

# 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

Robert L Sack, MD<sup>1</sup>; Dennis Auckley, MD<sup>2</sup>; R. Robert Auger, MD<sup>3</sup>; Mary A. Carskadon, PhD<sup>4</sup>; Kenneth P. Wright Jr, PhD<sup>5</sup>; Michael V. Vitiello, PhD<sup>6</sup>; Irina V. Zhdanova, MD<sup>7</sup>

<sup>1</sup>Department of Psychiatry, Oregon Health Sciences University, Portland, OR; <sup>2</sup>Cleveland, OH; <sup>3</sup>Mayo Clinic Sleep Disorders Center, Mayo Clinic, Rochester, MN; <sup>4</sup>Dept. Psychiatry & Human Behavior, Warren Alpert Medical School of Brown University, Providence, RI; <sup>5</sup>Department of Integrative Physiology, University of Colorado, Boulder, CO; <sup>6</sup>Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA; <sup>7</sup>Department of Anatomy and Neurobiology, Boston University, Boston, MA

**Objective:** This the second of two articles reviewing the scientific literature on the evaluation and treatment of circadian rhythm sleep disorders (CRSDs), employing the methodology of evidence-based medicine. We herein report on the accumulated evidence regarding the evaluation and treatment of Advanced Sleep Phase Disorder (ASPD), Delayed Sleep Phase Disorder (DSPD), Free-Running Disorder (FRD) and Irregular Sleep-Wake Rhythm ISWR).

**Methods:** A set of specific questions relevant to clinical practice were formulated, a systematic literature search was performed, and relevant articles were abstracted and graded.

**Results:** A substantial body of literature has accumulated that provides a rational basis the evaluation and treatment of CRSDs. Physiological assessment has involved determination of circadian phase using core body temperature and the timing of melatonin secretion. Behavioral assessment has

involved sleep logs, actigraphy and the Morningness-Eveningness Questionnaire (MEQ). Treatment interventions fall into three broad categories: 1) prescribed sleep scheduling, 2) circadian phase shifting ("resetting the clock"), and 3) symptomatic treatment using hypnotic and stimulant medications.

**Conclusion:** Circadian rhythm science has also pointed the way to rational interventions for CRSDs and these treatments have been introduced into the practice of sleep medicine with varying degrees of success. More translational research is needed using subjects who meet current diagnostic criteria.

**Keywords:** Circadian rhythm sleep disorders

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Address correspondence to: Standards of Practice Committee, American Academy of Sleep Medicine, One Westbrook Corporate Center, Suite 920, Westchester IL 60154, Tel: (708) 492-0930, Fax: (780) 492-0943, E-mail: aasm@aasmnet.org

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## 9.0 INTRODUCTION

This is the second of two articles authored by an American Academy of Sleep Medicine (AASM) Task Force charged by the Standards of Practice Committee with reviewing the scientific literature on the evaluation and treatment of circadian rhythm sleep disorders (CRSDs) as defined in the ICSD-2,<sup>1</sup> employing the methodology of evidence-based medicine. Our approach, as described in our first paper, was to formulate a set of specific questions relevant to clinical practice, extensively search the medical literature, abstract the core findings, and grade the quality of the

evidence. From this process, an evidence table was constructed (available online at <http://www.aasmnet.org/>). The methodology is described in more detail in the previous paper. In these two review articles, we provide a summary of the evidence gleaned through this process, and place this evidence regarding clinical issues within the context of current circadian science.

In the first paper we reviewed the circadian science and research strategies that have provided the framework for clinical investigation. We then reported on the accumulated evidence regarding shift work disorder (SWD) and jet lag disorder (JLD)—disorders that occur after a voluntary or imposed shift in the timing of sleep. In this paper we deal with circadian rhythm disorders that are thought to involve mechanisms intrinsic to the circadian system, although exogenous factors may be involved as well. Specifically, these disorders include: advanced sleep phase disorder (ASPD), delayed sleep phase disorder (DSPD), free-running disorder (FRD), and irregular sleep-wake rhythm (ISWD). Both of these papers will be accompanied by practice recommendations formulated by the AASM Standards of Practice Committee.

Before proceeding to the individual CRSDs, this paper will review research involving the application of molecular genetics to circadian sleep propensity. Genetic research aims to trace circadian variability in humans to polymorphisms or mutations of the recently identified “clock genes” that generate circadian cycles via intracellular protein transcriptional-translational feedback mechanisms. Because this research domain tends to subsume numerous diagnostic categories, it is more convenient to discuss it in one place.

## 10.0 CRSDS AND MOLECULAR GENETICS

The discovery of the molecular mechanisms generating the intrinsic near 24-h cycles in the mammalian suprachiasmatic nucleus (SCN), that can be entrained by environmental cues, has been hailed as one of the most important scientific breakthroughs of the decade. The data collected in animal models suggested that mutations in the clock genes can result in altered amplitude or period of the circadian rhythms, resembling some of the CRSD symptoms.<sup>2</sup> These findings, coupled with the research involving cloning of the human genome, have opened major opportunities to address the potential genetic causes of CRSDs.

Two main strategies have been used to apply the growing understanding of clock gene mechanisms to circadian pathology. The first has been the search for clock gene mutations in the pedigrees of families with identified circadian disorders. The second has been the correlation of circadian propensity as measured by the Morningness-Eveningness Questionnaire (MEQ), or as identified by CRSD diagnosis, with polymorphisms or mutations of clock genes.

In 1999, Jones, et al. described a high incidence of ASPD in three American families of Northern European descent (level 2).<sup>3</sup> A 3 to 4-hour phase advance in melatonin and temperature rhythms was documented in these ASPD subjects compared to controls. One of the family members was admitted to a time-free environment and shown to have a very short circadian period (*tau*) of 23.3 hours, based on the sleep-wake and temperature data collected. The trait segregated as an autosomal dominant inheritance pattern, with high penetrance.

Subsequently, the affected individuals of one of these ASPD families were shown to carry a missense mutation in a specific

locus of the clock gene *hPer2*, a gene critical for the resetting effects of light (level 1).<sup>4</sup> These studies were the first to apply “clock gene” science to a CRSD. However, the same study also revealed a genetic heterogeneity of ASPD, since other ASPD families examined did not show a mutation in the *hPer2*. Similarly, the familial ASPD disorder documented in two Japanese families using MEQ and melatonin measurements had no significant linkage with a mutation of *hPer2* (level 2).<sup>5</sup> A recent study in a Japanese pedigree with familial ASPD, diagnosed based on self-reported sleep schedule and structured interviews, revealed a missense mutation in another, *CKI-Δ*, gene (T44A) (level 4).<sup>6</sup>

Fewer genetic screenings have been performed in familial DSPD patients than in familial ASPD. The results suggested autosomal dominant mode of inheritance with incomplete penetrance or a multifactorial mode of inheritance in the North American patients (level 4).<sup>7</sup> Several studies have focused on the *hPer3*, the first one being conducted in Japan and reporting higher frequency of H4 haplotype in DSPD patients (level 4).<sup>8</sup> A British-based study found a frequency of the 4-repeat allele of the *hPer3* to be high in DSPD patients (88%), while the 5-repeat allele were associated with the morningness phenotype (level 3).<sup>9</sup> In contrast, a Brazilian group documented nearly 30% of DSPD patients as homozygous for the 5-repeat allele of the *hPer3* (level 3)<sup>10</sup> and suggested that the discrepancies between the studies might involve differences in patients’ ethnic origin or the environmental factors, e.g., latitude.

Another Japanese group has identified two more genes associated with DSPD: arylalkylamine (serotonin) N-acetyltransferase (AA-NAT) (level 3)<sup>11</sup> and HLA-DR1.<sup>12</sup> AA-NAT is the rate-limiting enzyme in the melatonin synthetic pathway from serotonin. The frequency of a single nucleotide polymorphism (amino acid substitution from alanine to threonine at position 129) was significantly higher in patients (16%) than in controls (3.1%).

Moreover, Takano and colleagues (level 4)<sup>13</sup> found a missense variation in human *CKIε* (N408 allele) that may be protective in the development of DSPD, since it occurred significantly less frequently in patients diagnosed with DSPD (and those with free-running disorder) than in control subjects.

A number of studies have correlated circadian propensity, i.e., *morningness* versus *eveningness* (not clinical diagnosis) with clock gene variations. One of the first was performed in 410 middle-aged adults in whom phase preference had been measured with the MEQ (level 2).<sup>14</sup> A single nucleotide polymorphism was identified, with a cytosine for threonine (C for T) substitution at the immediate 3’ region of the human *CLOCK* gene (*hClock*), 3111C versus 3111T. Participants homozygous for the T allele (*CLOCK* 3111T/T, n = 163) were less “evening type” than heterozygotes (*CLOCK* 3111C/T, n = 219) or all 3111C carriers (n = 247). Similarly, C allele homozygotes (*CLOCK* 3111 C/C, n = 28) exhibited lower but statistically insignificant MEQ values when compared to T homozygotes, a result perhaps influenced by the small sample size of the former group. The authors concluded that this association was strongest for the eveningness factor on the MEQ. In contrast, screening for polymorphisms of the *hClock* determined that they were infrequent in DSPD, and not different from controls (level 3).<sup>15</sup> Combined, these findings on the link between the *hClock* and eveningness but lack of such correlation with DSPD may question a direct etiological link between the circadian propensity and the disease, though more studies are needed to clarify this issue.

The picture emerging from both human and animal studies sug-

gests that a genetically-determined period of the intrinsic circadian rhythm or the degree to which this rhythm can be entrained by the environmental time cues defines the morningness or eveningness trends, or presence of CRSDs. However, multiple genes can underlie such disorders, with alterations in different circadian genes potentially resulting in a similar circadian phenotype, or a mutation in a different site of the same gene producing an opposite effect on the circadian system. In support of this notion, a recent study in mice shows that, depending on the site of *PER2* phosphorylation, the expression, degradation, and/or nuclear entry and retention of this protein may change, resulting in a different degree of advance or delay in the circadian period.<sup>16</sup>

*Conclusions: Intriguing research has begun to link clock gene polymorphisms to familial ASPD and DSPD, and perhaps to sub-clinical circadian propensity for morningness or eveningness. The results suggest that a number of mutations in different circadian genes might be involved in these phenomena, with familial or sporadic CRSDs being heterogeneous genetic disorders. Further research in this area is likely to bring important insights into the mechanisms of CRSDs but the research is in the early stage and does not yet have clinical application.*

## 11.0 ADVANCED SLEEP PHASE DISORDER (ASPD)

### 11.1 Diagnostic Issues

Advanced sleep phase disorder (ASPD) is characterized by a stable sleep schedule that is several hours earlier than the conventional or desired time. There is no strict definition of how advanced the sleep schedule needs to be in order to qualify as pathologic, and thus the diagnosis depends in large part on the degree of difficulty a patient experiences with conforming to a desired sleep schedule. Prior to ascribing the diagnosis, other causes of sleep maintenance insomnia must be ruled out; for example, depression.<sup>1</sup>

ASPD is thought to be much less common than DSPD, but because an early sleep pattern results in fewer social conflicts (e.g., people are not usually punished for getting to work too early), the incidence may be underestimated. The mechanisms leading to this condition are unknown, but hypotheses have usually been the opposite of those thought to underlie DSPD. For example, a shortening of the circadian period has been demonstrated in one patient with familial ASPD (level 2).<sup>3</sup>

### 11.2 Risk Factors

#### 11.2.1 Age

It is widely assumed that the tendency for an advanced sleep schedule is associated with aging, but data regarding the correlation between age and discrete ASPD are scarce. One pertinent study involved 110 healthy adults, aged 20-59,<sup>17</sup> who completed the MEQ, kept sleep diaries for two weeks, and underwent PSGs (level 2). Age was associated with increased morningness (M-type) and an objective, but not subjective, decline in sleep quality. After controlling for age, M-type was associated with an advanced sleep phase, less total sleep time, and increased wake time during the last 2 hours of sleep. Of primary importance, analyses with hierarchical regression demonstrated that M-type was a predominant mediator of various assessed age-sleep relationships. Supporting these

findings, one telephone survey (level 4)<sup>18</sup> found “advance-related” complaints to be more than twice as common (7.4% of respondents) as “delay-related” complaints in a cohort aged 40-64.

*Conclusions: Although inconclusive, the available data suggest that age may be a risk factor for ASPD.*

### **11.2.2 Gender**

There are insufficient data to definitively address this question.

### **11.2.3 Light Exposure**

A study by Buxton, et al (level 1),<sup>19</sup> described in our first report, found that napping for five hours in the dark in the evening (19:00-01:00) caused a phase advance in young normal subjects. In a more naturalistic study of older subjects, those who took evening naps (thereby gating light exposure) showed earlier sleep-offset times and a more advanced acrophase of the aMT6 rhythm than subjects who refrained from napping.<sup>20</sup> As the effect of evening napping vs. earlier morning light exposure was confounded in this case, the study could not differentiate the relative contribution of each variable to phase advances.

*Conclusions: A relationship between ASPD and excessive or inadequate light exposure during the pertinent portions of the light PRC remains conjectural, but the role of both variables in creating phase advances has been documented in those without CRSDs.*

## **11.3 Assessment Tools**

### **11.3.1 Sleep Logs and Actigraphy**

Sleep logs and actigraphy have face validity in documenting an advanced sleep schedule and an associated inability to sleep at a conventional time (see sections 12.3.1 and 12.3.2).

### **11.3.2 Morningness-Eveningness Questionnaire (MEQ)**

As ASPD is characterized by an advance in the phase of the major sleep period in relation to the desired sleep and wake times, individuals with this condition would be predicted to score as morning types (M-type) with high values on the MEQ. However, the current literature search yielded only three studies that used the MEQ as part of the clinical evaluation of patients with suspected ASPD.

Two studies evaluated families with familial ASPD and, as expected, affected family members scored significantly higher on the MEQ compared to unaffected counterparts, confirming a remarkable morning-lark trait (both level 2).<sup>3,5</sup> The earlier study<sup>3</sup> also reported that MEQ scores of first-degree relatives, both unaffected and of unknown status, of affected individuals were higher than those of “marry-in” spouses and unrelated control subjects, further supporting heritability of the “morningness” trait among this lineage. Finally, the authors of the more recent study reported that “morningness” was recognized in all familial ASPD-affected members who were at least 20 years of age, and highlighted the need for the establishment of criteria for MEQ scoring of younger age groups.<sup>5</sup>

Another study investigated the use of evening light treatment for patients with presumed ASPD, and reported that the MEQ

scores of 91% were consistent with “morningness” (i.e., MEQ  $\geq 59$ ) and that 53% provided scores consistent with “definite morning types” (i.e., MEQ  $\geq 70$ ) (level 3).<sup>21</sup> The authors utilized this data to support the validity of their recruitment process, but controls were not available for comparison.

*Conclusions: The MEQ can provide confirmatory evidence for a diagnosis of ASPD but is not sufficiently reliable to be the sole basis for the diagnosis. In the future, MEQ scores may need to be normalized for age.*

### **11.3.3 Polysomnography (PSG)**

No studies were identified that utilized PSG parameters as inclusion criteria for a diagnosis of ASPD. Nevertheless, a study of familial ASPD patients, discussed in more detail above, compared PSG variables between affected and unaffected subjects and demonstrated the expected advance in the timing of sleep onset (19:25  $\pm$  1:44 vs. 23:10  $\pm$  0:40) and offset (04:18  $\pm$  2:00 vs. 07:44  $\pm$  1:13) in the former group, with preservation of sleep quality and quantity in both groups (level 2).<sup>3</sup> Curiously, in a separate study of patients with ASPD (using ICSD-1 criteria) that included PSG as an outcome measure in a trial of evening phototherapy, baseline values actually revealed relatively orthodox bedtimes, with group means of 23:14 hours and 00:27 hours in the active and sham treatment groups, respectively (level 2), highlighting the ambiguous nature of the diagnostic criteria used to define this condition.<sup>22</sup>

*Conclusions: PSG data is not presently required for a formal diagnosis of ASPD,<sup>1</sup> but its use in research protocols may improve diagnostic validity and homogeneity of patient populations. It is unknown whether these data would confer greater diagnostic value than actigraphic parameters however and, in the clinical setting, the amount of time required to establish a stable circadian phase ( $\geq 7$  days) precludes practical use of PSG, and instead favors the use of actigraphy or sleep logs.*

### **11.3.4 Phase Markers**

Our search yielded three pertinent studies that measured the timing of melatonin secretion in subjects diagnosed (or presumed to have) ASPD. Salivary dim light melatonin onset (sDLMO) was measured in members of two Japanese families with familial ASPD (using ICSD criteria), and affected members were phase-advanced by more than two hours as compared to unaffected relatives (level 2).<sup>5</sup> In another study of patients with familial ASPD, plasma melatonin was used to assess DLMO, and affected individuals were phase-advanced by nearly 4 hours as compared to controls (level 2).<sup>3</sup> In a separate study, older subjects with advanced sleep phases (presumed ASPD) were recruited for a treatment trial of evening phototherapy (level 3).<sup>21</sup> Prior to treatment, the mean urinary aMT6s acrophases were regarded as “modestly” advanced, according to reference standards derived from other studies by the authors.

In four studies of evening phototherapy for older subjects with either ASPD, sleep maintenance, or terminal insomnia (the latter two diagnoses were presumed to be related to circadian factors, due to the treatment modality employed), the CBTmin was early—ranging between approximately 01:30 and 03:00, depending on the exact analysis used to assess CBT data (Level 2),<sup>22-24</sup> (level 4).<sup>25</sup> In the sole study of patients with familial

ASPD that utilized this assessment, the group CBTmin was extraordinarily early, occurring at approximately 23:30 (level 2),<sup>3</sup> roughly 7 hours earlier than that expected in the normal population.

*Conclusions: Although the data are limited and affected by heterogeneity of subjects, they are nevertheless generally consistent with an advance in the timing of phase markers in ASPD.*

## 11.4 Treatment

### 11.4.1 Prescribed Sleep/Wake Scheduling

There is one case report of successful phase advance chronotherapy (3 hours every 2 days for a 2-week period) in a patient with presumed ASPD, with successful maintenance of the desired phase at 5 months follow-up assessment (level 4).<sup>26</sup>

*Conclusion: Further research is required regarding the efficacy and practicality of phase-advance chronotherapy for patients with ASPD.*

### 11.4.2 Timed Light Exposure

In the largest study to date, involving 47 older adults diagnosed with ASPD (although the specific criteria used to make this determination are not clear), “enhanced evening light” (averaging 265 lux) administered for 2 to 3 hours was no more effective than placebo in counteracting advanced sleep phase (as indicated by actigraphy). Nevertheless, patients reported a subjective benefit (level 3).<sup>21</sup> The light treatment in this study (265 lux) was not as intense as bright light treatment (2000 to 10,000 lux) used in many other studies, and the timing was earlier than usual (15:00 to 17:00). Moreover, the degree of baseline circadian advancement, as assessed by aMT6 acrophases, was unclear, as the authors used unspecified reference standards culled from their other investigations.

Bright evening light exposure produced similarly lackluster results in a treatment trial in patients with complaints of early-morning awakenings, although no physiologic phase markers were utilized. The treatment was administered for 30 minutes, beginning approximately 1 hour before subjects’ habitual bedtimes, for a duration of 3 weeks (level 2).<sup>27</sup> As compared to the sham treatment condition, those receiving active treatment described subjective improvement in early morning awakenings, as manifested by an approximately 20 minute decrease of time in bed subsequent to final morning arising. No other differences were observed with respect to the additional subjective variables, or with respect to any of the actigraphic variables.

Greater success was demonstrated in a study of subjects with ICSD-1-defined ASPD, utilizing evening light therapy (4000 lux, 2-hour duration, between 20:00 and 23:00) for 12 consecutive days (level 2).<sup>22</sup> A greater-than-two-hour CBTmin post-treatment delay was demonstrated, in association with an average delay in bedtime of 29 minutes, an approximately 13% increase in sleep efficiency, and a related decrease in wakefulness after sleep onset (WASO). Post-treatment sleep architecture changes were also noted in the form of increased REM latency, decreased percentage Stage 1 NREM sleep, and increased percentage Stage 2 NREM sleep. The control group demonstrated no significant changes in either sleep or circadian parameters.

However, in their most recent study, the same group, utilizing an essentially identical protocol failed to replicate many of these findings. Although treatment resulted in significant delays in both group CBTmin (94 minutes) and sleep onset (44 minutes), in addition to a significant increase in the phase angle of CBTmin and sleep midpoint by more than 1 hour, no other significant improvements in PSG-determined sleep parameters were obtained (level 2).<sup>23</sup> Subsequently, patients received light therapy twice weekly for a 3-month period (maintenance treatment phase); they then demonstrated a trend toward reversion to the pre-treatment CBTmin (i.e., phase advance), and a lack of significant difference between any assessed parameter as compared with controls. Subjective sleep quality improved in the active group during maintenance treatment, but not in the control group. The authors proposed that the discrepancy in results may have been due to heterogeneous patient populations in their second study (a formal diagnosis of ASPD was not required, as it was in the first study), and/or unmonitored adherence to treatment.

Finally, capitalizing on the success of an earlier uncontrolled pilot investigation (level 4),<sup>25</sup> a different group recently designed a study specifically involving individuals with isolated early-morning awakenings and assessed the effects of two consecutive nights of light therapy (2500 lux, administered for four hours from 20:00 to 01:00 (level 2).<sup>24</sup> Both active and sham treatment groups had much earlier baseline CBTmin values than the aforementioned studies for which physiologic markers were available (active treatment CBTmin approximately 02:00). The active group exhibited a significant post-treatment delay of CBTmin of over two hours. Baseline DLMO values (as assessed by urinary aMT6) were referenced only in a figure (without raw data available), but also exhibited average post-treatment phase delays of approximately two hours in the active group. Sleep parameters (as assessed by actigraphy and sleep logs) demonstrated a significant decrease in actigraphically-determined WASO in the active treatment group at both 1- and 4-week follow-up periods, in addition to subjective (but not objective) improvement in total sleep time at the end of the 4-week follow-up period (90 minutes as compared with baseline, and 45 minutes as compared with sham treatment). There were otherwise few meaningful significant group differences with respect to sleep onset or offset times.

*Conclusions: The available data on the treatment of ASPD (and the treatment of insomnia utilizing phototherapy) consists exclusively of evening light therapy. While objective results are overall conflicting, subjective improvements have been consistently demonstrated. Comparison of treatment effects is limited by the heterogeneous nature of the patient population, perhaps in part influenced by the ambiguous criteria for ASPD in the ICSD, variable use of established circadian phase markers, differing intensity and durations of treatments, and nonsystematic assessments of treatment compliance. Future studies would benefit from addressing these factors, in the context of protocols that are cognizant of practical clinical scenarios (e.g., an established duration of nightly or maintenance treatments). The use of blue light, addressed in Part I, may also significantly influence treatment factors, possibly allowing for increased potency of the stimulus and/or a reduction in required exposure time, potentially increasing practical clinical application (and patient acceptance) of this treatment modality.<sup>28</sup>*

### **11.4.3 Timed Melatonin Administration**

There are no systematic reports of melatonin administration for ASPD, but consideration of the melatonin PRC provides a rationale for low-dose administration after early morning awakenings and upon final arising in the morning.<sup>29</sup>

*Conclusion: There are insufficient data to assess the safety and efficacy of timed melatonin administration in the treatment of ASPD.*

## **12.0 DELAYED SLEEP PHASE DISORDER (DSPD)**

### **12.1 Diagnostic Issues**

Delayed sleep phase disorder (DSPD), first described by Weitzman and colleagues,<sup>30</sup> is characterized by a stable sleep schedule that is substantially later than the conventional or desired time. Patients with DSPD have sleep onset insomnia and extreme difficulty arising when they attempt to conform to a conventional work schedule or other social demands. A tendency for a delayed sleep schedule is very common during adolescence and can be a factor in academic failure. However, in these otherwise normal young people, it is unclear whether this is a manifestation of intrinsic pathology (being “stuck” with a delayed sleep propensity) or a socially reinforced sleep-wake schedule that can be readily modified if circumstances require it.

Psychophysiological insomnia must be ruled out as a cause for the sleep onset insomnia characteristic of DSPD. Weitzman<sup>30</sup> originally proposed that a significant number of patients with sleep onset insomnia may have underlying DSPD, but this hypothesis has not been systematically pursued.

The etiology of DSPD is unknown. Some investigators have suggested that the pathophysiology may involve an intrinsic circadian period that is longer than average, but other explanations involving abnormalities in the light phase response curve (PRC) are also possible. For example, hypersensitivity to evening light could be a precipitating or maintaining factor for the phase delay in DSPD.<sup>31</sup> On the other hand, Ozaki and colleagues,<sup>32</sup> suggested that the inability of DSPD patients to phase advance normally might result from masking of the advance portion of their light PRC by elongated sleep bouts. Subsequent work has expanded possible mechanisms to include the sleep regulatory system: for example, Uchiyama et al.,<sup>33</sup> found reduced sleep in patients vs. controls following sleep deprivation, and suggest that DSPD patients may have a diminished ability to compensate for lost sleep, and thus have difficulty falling asleep even when they have previously awakened early and thereby have developed a homeostatic sleep drive.

### **12.2 Risk Factors**

#### **12.2.1 Age**

A tendency to stay up late and sleep in on weekends is very common among teenagers. In a study of sleep patterns and circadian rhythms in 32 normal children (level 2),<sup>34</sup> the transition from the 9<sup>th</sup> to the 10<sup>th</sup> grade (involving an earlier school start time) was also associated with a later bedtime and therefore reduced total sleep time (TST), assessed by actigraphy; furthermore, multiple sleep latency testing (MSLT) indicated more daytime sleepiness.

The transition was also associated with a 40-minute delay in the sDLMO. It should be emphasized, however, that none of these teenagers were diagnosed with DSPD.

In a retrospective description (level 4)<sup>35</sup> of a large cohort of patients from a clinical practice with CRSDs (N = 322; mean age not reported), DSPD was the most common CRSD diagnosis (83%), and 90% of the DSPD patients reported an onset of their symptoms during childhood or adolescence. In another study, the same group reported that, of 63 consecutive, nonselected admissions to an adolescent psychiatric inpatient unit, 10 patients (16%) were diagnosed with co-morbid DSPD (level 4),<sup>36</sup> supporting the conclusion that DSPD is common in teenagers, and that it may be associated with psychopathology. DSPD appears to be relatively rare among older people. A telephone survey of subjects aged 40-64, for example, found an incidence of “delay related” sleep complaints in 3.1% of the respondents (level 4).<sup>18</sup>

#### **12.2.2 Gender**

A large survey of unaffected university students (N = 2135) (level 2)<sup>37</sup> analyzed gender differences in morningness-eveningness preference, and found men have a more pronounced eveningness preference (P < 0.0001). More data needs to be obtained on patients who are clinically diagnosed with DSPD in order to draw conclusions about gender as a risk factor.

#### **12.2.3 Reduced Light Exposure**

As mentioned above, it has been suggested that one of the reasons some people develop DSPD is that they sleep too long and consequently do not get light exposure to the phase advance portion of the light PRC. Ozaki, et al. (level 3)<sup>32</sup> monitored the sleep schedule of seven DSPD patients and seven matched control subjects for four weeks and found that sleep length was significantly longer in the DSPD patients. Winter depression has also been related to reduced solar light intensity, especially at dawn, but it is considered a mood disorder, not a sleep disorder, thus that research was not included in our review.

#### **12.2.4 Excessive Light Exposure**

Exposure to bright light in the evening may promote phase delays and exacerbate DSPD; consequently, patients with DSPD may be advised to avoid light exposure near bedtime; however, no studies have addressed this issue.

*Conclusions: A number of studies have documented a tendency for teenagers and young adults to delay their sleep schedule, but the relative contribution of endogenous and exogenous factors underlying this phenomenon have not been fully delineated. Although many young people with delayed schedules are able to adapt to a conventional schedule when it is mandatory (and therefore do not meet diagnostic criteria for DSPD), diagnosed cases of DSPD usually have an onset at this age, and rarely in later life.*

### **12.3 Assessment Tools**

#### **12.3.1 Sleep Logs**

Sleep Logs are consistently recommended as a method for evaluating sleep schedules in CRSD patients. However, there are

no widely accepted, standardized sleep logs, and investigators and clinicians often construct their own. Sleep logs have apparent face validity, and can provide data on qualitative as well as quantitative aspects of sleep. Although many of the CRSD research studies we reviewed employed sleep logs, we did not find any studies that specifically evaluated their reliability or validity as a clinical assessment tool for CRSDs.

### **12.3.2 Actigraphy**

As indicated in previous reviews,<sup>38</sup> actigraphy is a useful tool for documenting sleep schedule in patients with DSPD.

### **12.3.3 Morningness -Eveningness Questionnaire (MEQ)**

The MEQ has not been tested as a diagnostic tool for DSPD. See discussion of MEQ in Part I.

### **12.3.4 Circadian Phase Markers**

The phase (timing) of melatonin secretion, as measured by serial sampling of plasma or saliva melatonin levels, or the excretion of the melatonin metabolite, 6-sulfatoxymelatonin (aMT6s), has been examined as a circadian marker by a number of investigators. An early study (level 4)<sup>39</sup> of DSPD patients (N = 12) failed to demonstrate a delay in plasma melatonin or urinary aMT6s, even though sleep times were delayed, according to sleep log data. However, a more recent study (level 3)<sup>40</sup> demonstrated that the sDLMO was significantly later in patients with DSPD than in controls. In contrast to some other studies, no difference in phase angle between circadian phase and sleep time was observed in this study; furthermore, circadian phase was stable (on an ad lib sleep schedule) between weekdays and weekends.

A melatonin administration trial for DSPD (discussed in more detail below) reported the average dim light melatonin onset (DLMO) at baseline, prior to initiating treatment, as  $23.46 \pm 1.62$  h, considerably later than published norms (level 2).<sup>41</sup>

### **12.3.5 Polysomnography**

In a descriptive study (level 4)<sup>42</sup> of 22 young patients (mean age 15.1 years) diagnosed with DSPD, nine had two PSGs, one to simulate a “weekday” schedule and another, a “weekend” sleep schedule. On the weekend night, when subjects had more freedom to choose their sleep schedule, they sleep longer (554 vs. 362 minutes), got up later (11:07 vs. 07:28), and had a greater proportion of REM sleep (22.9% vs. 14.6%). These data support the presumption that patients with DSPD have increased total sleep time and improved sleep architecture when given the opportunity to sleep later in the day.

*Conclusions: Sleep logs and actigraphy have face validity in documenting a delayed sleep schedule and an associated inability to sleep at a conventional time. Although DSPD patients would be expected to score in the “extreme eveningness” range of the MEQ, the sensitivity and specificity of the scale in substantiating a clinical diagnosis has not been evaluated. Circadian phase markers are usually delayed in DSPD, but are not available to the clinician. Two PSGs, one done on a conventional schedule, and one on an unconstrained schedule, could provide an ideal clinical assessment protocol, however financial constraints may limit the use of this option.*

## **12.4 Treatment**

### **12.4.1 Prescribed Sleep Scheduling**

The term *chronotherapy* was first coined to describe a treatment for DSPD that involved prescribed scheduling of sleep times according to the newly appreciated characteristics of the human circadian system.<sup>43</sup> The treatment was based on the observations that patients with DSPD had great difficulty shifting their rhythms in an advance direction, and therefore proposed shifting in a delay direction. Also, chronotherapy assumed that the timing of sleep (rather than light) was the main synchronizer of the circadian system, and that, if the sleep schedule could be normalized, the circadian system would follow. With these assumptions in mind, patients with DSPD were prescribed a sleep schedule that delayed several hours per day until sleep was aligned to the targeted bedtime. After the objective was reached, patients were advised to scrupulously maintain a regular sleep/wake schedule. If they drifted later, the procedure was repeated.

Although there are positive case reports using chronotherapy for DSPD (level 4),<sup>43</sup> there have been no controlled trials of its efficacy or safety. Ito, et al. (level 4)<sup>44</sup> reported that relapse after chronotherapy was common when patients were followed long term. In regard to safety, there is one report of a patient with DSPD who developed free-running rhythms (FRD) after chronotherapy (level 4).<sup>45</sup>

*Conclusions: A prescribed sleep schedule (chronotherapy) is a rational treatment for DSPD but there are no controlled clinical trials documenting its efficacy and safety.*

### **12.4.2 Timed Light Exposure**

Light exposure in the morning, on the advance portion of the light PRC, would be expected to shift circadian rhythms earlier, thereby correcting a pathological phase delay. Rosenthal et al. (level 2)<sup>46</sup> treated 20 patients diagnosed with DSPD for two weeks using two hours of bright light exposure (2,500 lux) and two hours of ordinary light (300 lux) exposure in the morning (between 06:00 and 09:00) in a crossover design. The bright light treatment produced a significant phase advance of the core body temperature rhythm, although there was no attempt to minimize masking, as well as an increase in morning alertness as measured with the MSLT.

In a novel study, Cole, et al. (level 1)<sup>47</sup> treated DSPD with an illuminated mask that provided light through closed eyelids during sleep. The light mask was reported as well tolerated, producing little sleep disturbance. The mask turned on (<0.01 lux) four hours before arising, ramped up for one hour, and remained on at full brightness until arising (2500 lux for active treatment, 0.1 lux for controls). The bright light treatment advanced the timing of aMT6s by one hour after 26 days of treatment, and advanced sleep onset times in the subset of patients with the most delayed phases.

*Conclusion: Although the evidence is limited, light exposure treatment, timed to advance rhythms based on the light PRC, appears to be a rational and effective intervention for DSPD. In the clinical context, compliance may be a significant problem.*

### **12.4.3 Timed Melatonin Administration**

Melatonin administration in the afternoon or evening, during the phase advance portion of the melatonin PRC, would be expected to shift rhythms earlier, thereby correcting a pathological phase delay. This hypothesis was supported in an early study of limited sample size (N = 8), (level 2).<sup>48</sup> In a large (N = 61), open-label study, those receiving 5 mg of melatonin given at 22:00 for six weeks reported significant benefit, but also a high rate of relapse when treatment was discontinued (level 4).<sup>49</sup>

In a double-blind, cross-over study, DSPD patients (N = 20) were treated with 5 mg melatonin or placebo, taken between 19:00 and 21:00 (time chosen by each patient) for four weeks (level 1).<sup>50</sup> Two consecutive PSGs were performed during an imposed sleep schedule (24:00 to 08:00) on three occasions: at baseline (before treatment), then after each arm of treatment. Melatonin treatment led to normalization in the rhythm of aMT6s excretion compared to placebo, and significantly reduced sleep onset latency as determined by PSG. However, PSG-determined TST was not increased, nor were self-reported measures of daytime alertness improved.

A recent double-blind study tested two doses of melatonin (0.3 and 3 mg) vs. placebo (level 2).<sup>41</sup> Circadian phase using DLMO and core body temperature minimum (CBTmin.) was measured before and after treatment. Treatment was administered between 1.5 and 6.5 hours prior to the DLMO for four weeks. Both doses advanced DLMO and CBTmin; the earlier the melatonin was administered relative to DLMO, the larger the phase advance, consistent with the reported melatonin PRC.<sup>51</sup>

*Conclusion: The evidence is quite strong that melatonin, timed to promote a corrective phase advance, is an effective treatment for DSPD. Determining the optimal parameters for scheduling and dosing will require more study.*

### **12.4.4. Vitamin B12**

Some early case reports and smaller studies suggested that vitamin B12 might be useful for CRSDs by some unknown mechanism. This hypothesis was quite rigorously tested in a large (N = 55), multicenter, placebo-controlled trial in which Vitamin B12 (1 mg), or placebo, was administered to DSPD patients three times a day for four weeks (level 1).<sup>52</sup> No benefit was seen from the sleep log data.

*Conclusion: Vitamin B12 is not an effective treatment for DSPD.*

### **12.4.5 Promoting Sleep with Hypnotic Medication**

There is one report involving uncontrolled clinical observations indicating some benefit of hypnotic medications for DSPD (level 4).<sup>44</sup>

*Conclusion: There is insufficient evidence to assess the safety and efficacy of hypnotic medication in the treatment of DSPD.*

### **12.4.6 Promoting Alertness with Stimulant Medication.**

A stimulant medication administered to promote alertness upon arising could be clinically justified, but there are no data on this practice.

*Conclusion: There is no evidence to assess the safety and efficacy of stimulant medication in the treatment of DSPD.*

## **13.0 FREE-RUNNING DISORDER (FRD)—ALSO REFERRED TO AS NON-24-HOUR SLEEP-WAKE SYNDROME.**

### **13.1 Diagnostic Issues**

Normal (unaffected) subjects who are maintained in an inpatient research environment devoid of time cues eventually develop free-running rhythms. The earliest studies of human subjects in time-free environments concluded that most people have an intrinsic circadian period much longer than 24 hours, averaging about 24.5 h; however, more recent studies using the forced desynchrony protocol have found the average to be significantly shorter; i.e., 24.15 h.<sup>53</sup> In either case, the human circadian period is usually longer than 24 h. Patients with free-running rhythms have circadian cycles that mimic those of subjects in time-free environments, and thus are thought to reflect a failure of entrainment. The condition is very rare in normally sighted people, but quite common in the totally blind who have no access to the entraining effects of the light/dark cycle.<sup>54</sup>

Because the condition is rare in sighted people, the data consist almost entirely of level 4, single case reports,<sup>45,55-67</sup> or studies with few subjects,<sup>68-71</sup> although Hayakawa et al.<sup>60</sup> recently reported an accumulated series of 57 patients. A high proportion (about 25%) of sighted people with FRD have associated psychiatric disorders.<sup>60</sup> A similar proportion of patients have a prodromal history of DSPD.<sup>45</sup>

### **13.2 Risk Factors**

#### **13.2.1 Age**

Judging from the limited number case reports, in sighted people this disorder typically begins in the teenage years and rarely after age 30. In the blind, FRD can occur at any age, depending on when light perception is lost.<sup>54</sup> It remains uncertain as to whether the free-running circadian period (*tau*) in humans changes from childhood, through teenage and young adult years, potentially modifying the periodicity of symptoms. Although a forced-desynchrony study reported a shortening of *tau* in an elderly man (level 4),<sup>72</sup> another study of blind subjects suggests a slight lengthening (level 4).<sup>73</sup>

*Conclusion: In sighted people, the onset of FRD occurs in the teens of twenties, and almost never after age 30. In the totally blind (i.e., those with retinas that are entirely nonfunctioning), the onset is probably coincident with the loss of sight.*

#### **13.2.2. Gender**

Twenty-two of the 25 single case reports of sighted patients with FRD were males. However, in the series of 57 patients reported by Hayakawa et al. (level 4),<sup>74</sup> 28% were female. There do not appear to be any sex differences in FRD caused by total blindness.

*Conclusion: Sighted males are at significantly greater risk for FRD. There are insufficient data to assess whether gender is a risk factor for FRD in totally blind individuals.*

#### **13.2.3 Light Exposure**

As mentioned above, most subjects who are maintained in an inpatient research environment devoid of time cues eventually develop free-running rhythms. There may also be some atypical

non-inpatient (natural) environments that give rise to free-running rhythms; for example, the 18-hour day on a submarine.<sup>75</sup> One study found a delayed sleep propensity onset relative to the circadian pacemaker in FRDs; this phase angle abnormality would accelerate light-induced phase delays, leading to a sleep-wake cycle that is longer than 24 hours (level 3).<sup>71</sup>

Totally blind people, living in normal society, often have a free-running circadian period of about 24.5 h, similar to research subjects living in time-free environments.<sup>54</sup> In these individuals, reduced total sleep time and other sleep abnormalities have been documented with PSG (levels 2 and 1, respectively).<sup>76,77</sup> The occurrence of free running rhythms in the totally blind indicates that some light/dark signal is critical, if not essential, for normal entrainment of humans. However, the light intensity threshold for entrainment appears to be quite low as legally blind subjects with some light perception are usually normally entrained. Also, in sighted subjects, exposure to a very dim light-dark cycle, with light levels of ~1.5 lux—equivalent to candle light—was sufficient to maintain circadian entrainment to the 24.0 h day in one study.<sup>78</sup> In addition, increasing the light intensity to ~25 lux was sufficient to entrain some sighted subjects to a 24.6 h day.<sup>79</sup>

*Conclusion: In sighted people, environments with continuous low light levels and atypical schedules (e.g., submarine duty) may predispose to FRD. A large proportion of totally blind people have FRD, indicating that light is very important for entrainment, but that nonphotic cues can be sufficient for some people.*

### **13.3 Assessment Tools**

#### **13.3.1 Sleep Log**

Sleep-wake diaries (sleep logs) are consistently recommended as a method for evaluating sleep schedules, and are especially useful for documenting sleep patterns in FRD's.

#### **13.3.2 Morningness-Eveningness Questionnaire**

There is insufficient data to evaluate the efficacy of the MEQ as an assessment tool for FRD.

#### **13.3.3 Polysomnography**

There is insufficient data to evaluate the efficacy of PSG as an assessment tool for FRD.

#### **13.3.4 Phase Markers**

The majority of recent case reports of *FRD* in sighted people have used the melatonin rhythm as a marker for circadian phase (level 4).<sup>57-60,66,67,71,80</sup>

The study by Lewy and Newsome<sup>81</sup> was the first to use the timing of melatonin secretion to detect free-running rhythms (and other phase abnormalities) in totally blind subjects. Subsequently, most of the studies of blind subjects have also used melatonin as a marker (level 2),<sup>54,77,82,83</sup> (level 4)<sup>84-87</sup> although a non-24-hour, free-running rhythm has also been demonstrated with serial measurements of core temperature in one subject (level 4).<sup>72</sup> Although about 50% of totally blind people have free-running rhythms, many are normally entrained or entrained at an abnormal phase.<sup>54</sup> Therefore, the diagnosis of FRD in a blind person is not secure

until circadian phase has been assessed three or four times at intervals separated by several weeks.

*Conclusion: Multiple serial determinations (separated by at least one week) of circadian phase (typically by measuring melatonin onsets) can be useful for the diagnosis of FRD.*

### **13.4 Treatment (Sighted)**

#### **13.4.1 Prescribed Sleep/Wake Scheduling**

An early study (n = 4) suggested that increasing the potency of time cues (*zeitgebers*) could improve sleep-wake rhythms in children with FRD caused by neurological disorders (level 4)<sup>88</sup> but this finding has not been replicated.

#### **13.4.2 Timed Light Exposure**

Because FRD is very uncommon in sighted people, the literature consists only of case reports (level 4). Timed (morning) bright light exposure was found to successfully entrain circadian rhythms in five separate cases (level 4).<sup>58,60,65,89,90</sup> However, no placebo-controlled trials have been conducted.

#### **13.4.3 Timed Melatonin Administration**

We found four level 4 case reports of successful treatment of sighted FRD with melatonin administered around the hour of the desired bedtime when it would be predicted to cause a phase advance.<sup>57,63,80,90</sup> The most common dose was 3 mg and the duration of treatment ranged from one month to six years. In one study,<sup>63</sup> the treatment was interrupted for a double-blind, placebo-controlled dose escalation.

*Conclusion: Although the studies are limited by the rarity of this condition, both appropriately timed bright light exposure and melatonin administration have shown to entrain patients with FRD.*

#### **13.4.4 Promoting Sleep with Hypnotic Medication**

There are no data to evaluate the safety and efficacy of hypnotic medication in the treatment of FRD.

#### **13.4.5 Promoting Alertness with Stimulant Medication**

There are no data to evaluate the safety and efficacy of stimulant medication in the treatment of FRD.

#### **13.4.6 Other Treatments**

One 15-year-old girl was successfully entrained for a year with vitamin B12 1.5 mg three times daily,<sup>91</sup> and a 17-year-old boy responded to high daily doses (3000 micrograms per day).<sup>92</sup> However, a multicenter trial of B12 for DSPD (N = 50) failed to find any benefit (level 2).<sup>52</sup>

### **13.5 Treatment (Blind)**

#### **13.5.1 Prescribed Sleep/Wake Scheduling**

In a single case study, described by Sack et al.<sup>54</sup> an FRD blind subject was provided with a prescribed sleep schedule that was

congruent with his previously determined free-running circadian period as derived from melatonin onset determinations. His sleep duration and quality greatly improved. It is unknown how many blind people with free-running rhythms adopt such sleep schedules on their own. However, many blind people keep strict 24-hour sleep wake schedules either on their own or as part of a research protocol and fail to entrain.<sup>54</sup>

### **13.5.2 Timed Melatonin Administration**

Following the demonstration of entrainment in animals with free-running rhythms,<sup>93</sup> melatonin has been tested as a treatment in totally blind people. In addition to several positive case reports (level 4),<sup>94-97</sup> there have been two small single-blind, placebo-controlled melatonin treatment trials demonstrating successful entrainment of free-running rhythms in totally blind people (level 2).<sup>77,82,83</sup> In one study,<sup>82</sup> 3 of 7 subjects entrained to 5 mg of melatonin given for 35-71 days at 21:00. In the other study,<sup>77</sup> 6 of 7 subjects entrained to 10 mg given at the usual bedtime for 3 to 9 weeks. In this study, three of the subjects were given a 10 mg dose that was gradually stepped-down every other week to 0.5. Melatonin treatment on this step-down dosing schedule maintained entrainment, and free-running rhythms recurred after the cessation of treatment. Subsequently, these same subjects were successfully entrained with 0.5 mg de novo (level 4).<sup>85</sup> The subject who failed to entrain in the initial trial to 10 mg was subsequently entrained with a 0.5 dose (level 4).<sup>86</sup> The effectiveness of the lower dose was attributed to its selective activity on the advance zone of the melatonin phase response curve with no “spillover” to the delay zone. In another recent trial,<sup>83</sup> the 0.5 mg dose entrained 6 of 10 subjects (level 2). In summary, the evidence is compelling that melatonin can entrain the majority of totally blind patients with FRD. Furthermore, a *physiological* dose (0.5 mg) appears to be as effective as a *pharmacological* dose (5 to 10 mg), and in some cases, more effective.<sup>86</sup>

*Conclusion: Appropriately timed melatonin, in doses from 0.5 mg to 10 mg, have been shown to entrain totally blind people who have FRD. The effective dose may be even less than 0.5 mg (the dose that approximates a physiological plasma concentration). Treatment must be sustained or relapse will occur. Entrainment may not occur for weeks or months after initiating treatment, depending on the phase of the patient's rhythm when treatment is started and the period of the patient's free-running rhythm.*

### **13.5.3 Promoting Sleep with Hypnotic Medication**

There are no data to evaluate the safety and efficacy of hypnotic medication in the treatment of FRD in the blind.

### **13.5.4 Promoting Alertness with Stimulant Medication**

There are no data to evaluate the safety and efficacy of stimulant medication in the treatment of FRD in the blind.

## **14.0 IRREGULAR SLEEP-WAKE RHYTHM (ISWR)**

### **14.1 Diagnostic Issues**

ISWR is characterized by the relative absence of a circadian pattern to the sleep-wake cycle. Total sleep time may be compara-

tively normal, but instead of being consolidated into distinct bout or bouts, sleep times are shortened, and in extreme cases, almost randomly distributed throughout the day and night. In otherwise healthy people, the condition may be a result of very poor sleep hygiene; however, ISWR is commonly associated with neurological impairment, such as mental retardation in children and dementia in older adults.

The cause (or more likely, the causes) of this association are unknown, but damage to the circadian pacemaker in the SCN is clearly implicated as an important, if not a major, etiological factor. Indeed, experimental ablation of the SCN in animals produces a loss of circadian rhythmicity that strongly resembles the sleep/wake pattern typically seen in older adults with dementing disorders, particularly in the later stages of the dementia.<sup>98</sup> However, it is important to note that clinical studies, the bulk of which have been carried out in older adults with dementia (particularly Alzheimer disease) have rarely used the formal sleep diagnostic criteria for ISWR, so for the purposes of this review of the literature, ISWR diagnosis was inferred based on the clinical description of the subjects.

### **14.2 Risk Factors**

#### **14.2.1 Age**

While complaints of nighttime sleep fragmentation and daytime napping have been consistently reported to increase with age,<sup>99</sup> a recent, and extremely comprehensive, meta-analysis of objective sleep changes across the human lifespan<sup>100</sup> strongly indicates that, although the prevalence of ISWR increases with age, this increase is secondary to the increased prevalence of associated medical disorders with increased age. Age is not an independent risk factor for ISWR; rather, it is the medical burdens (or the comorbid medical and psychiatric illnesses) which constitute the main risk factors for sleep pathology, including the increase in prevalence of ISWR with advancing age.<sup>101,102</sup> As will be discussed in detail below, ISWR is particularly associated with neurological impairment in older adults, most importantly, Alzheimer disease (AD).<sup>103-106</sup>

*Conclusion: Age is a risk factor for ISWR mainly due to the association of aging with increased medical and psychiatric illness, especially Alzheimer disease.*

#### **14.2.2 Gender**

As none of the neurodegenerative disorders that typically result in ISWR has a gender difference, there is no reason to suspect a gender difference in ISWR. We found no reports of a gender difference.

*Conclusion: We found no evidence suggesting any gender differences in ISWR, or that gender might be a risk factor for ISWR per se.*

#### **14.2.3 Light Exposure**

Older adults are exposed to reduced light levels in their daily lives relative to younger individuals (reviewed by Van Someren, et al.).<sup>107</sup> This reduction may be exacerbated by disorders of vision, which are common in older adults, and which may further attenuate the impact of ambient light on the SCN. Finally, the

SCN itself is adversely affected by age.<sup>108</sup> The impact of each of these factors is magnified in patients with AD, including those who are community-dwelling, who have been shown to be exposed to less light than age-matched healthy normal controls.<sup>109</sup> Furthermore, both the retina and optic nerve are compromised in AD, as is the SCN.<sup>108</sup> The inadequate exposure to ambient daytime light in AD patients, who typically occupy the majority of beds in nursing homes, has provided the rationale for the use of daytime light treatment in these patient populations.

*Conclusions: Older adults, especially those who are institutionalized, are exposed to less intense light than younger people, but questions remain as to the importance of reduced light exposure as an etiologic factor in ISWR.*

#### **14.2.4 Familial (Genetic) Predisposition**

While there is no direct evidence for a genetic basis for ISWR, there are several lines of evidence that suggest that the sleep disturbance seen in AD is at least partially based on genetic factors. Actigraphic studies of AD patients have demonstrated longitudinal deterioration of sleep quality,<sup>110,111</sup> and most of this longitudinal variance in sleep appears to be related to an inherent “trait” of the individual patient.<sup>112</sup> This suggests that genetic factors may help determine the ultimate course and level of sleep deterioration seen in a given AD patient,<sup>112,113</sup> a hypothesis consistent with considerable research suggesting that much of the circadian variation in many physiological systems is controlled by a limited number of similar genes across species (reviewed by Clayton, et al).<sup>2</sup>

*Conclusion: The tentative relationship of genetic factors as a risk for ISWR needs to be clarified by future studies.*

### **14.3 Assessment Tools**

#### **14.3.1 Sleep Log**

As indicated in our previous paper, there are no systematic studies comparing different sleep logs, and this question was not systematically pursued. For demented patients who are unable to keep logs themselves, structured behavioral observation has been used with considerable success in clinical settings.<sup>114</sup> However, outside of a clinical setting, unstructured caregiver reports can frequently be inaccurate when compared with more objective assessment, specifically actigraphic recording.<sup>115</sup>

#### **14.3.2 Morningness-Eveningness Questionnaire**

While the MEQ has been used to examine the circadian characteristics of healthy older adults<sup>116</sup> it has not been used to evaluate ISWR, which is characterized more by an absence of circadian sleep/wake patterns rather than in a phase shift.

#### **14.3.3 Actigraphy**

The Standards of Practice Committee of the American Academy of Sleep Medicine has provided practice guidelines for the use of actigraphy<sup>117</sup> concluding that, “actigraphy may be useful in characterizing and monitoring circadian rhythm patterns or disturbances in certain special populations (e.g., demented individuals), and appears useful as an outcome measure in certain applications and populations.” They further recommended the use of a “con-

comitant... sleep log for artifact rejection and timing of lights out and on” and “conducting actigraphy studies for a minimum of three consecutive 24-hour periods.”

#### **14.3.4 Polysomnography**

There have been numerous PSG studies of sleep/wake changes in AD patients.<sup>104-106,118-121</sup> All of these have consistently reported decreased slow wave sleep and increased nighttime wakefulness.

Prinz et al<sup>106</sup> demonstrated that not only was the nighttime sleep of AD patients significantly impaired relative to age-matched control subjects, with marked increased nighttime wakefulness and decreased slow wave sleep, but that these patients napped significantly during the day, although this increase in daytime sleep consisted of light sleep (Stages 1 and 2) and did not compensate for the SWS lost during the night. Vitiello et al<sup>104</sup> demonstrated that the increased nighttime wakefulness that characterizes AD increases with disease severity. Moe et al<sup>122</sup> used regression analyses to show that more waking episodes during the night, and longer REM latencies, were associated with impaired cognition and function, while more REM and slow wave sleep was associated with preserved cognition and function in a carefully screened sample of 78 community dwelling AD patients.

*Conclusion: PSG studies have been important in research studies for characterizing the sleep of AD patients, but the evidence does not suggest that PSG is necessary for the clinical evaluation of ISWR, as the sleep disturbance can readily be determined either by structured behavioral observation or by actigraphic recording.*

#### **14.3.5 Phase Markers**

##### **14.3.5.1 CBT Rhythm**

The impact of aging per se on human circadian rhythms has recently been reviewed by Monk<sup>123</sup> who concluded that healthy older people tend to have earlier circadian phases, with a corresponding tendency to go to bed and to arise from bed earlier than younger adults, but not to have reduced circadian amplitudes. Early studies comparing the core body temperature rhythm of AD to control subjects reported either no differences<sup>124,125</sup> or, seemingly counterintuitive with the phenomenology of the disorder, phase delays in the AD subjects.<sup>126</sup> More recent studies have also reported finding phase delays in AD patients relative to controls. In the most recent study, Harper<sup>127</sup> evaluated the consequences of aging and AD on the endogenous circadian rhythm. They measured rest/activity and core body temperature using a constant routine in groups of normal older adults, patients with probable AD, and a comparison group of young, normal volunteers.<sup>128</sup>

They noted that some of the observed changes in endogenous circadian rhythm in AD were consonant with those seen in normal aging; that is, a reduction in amplitude and a loss of phase coordination relative to the young subject group. But they also observed a phase delay in the AD group, which positively correlated with increasing AD severity.

It is important to note that all studies reporting a phase delay of temperature rhythms<sup>126,127,129,130</sup> studied institutionalized patients who were more impaired than the community-dwelling patients who were reported to have no phase difference relative to controls.<sup>125</sup>

*Conclusion: Limited evidence suggests that core body temperature phase delay might be a circadian marker for ISWR in late-stage, institutionalized AD patients, although this finding is somewhat counterintuitive with the phenomenology of the disorder, which would be more consonant with decreased circadian amplitude of the SCN-generated arousal/wakefulness signal.*

#### **14.3.5.2 Melatonin Rhythm**

Melatonin rhythms are impaired by both age and by cognitive impairment.<sup>131,132</sup> While an early study of this relationship reported no observable changes,<sup>133</sup> more recent studies have reported that nocturnal melatonin levels are reduced in AD<sup>131,134,135</sup> even in early, or preclinical AD patients,<sup>136</sup> while daytime levels are elevated.<sup>137</sup> According to some models, decreased melatonin secretion could permit greater expression of an SCN-generated arousal/wakefulness signal, which might explain some of the ISWR symptoms seen in AD patients. In contrast to these reports of changes in circadian amplitude of the melatonin rhythm, there are no reports of a change in the phase of this rhythm in AD, although there has been a report of larger variation in peak times relative to control subjects.<sup>134</sup>

*Conclusion: Evidence indicates that, while there is no phase shift of melatonin rhythms in AD patients, there is diminished circadian amplitude (this reduced secretion, might explain some of the ISWR symptoms seen in AD patients). The diminished amplitude of the melatonin rhythm has provided justification for treatment studies of melatonin supplementation in AD populations (see below).*

#### **14.3.5.3 Cortisol Rhythm**

In contrast to melatonin, nocturnal cortisol levels are elevated in healthy aging, particularly in the early morning hours,<sup>138,139</sup> and are further elevated in AD.<sup>140-142</sup> A recent study<sup>143</sup> examined both sleep/wake and cortisol rhythms in healthy older controls and mildly to moderately demented AD subjects. AD patients, particularly the moderately demented group, showed elevated cortisol levels in the afternoon.

*Conclusion: The maintenance of a highly rhythmic cortisol secretory pattern, even in moderate stage AD patients, suggests that cortisol rhythm is not a useful circadian marker for ISWR, although cortisol levels that are elevated relative to healthy older controls may contribute directly to the progressive neuropathology and cognitive impairment seen in AD.*

### **14.4 Treatment**

#### **14.4.1 Prescribed Sleep/Wake Scheduling.**

While there have been no studies examining prescribed sleep/wake scheduling per se, some of the mixed modality treatments, described below,<sup>144,145</sup> included structuring the sleep/wake schedule as parts of their treatment protocols.

#### **14.4.2 Circadian Phase Shifting (or Increasing Circadian Amplitude)**

Although abnormalities in both circadian phase and amplitude may underlie the other CRSDs, diminished circadian amplitude is

often hypothesized to be especially important in ISWR. Consequently, numerous studies have attempted to treat inferred ISWR by structuring and reinforcing relevant circadian time cues (*zeitgebers*) in order to increase the amplitude of the circadian cycle. These interventions have included daytime light exposure, melatonin supplementation, and mixed-modality treatments, typically combining daytime light exposure with behavioral interventions, such as sleep/wake scheduling and increasing daytime activity.

#### **14.4.2.1 Timed Light Exposure**

We found nine studies that tested the effects of bright light exposure on older nursing home patients who could be presumed to meet criteria for ISWR: (level 2),<sup>146-148</sup> (level 3),<sup>149,150</sup> level 4.<sup>151</sup>

Most of these studies report modest beneficial impact of daytime light exposure on measures of sleep. For example, in a light treatment trial (level 2),<sup>147</sup> AD patients with irregular sleep were randomly assigned by block stratification (morning, evening, or all-day agitation) to 1 of 3 treatment groups: AM (09:30-11:30) Bright, AM Dim Red, or Evening (17:30-19:30) Bright. Bright light (BL) exposure of 2500 lux consolidated nighttime sleep by lengthening the duration of the maximum sleep bouts during the night compared to baseline. Nighttime sleep increased >30 min under AM plus BL, and >20 minutes for PM plus BL. PM plus BL also strengthened the circadian activity rhythm. However, none of the three light treatment conditions had any significant effect on total amounts of actigraphically measured sleep or wakefulness across the 24-h day.

Nevertheless, not all studies reported positive effects. For example, in a 10-week trial of morning light treatment (2500 lux, 09:30 to 10:30), there were no significant effects on actigraphically measured nighttime sleep or daytime wakefulness (level 2);<sup>148,152</sup> however this group did report nonsignificant trends toward improved amplitude and acrophase of rest-activity rhythms.

We found just one study of light treatment in children with presumed ISWR (level 4).<sup>153</sup> Fourteen severely mentally retarded children who had failed treatment with hypnotics and behavioral therapy were given bright light (4000 lux) for 45 minutes in the morning for eight months, and five responded.

In general, treatment studies using light exposure hypothesize a circadian amplitude disturbance (rather than a phase disturbance) that is quite consistent with the phenomenology of the disorder. While it is possible that light therapy may be directly interfering with daytime napping, and thereby improving sleep consolidation at night by increasing nighttime sleep drive rather than through a circadian mechanism, the positive findings of better-controlled studies, which employ comparably timed control interventions mitigate against this possibility.

*Conclusion: A number of level 2 studies indicate that bright light exposure during the day may improve the consolidation of sleep and wake in nursing home patients with AD and associated ISWR, but the effect appears to be modest and more data are needed, particularly as to the most efficacious timing of light exposure.*

#### **14.4.2.2 Timed Melatonin Administration**

Melatonin has typically been used in studies seeking to improve sleep quality by increasing amplitude rather than phase shift sleep/wake rhythms. As noted above, exogenous melatonin

may increase circadian amplitude by facilitating melatonin-induced suppression of the SCN arousal/wakefulness signal.

Pillar et al (level 4)<sup>154</sup> reported some success in treating sleep disturbances in children with presumed ISWR and severe psychomotor retardation. However, this study was a poorly controlled and employed a small sample size. Jan and colleagues (level 4)<sup>155</sup> reported an incomplete, but nevertheless significant benefit in an open label trial of melatonin (2 to 20 mg) given at bedtime to neurologically multiply-disabled children with chronic sleep wake cycle disorders. A later report (level 4)<sup>156</sup> compared controlled release melatonin (CR) to immediate release (IR) (2 to 12 mg) in a similar population; the CR formulation was found to be superior to IR for sleep maintenance. A trial of melatonin which sought to improve sleep timing and quality in girls with Rett syndrome and associated mental retardation, was negative (level 2).<sup>157</sup>

Serfaty et al (level 1)<sup>158</sup> randomized forty-four participants with DSM-IV diagnosis of dementia and comorbid sleep disturbance to a seven-week double blind crossover trial of two weeks of slow release melatonin (6 mg) versus placebo. It should be noted that only 25 out of 44 patients completed the trial. Melatonin had no effect on actigraphically measured total time asleep, number of awakenings, or sleep efficiency. Singer et al. (level 1),<sup>159</sup> in a large multicenter trial, randomized 157 Alzheimer dementia patients with insomnia and daytime sleepiness to melatonin, 2.5 mg sustained-release; melatonin, 10 mg immediate-release, or placebo. The protocol consisted of 2 to 3 weeks of baseline measurement, 8 weeks of treatment, and 2 weeks placebo washout. Actigraphically monitored sleep was not significantly improved with either melatonin dose or placebo.

*Conclusion: the available data do not support the use of melatonin for treating ISWR, at least in association with AD. However, the impact of smaller doses of melatonin and that of the emerging melatonin receptor agonists has yet to be determined.*

#### **14.4.3 Mixed Modality Treatments**

Alessi et al. (level 2)<sup>144</sup> treated 118 older nursing home patients with presumed ISWR with a mixed modality treatment that combined 30 minutes or more of daily sunlight exposure (>10,000 lux) with four other behavioral strategies versus a usual-care control. The combined regimen produced a small but significant improvement in sleep (by shortening nighttime wake episodes) and a 46% decrease in observed daytime sleeping at follow-up compared to controls ( $P < 0.001$ ). However, the intervention was given for only five days, so the feasibility and effectiveness of longer-term mixed-treatment protocols such as this remains unknown.

Interestingly, a comparable study in community dwelling AD patients (again with inferred ISWR diagnoses) was conducted by McCurry et al. (level 1).<sup>145</sup> Thirty-six community-dwelling (AD) patients and their family caregivers participated. All participants received written materials describing age- and dementia-related changes in sleep, and standard principles of good sleep hygiene. Caregivers in active treatment received specific recommendations about setting up and implementing a sleep hygiene program for the dementia patients, and training in behavior management skills. Patients in active treatment were also instructed to walk daily and increase daytime light exposure with the use of a light box. Control subjects received general dementia education and caregiver support. Sleep outcomes were derived from one week of sleep-wake activity measured actigraphically at baseline, post-test

(2 months), and at 6-month follow-up. Active treatment patients showed significant ( $P < 0.05$ ) post-test reductions in number of nighttime awakenings and total time awake at night compared to control subjects. At 6-month follow-up, treatment gains were maintained and additional significant improvements in duration of night awakenings and circadian organization of sleep emerged.

*Conclusion: While the supporting data for such mixed modality approaches to the treatment of ISWR are very limited, they are also encouraging. More research is needed in this area to determine if such treatment approaches might be more efficacious than the use of light alone.*

#### **14.4.4 Promoting Sleep with Hypnotic Medication.**

Controversies regarding the use of sedating medications in demented patients revolve around issues of efficacy as well as potential toxicity, neither of which has been resolved by appropriately comprehensive empirical study. There is evidence, however, that sedative-hypnotics as a class may be inappropriately prescribed or overprescribed for demented patients. A two-year longitudinal study of 76 elderly patients with AD or vascular dementia in assisted living homes found that 24% used regular prescription hypnotics at baseline and this proportion remained relatively stable over time, while prescribing of “as-needed” hypnotics increased from 3% to 17% after one year and 13% at two years.<sup>160</sup> The total number of prescriptions for all drugs also rose over time, indicating increasing potential for drug interactions due to polypharmacy. A study of adverse drug events in residents of 18 skilled nursing facilities found that sedative-hypnotics accounted for 13% of all incidents and 18% of those considered preventable.<sup>161</sup> In a now-classic controlled trial, Avorn et al<sup>162</sup> reported that use of sedative-hypnotics could be substantially reduced by an educational program in geriatric psychopharmacology in nursing homes without apparent deterioration in residents’ clinical status (N = 823 residents in 12 nursing homes); although detailed data on sleep and dementia diagnosis were not reported.

Numerous other studies have now shown that use of prescription drugs do not necessarily improve subjective and objective ratings of sleep quality in community-dwelling or institutionalized older patients (level 2),<sup>163,164</sup> (level3).<sup>165</sup> However, no controlled clinical trials have evaluated the efficacy or toxicity of benzodiazepines or the newer non-benzodiazepine receptor agonists or the only available melatonin agonist in groups of demented patients.

It is important to note that the benzodiazepine and melatonin agonists are the only compounds FDA-approved for treatment of insomnia, and that the recent NIH State-of-the-Science Consensus Conference on Insomnia<sup>166</sup> has concluded that, despite the common use of sedating antidepressants, antipsychotics and antihistamines for sleep disturbance, all of these agents carry significant risks, and thus their use in the treatment of sleep disturbance cannot be recommended.

*Conclusion: There are no published reports of controlled trials assessing the efficacy of either FDA-approved or commonly used compounds for treatment insomnia in patients with Alzheimer disease. The absence of rigorous, well-controlled clinical trials of pharmacological treatments for sleep disturbance in demented patients represents a serious and continuing gap in our knowledge.*

#### 14.4.5 Promoting Alertness with Stimulant Medication

At this time there are no published reports on promoting alertness in AD patients with stimulant drugs such as modafinil.

#### 15.0 DISCUSSION

As we emphasized in Part I of our report, sound clinical practice is based on two fundamental considerations: 1) an understanding of the pathophysiology of a disorder, derived from biological science; 2) empirical evidence, derived from clinical application, ideally from well-designed clinical trials. A foundation for understanding the pathophysiology of ASPD, DSPD, FRD, and ISWR has been built on the principles of circadian rhythm science, and these principles have pointed the way to rational clinical interventions. We look forward to additional clinical trials that can translate circadian scientific principles into practice.

One of the major challenges for future clinical research is to define more precisely the boundaries between subclinical tendencies for delayed, advanced or irregular sleep schedules, and diagnosable CRSDs. Indeed, much of the research reviewed in this paper did not utilize formal (criteria based) diagnostic categories, leaving the clinician in somewhat of a dilemma regarding the application of this research to “real” patients.

For medical research and practice (in general), defining a disorder by establishing an appropriate “cut off” between “normal” and pathological can be a complex process; for example, it is not easy to achieve consensus on a definition of a pathological blood pressure or cholesterol profile. In sleep medicine, there is a fairly high level of agreement regarding a pathological respiratory disturbance index (RDI) or an abnormal MSLT, but consensus is not complete. In regard to the CRSDs, some quantitative markers for circadian phase and amplitude are becoming available, and in the future, such markers may provide the tools that are needed to objectively define the appropriate boundaries for diagnosis. Currently, serial phase determinations using the melatonin onset can define FRD disorder with a very high level of diagnostic consensus. Measuring the angle (temporal relationship) between circadian phase (e.g., DLMO) and the timing of sleep (actigraphy or sleep logs) is a metric that relates to the fundamental theories regarding the pathophysiology of CRSDs. Although quite feasible, phase angle determinations have rarely been reported, but seem a fruitful direction for future research.

Assessing circadian amplitude is more of a challenge than assessing phase. Alterations in the amplitude of circadian markers such as CBT or melatonin may reflect changes in the end organs, rather than the strength of the circadian signal.

Even if sophisticated objective measures such as phase angle are available, they may not totally explain the symptom complex of CRSDs. It is quite possible that some people are tolerant to large disparities in circadian synchronization, while others are quite sensitive. Furthermore, there is the problem that observed circadian/sleep abnormalities may be driven by complex underlying pathology; for example, depression or (especially in the cases of ISWR) neurodegenerative disease.

Limitations notwithstanding, the current body of research on CRSDs provides the clinician with reasonable guidance for practice, and the investigator with inviting directions for future research.

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