hygiene. While a major depressive disorder may present with early-morning awakenings, other associated symptoms such as low mood and anhedonia are not associated with an advanced sleep phase [24]. Physiologic phase markers such as salivary DLMO may also be useful as a marker of circadian rhythm, if feasible to obtain [5]. While normative data are not available, several studies have suggested its use to diagnose CRSWDs (reviewed by Keijzer et al. [39]). These patients may be more vulnerable to abusing substances such as alcohol or other hypnotics in an attempt to stay asleep longer at night and/or may use stimulants in the early evenings to reduce sleepiness [2]. Other differential diagnoses to consider include free running or non-24-hour sleep/wake rhythm disorder. A careful history can usually clarify. Most patients afflicted with this condition are blind, and sleep-related complaints vary in time and nature, depending upon the alignment of their circadian rhythm with the light/dark cycle [3].

Treatment Options

Using the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation), the American Academy of Sleep Medicine (AASM) published updated practice parameters for the treatment of circadian rhythm sleep-wake disorders in 2015 [5]. Recommendations can be divided into four main categories for practitioners' consideration: behavioral options, hypnotics and stimulant medications, strategically timed melatonin, and strategic use of light therapy.

Behavioral Options

Sleep scheduling There is insufficient evidence at this time to recommend sleep scheduling as a primary means of treating advance-related sleep complaints. A singular case report by Moldofsky et al. from the 1980s (62-year-old male patient) described a protocol of phase advancing the sleep initiation time by 3 hours every 2 days over a period of 2 weeks [40]. Referred to as chronotherapy (i.e., changing the sleep and wake time gradually in a manner that favors the individual's circadian preference, with subsequent strict adherence to the achieved/desired sleep/wake schedule), the intervention successfully changed the sleep onset time from 1830 to

2300 hours and sleep offset time from 0230 to 0600 hours. Previous daytime and evening somnolence resolved with chronotherapy as well, with maintained benefits over 5 months. Initial polysomnography 1 week following chronotherapy completion revealed a longer total sleep time, but more wakefulness after sleep onset and less deep sleep and rapid-eye-movement (REM) sleep compared to baseline polysomnography. These findings were thought to be related to adaptation effects to the initial chronotherapy. At 5 months, however, the prolonged wakefulness had resolved and the patient endorsed increased alertness and energy during the midday hours [40]. While not tested as an intervention directly for patients with advance-related sleep complaints, avoiding evening naps is also a routine intervention that can be suggested. Evening naps have been shown to advance the sleep phase. Buxton and colleagues performed a 1-week study on the effect of daytime and evening naps on circadian phase in 25 normal male subjects ages 20–30 years old. Their results showed that daytime naps can phase shift circadian rhythms in normal subjects, with evening naps (1900–0100 hours) showing the largest phase advancement of circadian rhythms (44 min ± 17 min) as measured by DLMO and nocturnal thyroid-stimulating hormone (TSH) secretion [41]. Another study by Yoon and colleagues showed that evening naps resulted in earlier sleep offset times and advances in sleep phase as measured by urinary 6-sulfatoxymelatonin [42]. Consequently, although it has not been studied as an ameliorative measure, the avoidance of evening naps is a reasonable recommendation to consider in patients with advance-related sleep complaints.

Hypnotic and Stimulant Medications

Neither hypnotic nor stimulant medications have been studied for the treatment of advance-related sleep complaints. While hypnotics may be reasonable to consider for sleep maintenance difficulties or early-morning awakenings, the known side effects and risks of these medications warrant careful consideration. Drugs such as benzodiazepines, as well as the "z" drugs including eszopiclone and zolpidem, can increase risk of falls and daytime somnolence, especially among the elderly [43–46]. Cognitive side effects, tolerance, and dependence are also concerns, but the incidence of these complications is not entirely clear, as limited numbers of high-quality studies and frequent variability in methodology and design limit conclusions that can be drawn [47–49]. These risks, however, should be balanced against the risks of sleep disturbances themselves being associated with higher fall risk, as suggested by Avidan and colleagues [50]. In their study of approximately 34,000 nursing home residents with up to a 210-day follow-up, insomnia but not hypnotic use was associated with a higher risk of falls, suggesting that hypnotic medication use in the community may have been a proxy for underlying sleep disturbances [3, 50]. Data on use of stimulants for early evening sleepiness for these patients are also lacking, but could be considered if such symptoms warrant clinical attention.

Melatonin

The phase response curve for melatonin in humans describes phase delays with melatonin administration in the biological morning, but its use has not been studied within relevant patient populations [51]. Moreover, because of its potential soporific effects, caution is warranted for clinical practice [5, 11], with use of the lowest doses and gradual uptitration as needed. Melatonin agonists such as ramelteon or agomelatine could also have therapeutic roles, but have not been studied for these purposes.

Light Therapy

Light administered prior to the CBT_{min} (occurs 3–4 hours prior to habitual sleep offset) will delay the circadian rhythm, while light therapy administered subsequent to this inflection point will advance the circadian rhythm in individuals normally entrained to the light/dark cycle [3, 52, 53]. As a result, light therapy for advance-related sleep complaints is provided during evening hours, as close to the period of sleep onset as possible, to maximize phase delays [11]. There are no evidence-based protocols to inform ongoing maintenance treatment, but maintaining or resuming an effective intervention is a reasonable clinical practice [5].

Campbell and colleagues demonstrated efficacy of light therapy for delaying the sleep phase among ASWPD patients [54]. Their protocol on 16 older patients (ages 62–81) described 2 weeks of light therapy (4000 lux, administered for 2 hours between 2000 and 2300 hours) and demonstrated a 3.13 hours phase delay (as measured by CBT_{min}) in comparison to an 8-minute delay among controls, with accompanying improvements in sleep quality as measured by polysomnography. However, when this group repeated a similar study in 15 older persons subjected to a nearly identical protocol in their homes, there was no accompanying improvement in sleep quality. While subjects demonstrated an initial average phase delay of 94 minutes (CBT_{min}) compared to controls, body temperature rhythms gradually advanced to their normal (preintervention) rhythms despite twice weekly evening (2100–2300 hours) light therapy over a 3-month follow-up period [55]. The authors speculate that possibly the proximity of the timing of the light exposure to CBT_{min} was not optimal and that inferior compliance to light therapy in this study compared to their previous protocol may have contributed to the negative results. Another pilot study by Lack and colleagues on nine patients (mean age 53.4 years) with complaints of early-morning insomnia demonstrated that two evenings of light therapy (2500 lux) from 2000 to 2400 hours resulted in a subsequent delay of 2–4 hours in CBT_{min} and 1–2 hours in urinary melatonin phase markers. While sleep onset was not significantly delayed as measured by actigraphy, total sleep time was increased by over an hour in these subjects due to a 1 hour and 12-minute delay in mean wake-up time [56]. This group did a separate controlled study on 24 subjects (average age 61.2 years) with early-morning awakenings and terminal

insomnia, which were presumed to be advance-related sleep complaints. Using an identical protocol of evening light therapy, data yielded average phase delays of 2 hours in these subjects based on rectal temperature and urinary melatonin measurements [34]. Evidence of phase delay persisted during a 4-week follow-up period. Another study by Palmer and colleagues showed a lack of efficacy with light therapy of 265 lux administered for 2–3 hours in the evening (1900–2200 hours) for 4 weeks in 47 older adults (age 60–86) [38]. Other negative studies on the efficacy of light therapy have been reported [38, 57], but there is significant variability in the definitions of an advanced sleep phase, as well as brightness, timing, frequency, and length of exposure to light therapy as well as distance to the light source. These issues make it difficult to provide specific recommendations. Figueiro et al. have explored delivering light therapy in pulses during the night with a light mask (through closed eyelids while patients are asleep) to provide light stimuli during the steepest portion of the phase response curve of light, but with no significant delay in sleep onset occurring in patients with an advanced sleep phase [58].

Reported side effects of light therapy have generally been modest and in a placebo-controlled trial included eye strain and headaches [59]. Other reported side effects include nausea, fatigue, and irritability [60, 61]. Caution should be considered for use in patients who are on photosensitizing medications such as tricyclic antidepressants, antibiotics such as fluoroquinolones or sulfonamide drugs, or acne treatment with isotretinoin [62]. Other conditions in which caution is warranted with use of light therapy include the presence of skin conditions with photosensitivity including lupus, porphyrias, or solar urticaria, as well as migraines, diabetic retinopathy, macular degeneration, or a history of bipolar disorder [62–65]. Light therapy can induce migraines in approximately one-third of those susceptible [66]. A 2017 systematic review by Brower and colleagues found light therapy to be safe for the eyes in the absence of underlying ocular problems [62]. Patients with relevant conditions should have appropriate monitoring of their respective ophthalmologic, dermatologic, and/or psychiatric condition [5]. Finally, although potentially intuitively helpful, strategic avoidance of light (i.e., during a period time of morning when light would be expected to affect phase advances) has not been studied as a method of achieving phase delays among these patients [5].

Morningness and Resilience

Factors other than occupational "rewards" conferred to "early risers" may relate to the infrequency of advance-related sleep complaints in the clinical setting. Lewy first proposed a "phase shift hypothesis" in 1988, suggesting that the therapeutic effects of light therapy for mood disorders, particularly seasonal affective disorder, may be due to the phase-advancing effects of light "correcting" the phase delay among afflicted patients [67]. This hypothesis was later revised to the "phase angle difference hypothesis," whereby the internal phase delay compared to the midpoint

of sleep is the determining factor for the therapeutic response [68]. Several data have supported this hypothesis [69, 70], but other data are conflicting [71, 72]. Burnout is a syndrome of emotional exhaustion and cynicism that occurs in people who have an occupation that involves working with other people [73]. Given that eveningness traits have been associated with a higher risk of mood disorders and burnout [74–78], some have speculated that morningness may be associated with counteracting protective factors. One study by Muller and colleagues on 93 nonseasonal depressed inpatients found that morning types were underrepresented in this sample compared to healthy samples [79]. Indeed, morningness has been associated with findings of higher resilience and optimism [80–82]. These findings have been postulated to be related to these persons having relatively more exposure to sunlight, less social jet lag, and as a result a greater likelihood of meeting sleep duration needs [15, 16]. Social jet lag refers to a chronic misalignment between the preferred sleep-wake schedule and the sleep/wake timing imposed by a person's social or occupational schedule [83, 84]. Social jet lag is seen more frequently in subjects with later chronotypes [85, 86]. In addition to an insufficient sleep quantity that is common for these persons because of this circadian and social/occupational schedule misalignment, sleep quality also suffers as it does not occur within the temporal window afforded by the circadian sleep cycle. Related to the latter, morning persons have been shown to have a faster dissipation rate of homeostatic sleep pressure compared to intermediate and evening type persons, leading to a shorter sleep satiation and subsequent lower sleep duration need [87]. Not all studies are consistent, however, as Lemoine and colleagues found in a large sample of psychiatric inpatients that patients with a depressive or psychotic disorder were more likely to be morning types [88]. Furthermore, Lavebratt et al. have found an association with genetic variations of the h*Per*2 gene and depression [89], suggesting further research is needed.

Summary

Patients with advance-related sleep complaints may be difficult to recognize in the clinical setting. While they may present with evening sleepiness, sleep maintenance difficulties, and/or early-morning awakenings, many may not view these as treatable problems and choose instead to adjust their lifestyles. Preterm birth may increase the risk of having an advanced sleep phase. Additionally, older age as well as African American heritage may be associated with a higher phenotypic frequency. Some data even suggest patients with these traits may have more resilience and optimism, which may be protective factors against depression and burnout. A thorough clinical history and evaluation is warranted to properly identify patients with advance-related sleep complaints. Additional clinical tools such as sleep logs or questionnaires such as the MEQ, MCTQ, or actigraphy can be helpful. Behavioral recommendations including maintaining proper sleep hygiene, as well as the avoidance of evening naps and early-morning light, are simple

recommendations (albeit not evidence-based) that are easily implemented. There is insufficient data to make a recommendation regarding the use of post-awakening melatonin for these patients [90], but melatonin may be reasonable to consider with appropriate precautions about potential soporific side effects. While evening light therapy may offer benefit for some patients, much work needs to be done regarding determination of the optimal timing, intensity, duration, and wavelength of such treatment. Other treatment options for symptomatic relief include hypnotic and stimulant medications, but these have not been studied for this patient population. Their use can be considered on a case-by-case basis, weighing anticipated benefits against predicted risks.

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