

Practice Parameters for the Clinical Evaluation and Treatment of Circadian Rhythm Sleep Disorders

An American Academy of Sleep Medicine Report

Timothy I. Morgenthaler, MD¹; Teofilo Lee-Chiong, MD²; Cathy Alessi, MD³; Leah Friedman, PhD⁴; R. Nisha Aurora, MD⁵; Brian Boehlecke, MD⁶; Terry Brown, DO⁷; Andrew L. Chesson Jr., MD⁸; Vishesh Kapur, MD, MP⁹; Rama Maganti, MD¹⁰; Judith Owens, MD¹¹; Jeffrey Pancer, DDS¹²; Todd J. Swick, MD¹³; Rochelle Zak, MD⁹; Standards of Practice Committee of the AASM

¹Mayo Sleep Disorders Center, Mayo Clinic, Rochester, MN; ²National Jewish Medical and Research Center, Denver, CO; ³UCLA/Greater Los Angeles VA Healthcare System, Sepulveda, CA; ⁴Department of Psychiatry, Stanford University School of Medicine, Stanford, CA; ⁵Center for Sleep Medicine, Mount Sinai Medical Center, New York, NY; ⁶University of North Carolina, Chapel Hill, NC; ⁷St. Joseph Memorial Hospital, Sleep Disorders Center, Murphysboro, IL; ⁸Neurology Department, Louisiana State University Medical Center, Shreveport, LA; ⁹University of Washington, Sleep Disorders Center at Harborview, Seattle, WA; ¹⁰Department of Neurology, Barrow Neurological Institute, Phoenix, AZ; ¹¹Department of Pediatrics/Ambulatory Pediatrics, Rhode Island Hospital, Providence, RI; ¹²Toronto, Ontario, Canada; ¹³The Methodist Neurological Institute, The Methodist Hospital, Houston, TX

The expanding science of circadian rhythm biology and a growing literature in human clinical research on circadian rhythm sleep disorders (CRSDs) prompted the American Academy of Sleep Medicine (AASM) to convene a task force of experts to write a review of this important topic. Due to the extensive nature of the disorders covered, the review was written in two sections. The first review paper, in addition to providing a general introduction to circadian biology, addresses “exogenous” circadian rhythm sleep disorders, including shift work disorder (SWD) and jet lag disorder (JLD). The second review paper addresses the “endogenous” circadian rhythm sleep disorders, including advanced sleep phase disorder (ASPD), delayed sleep phase disorder (DSPD), irregular sleep-wake rhythm (ISWR), and the non-24-hour sleep-wake syndrome (nonentrained type) or free-running disorder (FRD). These practice parameters were developed by the Standards of Practice Committee and reviewed and approved by the Board of Directors of the AASM to present recommendations for the assessment and treatment of CRSDs based on the two accompanying comprehensive reviews. The main diagnostic tools considered include sleep logs, actigraphy, the Morningness-Eveningness Questionnaire (MEQ), circadian phase markers, and polysomnography. Use of a sleep log or diary is indicated in the assessment of patients with a suspected circadian rhythm sleep disorder (Guideline). Actigraphy is indicated to assist in evaluation of patients suspected of circadian rhythm disorders (strength of recommendation varies from “Option” to “Guideline,” depending on the suspected CRSD). Polysomnography is not routinely indicated for the diagnosis of CRSDs, but may be indicated to rule out another primary sleep disorder (Standard). There is insufficient evidence to justify the use of MEQ for the routine clinical evaluation of CRSDs (Option). Circadian

phase markers are useful to determine circadian phase and confirm the diagnosis of FRD in sighted and unsighted patients but there is insufficient evidence to recommend their routine use in the diagnosis of SWD, JLD, ASPD, DSPD, or ISWR (Option). Additionally, actigraphy is useful as an outcome measure in evaluating the response to treatment for CRSDs (Guideline). A range of therapeutic interventions were considered including planned sleep schedules, timed light exposure, timed melatonin doses, hypnotics, stimulants, and alerting agents. Planned or prescribed sleep schedules are indicated in SWD (Standard) and in JLD, DSPD, ASPD, ISWR (excluding elderly-demented/nursing home residents), and FRD (Option). Specifically dosed and timed light exposure is indicated for each of the circadian disorders with variable success (Option). Timed melatonin administration is indicated for JLD (Standard); SWD, DSPD, and FRD in unsighted persons (Guideline); and for ASPD, FRD in sighted individuals, and for ISWR in children with moderate to severe psychomotor retardation (Option). Hypnotic medications may be indicated to promote or improve daytime sleep among night shift workers (Guideline) and to treat jet lag-induced insomnia (Option). Stimulants may be indicated to improve alertness in JLD and SWD (Option) but may have risks that must be weighed prior to use. Modafinil may be indicated to improve alertness during the night shift for patients with SWD (Guideline).

Keywords: Circadian, light therapy, melatonin, naps, jet lag, shift work
Citation: Morgenthaler TI; Lee-Chiong T; Alessi C; Friedman L; Aurora N; Boehlecke B; Brown T; Chesson AL; Kapur V; Maganti R; Owens J; Pancer J; Swick TJ; Zak R; Standards of Practice Committee of the AASM. Practice Parameters for the Clinical Evaluation and Treatment of Circadian Rhythm Sleep Disorders. *SLEEP* 2007;30(11):1445-1459.

Disclosure Statement

This is not an industry supported study. The authors have indicated no financial conflicts of interest.

Submitted for publication August, 2007

Accepted for publication August, 2007

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

1.0 INTRODUCTION

THIS PRACTICE PARAMETER PAPER IS WRITTEN AS A COMPANION ARTICLE TO THE TWO ACCOMPANYING REVIEW ARTICLES ON CIRCADIAN RHYTHM SLEEP disorders (CRSDs) authored by a task force of experts convened by the American Academy of Sleep Medicine (AASM).^{1,2} The companion review papers summarize the peer-reviewed scientific literature published through October 2006. The authors of the review papers evaluated the evidence presented by the reviewed studies according to the Oxford System for Evidence-Based Medicine³ <http://www.cebm.net/index.aspx?o=1025>. Using this infor-

Table 1—Levels of Evidence:

Level	Risk/ Assessment	Treatment
1	Validating ¹ cohort with well-validated reference standards ²	High quality randomized controlled trial (RCT) on well-characterized subjects or patients
2	Smaller or “exploratory” cohort study or one that has incompletely validated reference standards ²	Cohort study or flawed clinical trial (e.g., small N, blinding not specified, possible non-random assignment to treatment, incompletely validated reference standards ²)
3	Case control study or cross-sectional survey	Case control study
4	Case series (and poor quality cohort and case control studies)	Case series (and poor quality cohort and case control studies)

1. Validating studies test the quality of a specific diagnostic test, based on prior evidence.

2. Reference standards: PSG, sleep logs, actigraphy, phase markers, validated self-reports.

Oxford levels adapted from Sackett⁸

mation and a system described by Eddy⁴ (i.e., Standard, Guideline, or Option), the Standards of Practice Committee (SPC) and Board of Directors of the AASM determined levels of treatment recommendation presented in the practice parameters below. The purpose of the present document is to provide evidence-based recommendations for the assessment and treatment of CRSDs.

Due to the large volume of relevant literature, the review was divided into two papers. One discussed shift work disorder (SWD) and jet lag disorder (JLD), both of which are thought to be related to exogenously determined alterations in the timing of sleep and wakefulness rather than disturbances of the endogenous circadian system itself. A second paper discussed circadian rhythm sleep disorders that are considered to result from a primary endogenous cause, including advanced sleep phase disorder (ASPD), delayed sleep phase disorder (DSPD), free-running disorder (FRD), and irregular sleep-wake rhythm disorder (ISWR). The categorization of CRSDs in the two review papers and this practice parameter paper follows the classification provided by the International Classification of Sleep Disorders, 2nd edition (ICSD-2),⁵ with some simplification of terminology. We acknowledge that while the disorders are classified as endogenous or exogenous, the physiologic underpinnings of each disorder are not so surgically separated. In reality, combinations of endogenous and exogenous factors lead to the manifestations of each disorder.

Based upon the accompanying review papers and systematic grading of this evidence, members of the SPC developed these practice parameters as a guide to the appropriate assessment and treatment of CRSDs. The task force did not intensively review the role of actigraphy in the diagnosis of CRSDs since a recently published updated practice parameter paper addresses the use of actigraphy.⁶ To provide a succinct yet comprehensive parameter paper, key recommendations from the recently published actigraphy parameter paper regarding the use of actigraphy in CRSDs are repeated here. In addition, where appropriate, recommendations regarding the use of light therapy in the treatment of CRSDs are presented here as an update of the prior practice parameter paper on the use of light therapy.⁷

2.0 METHODS

The SPC of the AASM commissioned content experts in circadian rhythm sleep disorders in 2005 to review and grade evidence in the peer-reviewed scientific literature regarding the assessment and treatment of circadian rhythm disorders. An extensive review designed to find relevant published evidence retrieved 2084 articles,

and is described in detail in the review paper.¹ Abstracts of these articles were reviewed by task force members to determine if they met inclusion criteria. Initial data extraction, preliminary evidence grading in accordance with the standards in Table 1, and initial data entry into evidence tables were performed by professionals contracted by the SPC to expedite the review process. All evidence table entries were reviewed by at least one other task force member. Thus, all evidence grading was performed by independent review of the article by a minimum of two experts—one, a professional experienced in the evidence review process, and the other a content expert. Areas of disagreement were addressed, and if needed, the chair of the task force arbitrated the final decision on evidence level. Final summaries of information from included articles are listed in an evidence table available at <http://www.aasmnet.org/>.

On the basis of these reviews and noted references, the Standards of Practice Committee of the American Academy of Sleep Medicine (AASM), in conjunction with specialists and other interested parties, developed the recommendations included in this practice parameters paper related to the evaluation and therapy of CRSDs.

In most cases, the strength of the recommendation is based on evidence from studies published in peer-reviewed journals that were evaluated as noted in the evidence table of the companion review papers. However, when scientific data were absent, insufficient, or inconclusive, the recommendations are based upon consensus after review and discussion by the SPC. Those recommendations for which consensus formed the main basis for the recommendation are specifically indicated.

The Board of Directors of the AASM approved these recommendations. All authors of the accompanying review paper, members of Standards of Practice Committee, and the AASM Board of Directors completed detailed conflict-of-interest statements.

These practice parameters define principles of practice that should meet the needs of most patients in most situations. These guidelines should not, however, be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably expected to obtain the same results. The ultimate judgment regarding appropriateness of any specific therapy must be made by the clinician and patient, in light of the individual circumstances presented by the patient, available diagnostic tools, accessible treatment options, resources available, and other relevant factors.

The AASM expects these guidelines to have a positive impact on professional behavior, patient outcomes, and possibly, health care costs. These practice parameters reflect the state of knowledge at the time of development and will be reviewed, updated, and revised

Table 2— AASM Levels of Recommendations

Strength of Recommendation	Definition
Standard	This is a generally accepted patient-care strategy that reflects a high degree of clinical certainty. The term standard generally implies the use of Level 1 Evidence, which directly addresses the clinical issue, or overwhelming Level 2 Evidence.
Guideline	This is a patient-care strategy that reflects a moderate degree of clinical certainty. The term guideline implies the use of Level 2 Evidence or a consensus of Level 3 Evidence.
Option	This is a patient-care strategy that which reflects uncertain clinical use. The term option implies either inconclusive or conflicting evidence or conflicting expert opinion.

as new information becomes available. Each article entered in the evidence tables of the companion review paper was evaluated using the Standards of Practice Committee's levels of evidence (Table 1). This evidence is used to support the strength of the recommendations (Table 2) in this paper. Square-bracketed numbers in this paper refer to sections, tables, or references in the accompanying review papers. Other citations, noted by superscripted numbers, refer to the reference list at the end of this paper.

3.0 RESULTS AND RECOMMENDATIONS

The following recommendations reflect the evidence regarding the diagnosis and treatment of CRSDs in clinical practice obtained from the two accompanying reviews. For brevity, the findings and recommendations are summarized in Table 3. Specific details are reviewed in the practice parameters below.

3.1 General Recommendations for Evaluation of Circadian Rhythm Sleep Disorders

3.1.1 Use of a sleep log or diary is indicated in the assessment of patients with a suspected CRSD. (Guideline)

This recommendation was determined by inclusion of the use of sleep logs in the International Classification of Sleep Disorders, 2nd Edition (ICSD-2)⁵ diagnostic criteria for all CRSDs except jet lag. This recommendation was additionally supported by consensus opinion of the AASM SPC committee.

3.1.2 Actigraphy is indicated to assist in evaluation of patients suspected of CRSDs, including irregular sleep-wake disorder (ISWR), free-running disorder (FRD) (with or without blindness) (Option), and in advanced sleep phase disorder (ASPD), delayed sleep phase disorder (DSPD), and shift work disorder (SWD). (Guideline)

This recommendation reiterates the recently updated practice parameter paper on the use of actigraphy.⁶ Here, we indicate specific disorders. There is generally good agreement among studies showing that actigraphy data correlate with polysomnography (when used), sleep logs, and markers of circadian phase in patients with circadian rhythm sleep disorders, with the conditions indicated.

3.1.3 Actigraphy is useful as an outcome measure in evaluating the response to treatment for CRSDs. (Guideline)

This recommendation is unchanged from the recently updated practice parameter paper on the use of actigraphy.⁶ This prior practice parameter paper and accompanying review provided evi-

dence that changes in actigraphy measures are in agreement with other outcome measures in the assessment of response to intervention in patients with CRSDs.

3.1.4 There is insufficient evidence to recommend the routine use of the Morningness-Eveningness Questionnaire (MEQ) for the clinical evaluation of CRSDs. (Option)

Information regarding evidence for utility of MEQ in specific CRSDs is discussed under the disorder headings in the section below.

3.1.5 Circadian phase markers are useful to determine circadian phase and confirm the diagnosis of FRD in sighted and unsighted patients but there is insufficient evidence to recommend their routine use in the diagnosis of SWD, JLD, ASPD, DSPD, or ISWR. (Option)

Information regarding evidence for specific CRSDs is discussed under the disorder headings in the section below.

3.1.6 Polysomnography is indicated to rule out another primary sleep disorder in patients with symptoms suggestive of both a CRSD and another primary sleep disorder, but is not routinely indicated for the diagnosis of CRSDs. (Standard)

This recommendation reiterates the recently updated practice parameter paper on the indications for polysomnography and related procedures.¹⁰ Polysomnography may be indicated when considering a diagnosis of a CRSD to exclude other potential causes for sleep related complaints. For example, shift workers with hypersomnia may have both suspected obstructive sleep apnea and clinical characteristics consistent with shift work disorder. In this event, PSG is indicated to evaluate and establish appropriate therapy for OSA.

3.2 Recommendations for Evaluation and Treatments of Circadian Rhythm Sleep Disorders

3.2.1 Shift Work Disorder

Shift work refers to non-standard work schedules, including permanent or intermittent night work, early morning work, and rotating schedules. An estimated 20% of U.S. workers are involved in some form of shift work. The percentage of workers who meet criteria for the diagnosis of shift work disorder (SWD) (i.e., development of sleep disturbances and impairment of waking alertness and performance) is unclear, and there appear to be individual differences in susceptibility to SWD (phase tolerance).

Table 3— Summary of Recommendations

Evaluation Tools	Shift Work Disorder	Jet Lag Disorder	Advanced Sleep Phase Disorder	Delayed Sleep Phase Disorder	Free Running Disorder	Irregular Sleep-Wake Rhythm
Polysomnography	Not Routinely Indicated (Standard)	Not Routinely Indicated (Standard)	Not Routinely Indicated (Standard)	Not Routinely Indicated (Standard)	Not Routinely Indicated (Standard)	Not Routinely Indicated (Standard)
Morningness-Eveningness Questionnaire (MEQ)	Insufficient evidence to recommend (Option)	Insufficient evidence to recommend (Option)	Insufficient evidence to recommend (Option)	Insufficient evidence to recommend (Option)	Insufficient evidence to recommend (Option)	Insufficient evidence to recommend (Option)
Circadian phase markers	Insufficient evidence to recommend (Option)	Insufficient evidence to recommend (Option)	Insufficient evidence to recommend (Option)	Insufficient evidence to recommend (Option)	Indicated (Option)	Insufficient evidence to recommend (Option)
Actigraphy for diagnosis	Indicated (Option)	Not routinely indicated (Option)	Indicated (Guideline)	Indicated (Guideline)	Indicated (Option)	Indicated (Option)
Actigraphy for response to therapy	Indicated (Guideline)	Indicated (Guideline)	Indicated (Guideline)	Indicated (Guideline)	Indicated (Guideline)	Indicated (Guideline)
Sleep log or diary	Indicated (Guideline)	Indicated (Guideline)	Indicated (Guideline)	Indicated (Guideline)	Indicated (Guideline)	Indicated (Guideline)
Therapy						
Planned Sleep Schedules	Indicated (Standard)	Indicated (Option)	Indicated (Option)	Indicated (Option)	Indicated (Option)	Mixed modality indicated (Option/Guideline)*
Timed Light Exposure	Indicated (Guideline)	Indicated (Option)	Indicated (Option)	Indicated (Guideline)	Indicated (Option)	Indicated (Option)
Timed Melatonin Administration	Indicated (Guideline)	Indicated (Standard)	Indicated (Option)	Indicated (Guideline)	Indicated ^{Sighted} (Option) Indicated ^{Un sighted} (Guideline)	Indicated for certain population [#] (Option)
Hypnotics	Indicated (Guideline)	Indicated (Option)	-	Not Recommended (Option)	-	-
Stimulants	Indicated ^{Caff} (Option)	Indicated (Option)	-	-	-	-
Alerting Agents ⁹	Indicated (Guideline)	-	-	-	-	-

* Mixed modality therapy may be effective in elderly-demented/Nursing Home ISWR patients (Guideline) or those with moderate to severe mental retardation (Option)

#Timed melatonin may be effective in those with moderate to severe mental retardation, but is not recommended at present for elderly-demented/Nursing Home patients (Option)

Caff = caffeine; Sighted=sighted persons; Un sighted=unsighted persons; - = no recommendation formulated due to lack of evidence.

3.2.1.1 Both the Morningness-Eveningness Questionnaire (MEQ) and measurement of circadian phase markers (e.g., core body temperature nadir or timing of melatonin secretion) are at present of unproved usefulness in evaluation of patients with suspected SWD. [6.3.2; 6.3.5] (Option)

One level 3 study¹¹ showed that the Morningness-Eveningness Questionnaire (MEQ) score did not reliably predict an individual's adaptability to perform shift work. Another level 3¹² study demonstrated that morning-type individuals may be significantly sleepier than evening-type persons during simulated night shift work. One level 2¹³ and two level 3^{14,15} studies have utilized timing of melatonin rhythm (urinary aMT6s, DLMO) to evaluate phase shift among night shift workers; results from these studies have varied ranging from an absence of phase shifts to complete adaptation. Using mathematical de-masking algorithms, core body temperature minimum (CBTmin) has been used in several simulated shift work studies to evaluate phase shifting,¹⁶⁻²⁰ its application in the field appears limited. While these measures have, for the most part, been used in simulated shift work studies, there are no trials evaluating the diagnostic accuracy of these tests in clinical practice.

3.2.1.2 Planned napping before or during the night shift is indicated to improve alertness and performance among night shift workers. [6.4.1] (Standard)

One level 1,²¹ two level 2,^{22,23} one level 3,²⁴ and one level 4²⁵ studies utilizing both shift work laboratory simulation and field investigations have shown that napping, including early pre-shift sleep periods, increased alertness and vigilance, improved reaction times, and decreased accidents during night shift work, without affecting post-shift daytime sleep.

3.2.1.3 Timed light exposure in the work environment and light restriction in the morning, when feasible, is indicated to decrease sleepiness and improve alertness during night shift work. [6.4.2.1] (Guideline)

One level 2²⁶, five level 3^{11,27-30} and one level 4³¹ studies, utilizing different light intensities (2,350 to 12,000 lux) administered in various schedules (20 minutes during breaks; four 20-minute periods throughout the night shift; 30 minute exposures; at least 50% of the shift; during the first half of the shift; or as long as possible during the shift; and with or without restriction of daytime light exposure using goggles) have demonstrated subjective improvements in work time performance tasks, alertness, and mood compared to ordinary light exposure. Some studies, but not others, have also shown shifts in certain phase markers of circadian rhythms (e.g., salivary melatonin, CBTmin), and improvements in daytime sleep.

3.2.1.4 Administration of melatonin prior to daytime sleep is indicated to promote daytime sleep among night shift workers. [6.4.2.2] (Guideline)

Results from two level 1^{32,33} shift work simulation studies, as well as one level 1,³⁴ three level 2³⁵⁻³⁷ and one level 3³⁸ field studies among night workers were analyzed. Compared to placebo, melatonin administration prior to daytime sleep after night work

shift improved daytime sleep quality and duration, caused a shift in circadian phase in some but not all subjects, but failed to enhance alertness at night. Melatonin doses in these studies ranged from 0.5 to 10 mg. From these data, effectiveness did not appear to correlate with dosage strength or form. However, both level 1 simulation studies showed a positive effect on sleep quality and used dosages ranging from 1.8 to 3 mg.

3.2.1.5 Hypnotic medications may be used to promote daytime sleep among night shift workers. Carryover of sedation to the nighttime shift with potential adverse consequences for nighttime performance and safety must be considered. [6.4.2.3] (Guideline)

This recommendation is based on both night shift simulation experiments (two level 1 studies using triazolam^{39,40} and one level 2 study of temazepam⁴¹) and night shift field investigations (one level 1⁴² and one level 2⁴³ study of zopiclone, and one level 3⁴⁴ study of triazolam). These studies have generally demonstrated improvements in the duration and quality of daytime sleep compared to controls but without consistent effects on objective measures of nighttime alertness. Although the evidence for a positive effect on daytime sleep is strong (favoring a "Standard" strength recommendation), the balance of risk and benefit for shift workers is less clear. The clinician should consider that such medications might worsen other coexisting sleep conditions such as sleep related breathing disorders, and take care to individualize therapy and monitor for adverse effects by close follow-up.

3.2.1.6 Modafinil is indicated to enhance alertness during the night shift for SWD. [6.4.2.4] (Guideline)

Caffeine is indicated to enhance alertness during the night shift for SWD. [6.4.2.4] (Option)

Studies (field or simulated shift work) using psychostimulants, such as modafinil (two level 1)^{9,45} caffeine (one level 1),²¹ and methamphetamine (one level 2)⁴⁶ for SWD have demonstrated efficacy in countering sleepiness and improving psychomotor performance during the night shift compared to placebo. Modafinil and caffeine in medical doses have established safety records, so in most cases when enhanced alertness is necessary, the benefits outweigh the risks for this application. However, the practitioner needs to take care when using alerting or stimulant agents that they do not impair daytime sleep periods. Furthermore, although methamphetamine has also been shown to have efficacy in improving sleepiness, the evidence is less strong, and chronic use of methamphetamine can be associated with significant abuse liability. Finally, stimulants have not been shown to be a safe substitute for adequate sleep.

3.2.2 Jet Lag Disorder

Jet lag disorder (JLD) is a temporary circadian rhythm disorder related to travel across time zones in which there is a misalignment between the timing of the sleep and wake cycles generated by the endogenous circadian clock and that required in the new time zone. Associated symptoms occur within one to two days after travel, and include a complaint of insomnia or excessive

daytime sleepiness and may also include general malaise, somatic symptoms, or other impairments of daytime function.

3.2.2.1 There is insufficient evidence to recommend the routine use of actigraphy, polysomnography, or measurement of circadian phase markers in the evaluation of jet lag disorder. [7.3] (Option)

The diagnosis of JLD is made based on subjective complaints in the context of travel across multiple time zones.⁵ As described in the accompanying review paper, only one questionnaire (Columbian Jet Lag Scale) designed to assess the presence and severity of JLD has been validated (level 1).⁴⁷ This questionnaire is not yet used routinely in clinical settings. Actigraphy has been used in several studies of JLD, but only one study attempted to validate actigraphy as a measure of JLD-related changes in the rest-activity cycle (level 1).⁴⁸ Polysomnography has been primarily used in the laboratory setting in studies of simulated JLD, and is generally not felt to be practical in the clinical evaluation of JLD. Circadian phase markers (including skin and core body temperature; salivary and urinary melatonin; salivary, urinary and plasma cortisol; and plasma growth hormone and thyroid stimulating hormone levels) have been used in studies of JLD, generally as measures of phase response to treatments. However, the role of circadian markers in clinical practice is unclear.

3.2.2.2 When time at destination is expected to be brief (i.e., two days or less), keeping home-based sleep hours, rather than adopting destination sleep hours, may reduce sleepiness and jet lag symptoms. [7.4.1] (Option)

One level 2 study compared keeping home-base sleep hours versus adopting destination sleep hours during a two-day layover after a 9-hour westward flight, and found that the group that kept home-base sleep hours experienced less sleepiness and jet lag symptoms.⁴⁹ However, in that study, keeping home-base sleep hours was associated with a longer awake period from last layover sleep to first recovery sleep following the return flight, and one third of subjects expressed a preference for adopting destination sleep hours.

3.2.2.3 The combination of morning exposure to bright light and shifting the sleep schedule one hour earlier each day for three days prior to eastward travel may lessen symptoms of jet lag. [7.4.2.1] (Option)

In one level 2 simulation study, subjects were phase shifted in the laboratory in anticipation of eastward travel by the combination of adjusting their sleep schedule one hour earlier per day for three days, plus 3.5 hours of bright light (>3000 lux) exposure (continuously or intermittently), resulting in DLMO phase advance with both bright light conditions and fewer JLD symptoms in the continuous bright light group.⁵⁰ Another level 2 field study of light treatment (3000 lux) for 3 hours (compared to dim red light) at 19:00 destination time for two evenings following a westward flight (Zurich to New York) found a greater phase delay in DLMO with bright light, but no significant differences in sleep or other performance measures, including a scale of JLD symptoms.⁵¹ Although these measures appear to have a positive effect on JLD symptoms, studies on patient populations using intention to treat analysis are lacking. Such analyses are particularly salient

because the regimen requires significant diligence on the part of the patient.

3.2.2.4 Melatonin administered at the appropriate time is indicated to reduce symptoms of jet lag and improve sleep following travel across multiple time zones. [7.4.2.2] (Standard)

The accompanying review identified 12 double-blind, placebo-controlled field trials of melatonin. The dose of melatonin ranged from 0.5 to 10 mg, administered at bedtime, for up to 3 days prior to departure and up to 5 days upon arrival at the destination. Two level 1^{52,53} and four level 2⁵⁴⁻⁵⁷ studies demonstrated improvement in JLD symptoms with melatonin administration. Conversely, one level 1⁴⁷ study did not demonstrate improvement in JLD symptoms with melatonin, and another level 2⁵⁸ study found melatonin was more effective than placebo during the first 3 days post-travel, but after 3 additional days melatonin lost its advantage. Four level 1^{52,53,59,60} and one level 2⁶¹ studies found that melatonin administered following travel improves the duration and quality of sleep, based on both subjective and objective measures of sleep. In addition, one level 2 study⁶² found that melatonin accelerated entrainment of cortisol rhythms to the new time zone, and another level 2 study⁶¹ found that melatonin accelerated circadian entrainment based on oral temperature rhythms.

Although the majority of studies involved use of melatonin for eastward travel, two level 2 studies^{56,57} found improvements in JLD scores and sleep in participants after westward travel crossing 12 or more time zones.

The most effective dose of melatonin for JLD is unclear. One level 1 study⁵³ found 5 mg immediate-release melatonin to be more effective at relieving symptoms of JLD compared to a 2 mg slow-release formulation, but it was only marginally more effective than a 0.5 mg immediate-release formulation. These results suggest that immediate-release formulations in doses of 0.5 to 5 mg may be effective at relieving JLD symptoms. Melatonin preparations are not regulated by the Food and Drug Administration. However, the medical literature has not produced evidence of significant risk derived from its use. Thus, the benefits are well supported, and the risks seem low.

3.2.2.5 Short-term use of a benzodiazepine receptor agonist hypnotic is indicated for the treatment of jet lag-induced insomnia, but potential adverse effects must be considered, and effects on daytime symptoms of jet lag disorder have not been adequately addressed. [7.4.2.3] (Option)

Three level 1^{52,60,63} and six level 2⁶⁴⁻⁶⁹ studies tested the use of hypnotic agents for JLD-induced insomnia. Four studies involved use of traditional benzodiazepine hypnotics. One level 2 study⁶⁹ found that temazepam 10 mg had little effect on JLD symptoms, sleep quality, or circadian entrainment following westward travel. However in another level 2 study,⁶⁶ temazepam 20 mg improved subjective sleep quality following eastward travel, but sleep and circadian measures did not improve. One level 2 study⁶⁸ involving use of midazolam found improvements in subjective sleep following eastward travel. Finally, one level 2 simulation study⁶⁴ designed to mimic westward travel found that triazolam was not different from placebo in sleep efficiency or total sleep time (measured by PSG).

Five studies used one of the newer non-benzodiazepine hypnotics. One large level 1 study⁶³ found that zolpidem 10 mg administered at bedtime for 3–4 nights following eastward travel across 5–9 time zones improved self-reported total sleep time and sleep quality, and reduced awakenings from sleep; however daytime symptoms of JLD were not addressed. Another level 2 study⁶⁵ found that zopiclone 7.5 mg given at bedtime improved sleep duration (measured by actigraphy) for the four post-flight days following a 5-hour westward flight. Daytime activity was also greater, but subjective JLD scores were not improved (compared to placebo).

Two studies compared a non-benzodiazepine hypnotic with melatonin or placebo following eastward travel. One large level 1 study⁵² found that zolpidem 10 mg administered during a night flight and for 4 days after arrival following eastward travel across 6–9 time zones was significantly better than melatonin 5 mg (or placebo) in counteracting JLD symptoms, and better at achieving self-reported sleep duration and self-reported sleep quality (but not verified by actigraphy). In this study, a group receiving zolpidem plus melatonin did not report better sleep or better JLD scores than the zolpidem alone group. Another level 1 study⁶⁰ found that zopiclone 15 mg (compared to melatonin 2 mg or placebo) administered for one night only after arrival found that zopiclone and melatonin were equally effective at improving both subjective and objective (actigraphy) sleep duration and quality. Other symptoms of JLD were not assessed.

One small level 2 study of simulated eastward 8 hour time shift⁶⁷ compared zolpidem 10 mg (versus placebo) given at the new bedtime on the first two nights following the shift with the effects of continuous bright light exposure (versus dim light) upon awakening on the day of the advance and the following day. Total sleep times (by polysomnography) did not differ between treatments, though sleep efficiency improved with zolpidem (on the night of the shift only) or with bright light (on the night after shift only). No other symptoms of JLD were reported.

Thus, these agents are in general effective for treatment of the insomnia of JLD, but of unproved benefit for the daytime symptoms. In addition, some caution is warranted in the use of hypnotics for JLD, since adverse effects have been reported, including global amnesia,⁷⁰ and at least one study reporting a much higher rate of adverse events with a hypnotic (zolpidem) compared to other treatment groups.⁵²

3.2.2.6 Caffeine is indicated as a way to counteract jet lag-induced sleepiness, but may also disrupt nighttime sleep. [7.4.2.4] (Option)

Two level 2 studies tested the use of slow-release caffeine after travel across time zones. One level 2 study found that either slow-release caffeine 300 mg daily for 5 days after flight or melatonin 5 mg daily starting on the day of travel to 3 days post flight following eastward travel across 7 time zones (compared to placebo) was associated with faster entrainment of circadian rhythms as measured by salivary cortisol levels.⁶² In another level 2 study utilizing the same protocol,⁶¹ slow-release caffeine resulted in less daytime sleepiness (compared to melatonin or placebo) by objective but not subjective measures, but also reported longer sleep onset and more awakenings at night. The benefit of improved daytime sleepiness must be weighed against disrupted nocturnal sleep. Additionally, information was lacking on the effect of caffeine on other daytime symptoms of jet lag. Individualized therapy and clinical follow-up is recommended.

3.2.3 Advanced Sleep Phase Disorder

Advanced sleep phase disorder (ASPD) is defined as a sleep pattern scheduled several hours earlier than is usual or desired. There is no standard for how much earlier a sleep schedule needs to be in order to qualify as pathological. Diagnosis depends on the amount of distress the patient expresses about being unable to conform to a more conventional sleep schedule after ruling out other causes of sleep maintenance insomnia.

3.2.3.1 There is insufficient evidence to recommend the use of the Morningness-Eveningness Questionnaire (MEQ) for the routine diagnosis of ASPD. [11.3.2] (Option)

This parameter is based upon committee consensus. There were two level 2 studies^{71,72} that found ASPD patients scored high on the MEQ indicating morning-lark traits. A third study (level 3)⁷³ also found high MEQ scores in subjects presumed to have ASPD. However, there were no studies that evaluated the sensitivity or specificity of this questionnaire as a diagnostic tool in sleep clinic or general populations. The MEQ can serve a confirmatory role for ASPD diagnosis but may not by itself serve as a basis for this diagnosis.

3.2.3.2 Polysomnography is not routinely indicated for the diagnosis of ASPD. [11.3.3] (Standard)

This is a reiteration of the prior practice parameter paper provided regarding indications for PSG.¹⁰ Regarding ASPD, no studies retrieved for review utilized PSG to make this diagnosis. One level 2 study⁷² found the expected advance in the time of sleep onset in ASPD subjects; on the other hand, another level 2 study⁷⁴ found fairly standard bedtimes in ICSD-ASPD diagnosed subjects.

3.2.3.3 There is insufficient evidence to recommend the use of circadian markers for the routine diagnosis of ASPD. [11.3.4] (Option)

There were two level 2 studies^{71,72} using DLMO as a circadian marker and one level 3 study⁷³ using urinary 6-sulfatoxy melatonin (MT6) acrophase which found advanced melatonin secretion in presumed ASPD subjects. Three level 2 studies⁷⁴⁻⁷⁶ and one level 4 study⁷⁷ found early core body temperature minima in patients with ASPD, sleep maintenance or terminal insomnia. The review indicated that the available data are limited by heterogeneity of subjects. Additionally, none of the studies evaluated the use of circadian markers as diagnostic aids (no measures of the sensitivity or specificity of the tests). Thus, although the results of such measures are generally consistent with advanced circadian timing, measuring circadian markers can not yet be recommended as diagnostic aids.

3.2.3.4 Prescribed sleep/wake scheduling, timed light exposure, or timed melatonin administration are indicated as treatments for patients with ASPD. [11.4] (Option)

This recommendation is based on available evidence and committee consensus. One level 4 study⁷⁸ achieved sleep advance with sleep scheduling. There have been six studies using scheduled bright light as a treatment. One level 3 study⁷³ found

evening light exposure no more effective than placebo in shifting circadian phase. A level 2 study⁷⁹ succeeded in reducing time in bed after awakening in the morning. Another level 2 study⁷⁴ that used ICSD criteria to determine ASPD presence succeeded in improving sleep variables but another level 2 replication of this study⁷⁵ did not. One level 4⁷⁷ and one level 2 study⁷⁶ achieved post-treatment DLMO phase delays and improved sleep quality in patients with complaints of terminal insomnia. Although there is a rationale for using melatonin for ASPD, there is no reported evidence in support of this treatment. Overall, the evidence for efficacy of these interventions is weak or conflicting, but the risks and costs entailed are low. As there are few alternatives, an individualized approach using one or more of these treatments with follow up to ascertain efficacy or side effects may be appropriate.

3.2.4 Delayed Sleep Phase Disorder

Delayed sleep phase disorder (DSPD) is characterized by a stable delay of the habitual nocturnal sleep period. Individuals with DSPD are often unable to fall asleep until the early morning hours and unable to awaken until late morning or early afternoon. During their preferred sleep schedules, sleep duration and quality are generally normal. However, sleep-onset insomnia and morning sleepiness occur if sleep and waking are attempted at an earlier time.

3.2.4.1 Polysomnography is not indicated in the routine assessment of DSPD. [12.3.5] (Standard)

This is a reiteration of the indications for PSG practice parameters.¹⁰ In the present review, one study using PSG in patients with DSPD that compared conventional and habitual sleep schedules demonstrated differences in sleep duration and sleep architecture. Nevertheless, PSG rarely provides additional information from that obtained from sleep history and sleep logs, and no new studies addressed the use of PSG as a diagnostic aid in DSPD.

3.2.4.2 Morning light exposure is indicated in the treatment of DSPD. Optimal timing, duration, and dosing of morning light treatment for DSPD remain to be determined. [12.4.2] (Guideline)

One level 1⁸⁰ and one level 2⁸¹ study demonstrated that properly timed morning light exposure causes a phase advance of sleep onset time and circadian rhythms (CBTmin), and increases objectively determined daytime alertness. In the reviewed studies, 2500 lux for 2-3 hours prior to or at rise time was used. The effects of lower doses, blue light wavelengths, or other timings are not yet known. The treatments were generally well tolerated and of some beneficial effect, but more potent and less difficult to follow treatments are needed.

3.2.4.3 Chronotherapy (i.e., prescribed progressive delay in the schedule of sleep time until the desired sleep schedule is reached) may be useful for DSPD. [12.4.1] (Option)

This recommendation for chronotherapy is based only on two level 4 case report studies^{82,83} and committee consensus; there are no controlled trials supporting its efficacy or safety. Longer lasting and more practical alternatives are needed given that compli-

ance with the treatment is difficult and lasting benefit has not been demonstrated.

3.2.4.4 Properly timed melatonin administration is indicated as a therapy for DSPD. [12.4.3] (Guideline)

This recommendation is supported by one level 1⁸⁴ two level 2^{85,86} and one level 4⁸⁷ studies. Afternoon or evening administration of melatonin shifts circadian rhythms (indicated by dim light melatonin onset [DLMO] and core body temperature minimum, [CBTmin]) to an earlier time. Compared to placebo, melatonin treatment reduced sleep onset latency, but there was no change in total sleep time or subjective daytime alertness. As with other studies involving melatonin, the optimal timing and dosing of melatonin administration are not established. In the reviewed studies, three used 5 mg^{84,85,87} while one⁸⁶ used two strengths (0.3 mg and 3 mg). Effective times of administration varied between 1.5 and 6 hours prior to the habitual bedtime.

3.2.4.5 Vitamin B12 is not indicated in the treatment for DSPD. [12.4.4] (Guideline)

This recommendation is based on one level 1⁸⁸ multicenter study in which no benefit compared to placebo was noted following administration of vitamin B12 (1 mg) three times a day to 50 subjects for four weeks.

3.2.4.6 There is insufficient evidence supporting the use of hypnotic medications to promote sleep or the use of stimulant medications to promote alertness for DSPD. [12.4.5; 12.4.6] (Option)

This parameter is based on committee consensus. There was only one level 4 report⁸³ indicating some benefit, but sufficient evidence to support this practice is lacking.

3.2.5 Free-Running Circadian Rhythm Sleep Disorder

Patients with free-running (FRD) rhythms are thought to reflect a failure of entrainment. This condition is most common in blind individuals (about 50% of whom have FRD) and is highly unusual in sighted individuals. Because of this, as noted in the accompanying review, most studies are level 4 single case reports. Roughly one-fourth of sighted individuals with FRD have related psychiatric diagnoses.

3.2.5.1 Sleep logs are useful for assessment in FRD patients. [13.3.1] (Option)

This recommendation is based on committee consensus and clinical practice rather than data. Sleep logs have been found useful in determining sleep patterns in people with FRD.

3.2.5.2 Circadian phase markers are useful to determine circadian phase and confirm the diagnosis of FRD in sighted and unsighted patients. [13.3.4] (Option)

This parameter is supported by evidence presented in the accompanying review and by committee consensus. There are one level 2⁸⁹ and seven level 4 studies⁹⁰⁻⁹⁶ that have used the melatonin rhythm

as an indicator of phase in sighted individuals. In addition, there are four level 2 studies⁹⁷⁻¹⁰⁰ and four level 4 studies¹⁰¹⁻¹⁰⁴ that have used the timing of melatonin secretion to determine free running rhythms in blind individuals. There is also one level 4 study¹⁰⁵ that used core body temperature measurements to detect free-running rhythms. Multiple measurements of circadian phase over the course of several weeks are suggested for all circadian markers. The ICSD-2 suggests use of sleep logs or actigraphy for more than seven days in order to establish the daily drift of the endogenous rhythm. Since sleep-wake times are influenced by social schedules and requirements, these data may be less compelling than phase markers, which provide a more direct measure of the intrinsic circadian rhythm. This is particularly the case when the diagnosis is suggested by sleep log data or actigraphy, but these data are conflicting or thought unreliable.

3.2.5.3 Prescribed sleep/wake scheduling as a method to improve circadian rhythms may be useful for therapy of FRD in sighted individuals. [13.4.1] (Option)

Improving the structure of the sleep wake cycle in sighted patients with FRD (sometimes with the help of family and friends) is a reasonable treatment approach, but there have been no clinical trials to test the efficacy of specific interventions.

3.2.5.4 Circadian phase shifting by timed light exposure may be used to treat FRD in sighted individuals. [13.4.2] (Option)

There are five level 4 reports^{91,93,106-108} that morning light exposure was successful in entraining circadian rhythms in sighted individuals.

3.2.5.5 Circadian phase shifting by timed melatonin administration may be used to treat FRD in sighted individuals. [13.4.3] (Option)

There are four level 4 reports^{94,95,107,109} in which sighted FRD patients treated with melatonin at bedtime achieved successful phase advance. The most common dose used was 3 mg.

3.2.5.6 Timed melatonin administration is indicated for the therapy of FRD in blind individuals. [13.5.2] (Guideline)

There are four level 4 case reports¹¹⁰⁻¹¹³ and five small level 2 studies⁹⁸⁻¹⁰² which successfully entrained FRD rhythms in blind individuals using a variety of doses, timing and duration of melatonin treatment. A recent level 4 case report¹⁰³ suggests that physiological doses (approximately 0.3 mg) may be more effective than pharmacologic doses (typically >2 mg) for this indication.

3.2.5.7 There is insufficient evidence to support using vitamin B12 in treating FRD in sighted individuals. [13.4.6] (Option)

The evidence for use of vitamin B12 is conflicting, and there is little physiologic rationale for its effectiveness. There were two case reports (level 4)^{114,115} using vitamin B12 that were successfully entrained.

3.2.6 Irregular Sleep-Wake Rhythm

An irregular sleep-wake rhythm (ISWR) is characterized by a relative absence of a circadian pattern to the sleep-wake cycle.

Total sleep time is essentially normal, but there are multiple irregular sleep bouts during a 24-hour period. ISWR is commonly associated with neurological impairment, and much of the clinical research in this condition has involved older people with dementia.

3.2.6.1 The use of sleep logs and/or actigraphy are indicated to identify and monitor treatment outcomes in ISWR, including in older people with dementia and those living in nursing homes. [14.3.1; 14.3.3] (Guideline)

This recommendation expands the recently updated AASM practice parameters on the use of actigraphy in the assessment of sleep and sleep disorders.⁶ The review paper accompanying this current practice parameter paper did not systematically review the use of actigraphy in general or the use of sleep logs in ISWR. This recommendation addresses the use of actigraphy specifically in ISWR. The accompanying review paper to this CRSD practice parameters paper also addresses the use of sleep logs. In addition, this recommendation is further supported by inclusion of the use of sleep logs or actigraphy in the ICSD-2 diagnostic criteria for CRSD.⁵ However, the review cited studies using actigraphy which included patients with evidence of ISWR (the diagnosis of which had to be inferred based on description of participants) using actigraphy among older people with dementia and/or living in a nursing home were cited in the review. This included two Level 1^{116,117} and 6 Level 2 studies.¹¹⁸⁻¹²³ Although these studies are well designed, they generally did not compare actigraphy to some other gold standard in diagnosing ISWR. Sleep logs were generally not used in these studies (likely due to patients' cognitive impairment).

3.2.6.2 Daytime bright light exposure may improve circadian rest-activity rhythms and consolidation of sleep and wake in nursing home residents with dementia and ISWR. [14.4.2.1] (Option)

There were 9 studies that tested the effects of bright light exposure alone among nursing home residents (the majority with dementia) in whom sleep disturbance was presumably consistent with an ISWR, with positive results reported in all but one study.¹²¹ Three level 2 studies^{119,120,123}, two level 3 studies^{124,125} and two level 4 studies^{126,127} found positive effects on circadian rest-activity rhythms and/or sleep with bright light exposure (provided for two hours in most studies, with a range of 1500–8000 lux across studies). Three of these studies tested morning bright light, one tested evening bright light, two tested both morning and evening bright light, and one tested increased light exposure throughout the day. The negative level 2 study¹²¹ tested morning bright light (2 hours >2500 lux) which did not result in significant changes in sleep or circadian rest-activity rhythms.

3.2.6.3 Melatonin is not indicated for the treatment of ISWR in older people with dementia, but may be indicated for children with ISWR and severe psychomotor retardation. [14.4.2.2] (Option)

Two studies tested melatonin administration for ISWR in patients with dementia. The first was a large level 1 study¹¹⁷ which tested administration of 8 weeks of melatonin (10 mg or 2.5 mg,

sustained release formulations) among patients with Alzheimer disease with disturbed sleep patterns that were presumably consistent with an ISWR. The study found no evidence of improvement in sleep (by actigraphy). A second smaller level 1 trial¹²⁸ found that slow-release melatonin (6 mg) also had no effect on actigraphically estimated sleep.

Three level 4 studies found some benefit in treating sleep disturbances in severely impaired children with presumed ISWR, including children with severe psychomotor retardation,¹²⁹ and neurologically multiply disabled children.^{130,131} However, one level 2 study¹³² which involved use of melatonin to improve sleep in girls with Rett syndrome and associated mental retardation was negative.

3.2.6.4 Mixed modality approaches combining bright light exposure, physical activity, and other behavioral elements are indicated in treatment of ISWR among older people with dementia (Guideline), including nursing home residents (Guideline), and children with ISWR and moderate to severe mental retardation. [14.4.3] (Option)

Two studies tested mixed modality approaches for sleep disturbance (presumably consistent with ISWR) in older people with dementia. One level 2 study¹¹⁸ in nursing home residents (the majority with dementia) tested a short (5-day) mixed modality intervention (increased daytime sunlight exposure, increased physical activity, structured bedtime routine, and decreased nighttime noise and light) decreased daytime sleeping. Another level 1 study¹¹⁶ in community-dwelling dementia patients tested an 8-week mixed modality intervention (combining light exposure, exercise, sleep scheduling, and sleep hygiene) which decreased nighttime awakenings, decreased total wake time, decreased daytime sleepiness and decreased symptoms of depression. A Level 4 study¹³³ in children with moderate to severe mental retardation who had failed prior medication/behavior treatment for sleep disturbance, combined bright light exposure (for 8 months) with a behavioral program, and found that 5 out of 14 patients responded to treatment with improvement in nocturnal and 24-hour sleep.

4.0 SUMMARY AND FUTURE RESEARCH

Basic science developments have outpaced research in the development of clinical interventions for the treatment of CRSDs. A foundation for understanding of the pathophysiology of CRSD has been built by the discipline of circadian rhythm science that now extends from molecular biology to behavior. However, sound clinical practice must be based on both a scientific understanding of pathophysiology as well as empirical evidence derived from clinical application, ideally from well-designed clinical trials. It is in the area of clinical application that future advances are sorely needed. In what follows we outline areas for future development for each aspect of the CRSDs.

4.1 Molecular Genetics of CRSD

Further research in this basic science area is likely to bring important insights into the mechanisms of CRSDs but the research is in its early stage and does not yet have clinical application.

4.2 Jet Lag

Additional studies are needed to support the finding that staying on one's home-based sleep schedule is helpful when time spent at destination is brief and to support the impact on jet lag symptoms of alteration of the timing of sleep prior to eastward travel. More research with larger samples is needed to determine the clinical feasibility of a program of appropriately timed light exposure scheduled prior to travel or on arrival at the traveler's destination. Because the effects of hypnotics on daytime symptoms of jet lag have not been well studied and are unknown, more research is needed. Further, research is needed to weigh the benefit of using hypnotics against the risk of side effects. Lastly, more research is needed to study the efficacy of caffeine to counteract jet lag induced sleepiness. These studies should weigh the stimulant benefits of caffeine on daytime sleepiness against their tendency to disrupt nighttime sleep.

4.3 Shift Work Disorder

Formal diagnoses have seldom been performed on subjects in SWD research. It is important that subjects be diagnosed according to formal SWD criteria to test the reliability and validity of ICSD-2 Diagnostic Criteria as well to test the reproducibility of treatment results. Diagnostic evaluation is also necessary to determine the parameters of normal or pathological responses to the stress of the unnatural sleep schedules associated with shift work. More studies are required to support the use of planned napping before or on the job to counteract sleepiness during shift work; current research evidence is limited but consistent in demonstrating an increase in alertness on the job. Although phase shifting and circadian realignment has been achieved with timed light exposure in simulated shift work situations, to determine the clinical utility of the treatment there is need for studies with larger sample of subjects meeting SWD criteria that also use a credible placebo control. Further there is need for comparative testing of specific timing, intensity of light exposure, and duration of treatment. There is mixed evidence supporting melatonin administration prior to daytime sleep. It is difficult to draw firm conclusions from current research due to variability in shift schedules, as well as in melatonin dosage and timing among these studies. There are good theoretical reasons why melatonin (or melatonin agonists) might benefit daytime sleep in night workers, but more research is needed in which comparisons are made between similar dosage and timing. Attempts should be made to tease out whether observed improvement in daytime sleep is related to a hypnotic effect rather than a phase shifting effect. Although night shift simulation studies have demonstrated that hypnotics increase daytime sleep, there are doubts that the treatment improves nighttime alertness. To assess the efficacy and safety of hypnotics for improving nighttime performance, studies are needed that employ objective as well as subjective outcome measures of sleep and alertness. Given the varying pharmacokinetics of individual drugs, studies of specific medications should be compared. Finally, although modafinil has received FDA approval for use in improving nighttime alertness in shift workers, caffeine, a stimulant not considered a drug, is an inexpensive easily available alternative stimulant. Further research is required to demonstrate its effectiveness and potential side-effects.

4.4 Advanced Sleep Phase Disorder

Because there is no strict definition of how advanced the sleep schedule needs to be in order to qualify as pathologic, current diagnosis depends on the degree of difficulty a patient experiences with conforming to a desired sleep schedule. It would be helpful if future research characterized the complaints associated with this diagnosis in terms of actual sleep times, sleep schedules and other subject characteristics (such as employment status). Further research is required regarding the efficacy and practicality of phase-advance chronotherapy for patients with ASPD. Treatment of ASPD (or presumed ASPD) at this time consists exclusively of evening light therapy achieving overall conflicting results except for subjective improvement. In future research, subjects should be screened to meet standard ICSD-2 criteria and consistent use of established circadian phase markers. Comparisons should be made between standard intensity and durations of treatments. Systematic measures of treatment compliance should be assessed. The safety and treatment benefits of blue light, such as reduction in the amount of exposure time required to achieve treatment effects, should be explored. The utility of melatonin administration in the treatment of putative ASPD should be studied in large randomized, controlled, clinical trials.

4.5 Delayed Sleep Phase Disorder

The etiology of DSPD is unknown, and it is unclear whether this is a manifestation of intrinsic pathology or a socially reinforced sleep-wake schedule that can be readily modified if circumstances require it. Future research should attempt to sort out the contributions of these factors to research participants' delayed sleep schedules. Even though a prescribed sleep schedule (chronotherapy) is a reasonable treatment for DSPD, there are no controlled clinical trials documenting its efficacy and safety. Thus future research should be conducted to determine these issues. Although the evidence is limited, light exposure treatment, timed to advance rhythms (based on the light PRC) appears to be a reasonable and effective intervention for DSPD. In the clinical context, compliance may be a significant problem. Although there is strong evidence that melatonin, timed to promote a corrective phase advance, is an effective treatment for DSPD, further study is required to determine the optimal parameters for scheduling and dosing. Finally, future research on promoting sleep with hypnotic medication and promoting alertness with stimulant medication should be considered.

4.6 Free-Running Disorder

Although appropriately timed bright light exposure and melatonin administration have been shown to be effective, there are few treatment studies of free-running disorder CRSD among sighted individuals because of the rarity of the condition. 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. There are limited data on the use of

hypnotic medications to promote sleep and on stimulant medications to enhance alertness.

4.7 Irregular Sleep-Wake Rhythm Disorder

It is important that future studies of ISWR patients (such as elderly dementia patients) characterize them according to formal sleep diagnostic criteria. This will enable the development of a body of knowledge describing the effectiveness of clinical treatments for patients with specific clinical characteristics. While there have been no studies examining prescribed sleep/wake scheduling per se, some of the mixed modality treatments^{116,118} included structuring the sleep/wake schedule as part of their treatment protocols. 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. Bright light exposure during the day has had modest effects on the consolidation of sleep and wake in nursing home patients with Alzheimer disease (AD) and associated ISWR. More data are needed to support the effectiveness of this treatment, as well as information regarding the most efficacious timing of light exposure. Current data do not support the use of melatonin for treating ISWR, at least in association with AD. However, the efficacy of smaller doses of melatonin and emerging melatonin receptor agonists has yet to be determined. More research is needed in the area of mixed modality approaches to determine if such treatment approaches might be more efficacious than the use of light alone. There is great need for rigorous, well-controlled clinical trials of hypnotic treatments for sleep disturbance in demented patients to fill a serious and continuing gap in our knowledge. There is also a great need to conduct carefully controlled clinical trials of the efficacy of stimulant medications, such as modafinil in AD patients.

A foundation for understanding the pathophysiology of DSPD, ASPD, FRD, ISWR, JLD, and SWD has been built on the principles of circadian rhythm science, and these principles have pointed the way to rational clinical interventions. Future emphasis should be placed on clinical trials utilizing formal (criteria based) diagnostic categories that can translate circadian scientific principles into practice with "real" patients.

REFERENCES

1. Sack, R, Auckley, D, Auger, RR, et al. Circadian Rhythm Sleep Disorders: Part I, Basic Principles, Shift Work and Jet Lag: An American Academy of Sleep Medicine Review. *Sleep* 2007;30:1460-83.
2. Sack, R, Auckley, D, Auger, RR, et al.,. Circadian Rhythm Sleep Disorders: Part II, Advanced Sleep Phase Syndrome, Delayed Sleep Phase Syndrome, Free-running Type, and Irregular Sleep Wake Disorder: An American Academy of Sleep Medicine Review *Sleep* 2007;30:1484-1506
3. Levels of Evidence. Oxford Centre for Evidence Based Medicine Web site. Available at: <http://www.cebm.net/?o=1011>. Accessed June 23, 2007.

4. Eddy, D. A manual for assessing health practices and designing practice policies: the explicit approach. Philadelphia: American College of Physicians, 1992.
5. American Academy of Sleep Medicine. The international classification of sleep disorders: diagnostic & coding manual (2nd ed). Westchester, IL: American Academy of Sleep Medicine, 2005.
6. Morgenthaler, T, Alessi, C, Friedman, L, et al. Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. *Sleep* 2007;30:519-529.
7. Chesson, AL, Jr, Littner, M, Davila, D, et al. Practice parameters for the use of light therapy in the treatment of sleep disorders. Standards of Practice Committee, American Academy of Sleep Medicine. *Sleep* 1999;22:641-660.
8. Sackett D. Rules of evidence and clinical recommendation. *Can J Cardio* 1993;487-489.
9. Czeisler, CA, Walsh, JK, Roth, T, et al. Modafinil for excessive sleepiness associated with shift-work sleep disorder. *New England Journal of Medicine* 2005;353:476-486.
10. Kushida, CA, Littner, MR, Morgenthaler, T, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. *Sleep* 2005;28:499-521.
11. Stewart, KT, Hayes, BC, and Eastman, CI. Light treatment for NASA shiftworkers. *Chronobiology International* 1995;12:141-151.
12. Hilliker, NA, Muehlbach, MJ, Schweitzer, PK, and Walsh, JK. Sleepiness/alertness on a simulated night shift schedule and morningness-eveningness tendency. *Sleep* 1992;15:430-433.
13. Sack, RL, Hughes, RJ, Edgar, DM, and Lewy, AJ. Sleep-promoting effects of melatonin: at what dose, in whom, under what conditions, and by what mechanisms? *Sleep* 1997;20:908-915.
14. Roden, M, Koller, M, Pirich, K, Vierhapper, H, and Waldhauser, F. The circadian melatonin and cortisol secretion pattern in permanent night shift workers. *American Journal of Physiology* 1993;265: R261-267.
15. Benhaberou-Brun, D, Lambert, C, and Dumont, M. Association between melatonin secretion and daytime sleep complaints in night nurses. *Sleep* 1999;22:877-885.
16. Minors, DS, and Waterhouse, JM. Separating the endogenous and exogenous components of the circadian rhythm of body temperature during night work using some 'purification' models. *Ergonomics* 1993;36:497-507.
17. Baehr, EK, Revelle, W, and Eastman, CI. Individual differences in the phase and amplitude of the human circadian temperature rhythm: with an emphasis on morningness-eveningness. *Journal of Sleep Research* 2000;9:117-127.
18. Baehr, EK, Fogg, LF, and Eastman, CI. Intermittent bright light and exercise to entrain human circadian rhythms to night work. *American Journal of Physiology* 1999;277:R1598-1604.
19. Eastman, CI, Stewart, KT, Mahoney, MP, Liu, L, and Fogg, LF. Dark goggles and bright light improve circadian rhythm adaptation to night-shift work. *Sleep* 1994;17:535-543.
20. Eastman, CI, Liu, L, and Fogg, LF. Circadian rhythm adaptation to simulated night shift work: effect of nocturnal bright-light duration. *Sleep* 1995;18:399-407.
21. Schweitzer, PK, Randazzo, AC, Stone, K, Erman, M, and Walsh, JK. Laboratory and field studies of naps and caffeine as practical countermeasures for sleep-wake problems associated with night work. *Sleep* 2006;29:39-50.
22. Sallinen, M, Harma, M, Akerstedt, T, Rosa, R, and Lillqvist, O. Promoting alertness with a short nap during a night shift. *Journal of Sleep Research* 1998;7:240-247.
23. Purnell, MT, Feyer, AM, and Herbison, GP. The impact of a nap opportunity during the night shift on the performance and alertness of 12-h shift workers. *Journal of Sleep Research* 2002;11:219-227.
24. Garbarino, S, Mascialino, B, Penco, MA, et al. Professional shift-work drivers who adopt prophylactic naps can reduce the risk of car accidents during night work. *Sleep* 2004;27:1295-1302.
25. Bonnefond, A, Muzet, A, Winter-Dill, AS, Bailloeuil, C, Bitouze, F, and Bonneau, A. Innovative working schedule: introducing one short nap during the night shift. *Ergonomics* 2001;44:937-945.
26. Yoon, IY, Jeong, DU, Kwon, KB, Kang, SB, and Song, BG. Bright light exposure at night and light attenuation in the morning improve adaptation of night shift workers. *Sleep* 2002;25:351-356.
27. Boivin, DB, and James, FO. Circadian adaptation to night-shift work by judicious light and darkness exposure. *Journal of Biological Rhythms* 2002;17:556-567.
28. Budnick, LD, Lerman, SE, and Nicolich, MJ. An evaluation of scheduled bright light and darkness on rotating shiftworkers: trial and limitations. *American Journal of Industrial Medicine* 1995;27:771-778.
29. Costa, G, Ghirlanda, G, Minors, DS, and Waterhouse, JM. Effect of bright light on tolerance to night work. *Scandinavian Journal of Work, Environment & Health* 1993;19:414-420.
30. Lowden, A, Akerstedt, T, and Wibom, R. Suppression of sleepiness and melatonin by bright light exposure during breaks in night work. *Journal of Sleep Research* 2004;13:37-43.
31. Bjorvatn, B, Kecklund, G, and Akerstedt, T. Bright light treatment used for adaptation to night work and re-adaptation back to day life. A field study at an oil platform in the North Sea. *J Sleep Res* 1999;8:105-112.
32. Sharkey, KM, and Eastman, CI. Melatonin phase shifts human circadian rhythms in a placebo-controlled simulated night-work study. *American Journal of Physiology - Regulatory Integrative & Comparative Physiology* 2002;282:R454.
33. Sharkey, KM, Fogg, LF, and Eastman, CI. Effects of melatonin administration on daytime sleep after simulated night shift work. *Journal of Sleep Research* 2001;10:181-192.
34. Sack, RL, and Lewy, AJ. Melatonin as a chronobiotic: treatment of circadian desynchrony in night workers and the blind. *J Biol Rhythms* 1997;12:595-603.
35. James, M, Tremea, MO, Jones, JS, and Krohmer, JR. Can melatonin improve adaptation to night shift? *American Journal of Emergency Medicine* 1998;16:367-370.
36. Jorgensen, KM, and Witting, MD. Does exogenous melatonin improve day sleep or night alertness in emergency physicians working night shifts? *Annals of Emergency Medicine* 1998;31:699-704.
37. Yoon, IY, and Song, BG. Role of morning melatonin administration and attenuation of sunlight exposure in improving adaptation of night-shift workers. *Chronobiology International* 2002;19:903-913.
38. Folkard, S, Arendt, J, and Clark, M. Can melatonin improve shift workers' tolerance of the night shift? Some preliminary findings. *Chronobiology International* 1993;10:315-320.
39. Walsh, JK, Schweitzer, PK, Anch, AM, Muehlbach, MJ, Jenkins, NA, and Dickins, QS. Sleepiness/alertness on a simulated night shift following sleep at home with triazolam. *Sleep* 1991;14:140-146.
40. Walsh, JK, Sugeran, JL, Muehlbach, MJ, and Schweitzer, PK. Physiological sleep tendency on a simulated night shift: adaptation and effects of triazolam. *Sleep* 1988;11:251-264.
41. Porcu, S, Bellatreccia, A, Ferrara, M, and Casagrande, M. Performance, ability to stay awake, and tendency to fall asleep during the night after a diurnal sleep with temazepam or placebo. *Sleep* 1997;20:535-541.
42. Monchesky, TC, Billings, BJ, Phillips, R, and Bourgooin, J. Zopiclone in insomniac shiftworkers. Evaluation of its hypnotic properties and its effects on mood and work performance. *International Archives of Occupational & Environmental Health* 1989;61:255-259.
43. Moon, CA, Hindmarch, I, and Holland, RL. The effect of zopiclone 7.5 mg on the sleep, mood and performance of shift workers. *International clinical psychopharmacology* 1990;5:79-83.
44. Puca, FM, Perrucci, S, Prudenzano, MP, et al. Quality of life in shift work syndrome. *Functional neurology* 1996;11:261-268.

45. Walsh, JK, Randazzo, AC, Stone, KL, and Schweitzer, PK. Modafinil improves alertness, vigilance, and executive function during simulated night shifts. *Sleep* 2004;27:434-439.
46. Hart, CL, Haney, M, Nasser, J, and Foltin, RW. Combined effects of methamphetamine and zolpidem on performance and mood during simulated night shift work. *Pharmacology, Biochemistry & Behavior* 2005;81:559-568.
47. Spitzer, RL, Terman, M, Williams, JB, Terman, JS, Malt, UF, Singer, F, and Lewy, AJ. Jet lag: clinical features, validation of a new syndrome-specific scale, and lack of response to melatonin in a randomized, double-blind trial. *American Journal of Psychiatry* 1999;156:1392-1396.
48. Carvalho Bos, S, Waterhouse, J, Edwards, B, Simons, R, and Reilly, T. The use of actimetry to assess changes to the rest-activity cycle. *Chronobiology International* 2003;20:1039-1043.
49. Lowden, A, and Akerstedt, T. Retaining home-base sleep hours to prevent jet lag in connection with a westward flight across nine time zones. *Chronobiology International* 1998;15:365-76.
50. Burgess, HJ, Crowley, SJ, Gazda, CJ, Fogg, LF, and Eastman, CI. Preflight adjustment to eastward travel: 3 days of advancing sleep with and without morning bright light. *Journal of Biological Rhythms* 2003;18:318-328.
51. Boulos, Z, Macchi, MM, Sturchler, MP, et al. Light visor treatment for jet lag after westward travel across six time zones. *Aviation Space & Environmental Medicine* 2002;73:953-963.
52. Suhner, A, Schlagenhauf, P, Hofer, I, Johnson, R, Tschopp, A, and Steffen, R. Effectiveness and tolerability of melatonin and zolpidem for the alleviation of jet lag. *Aviation Space & Environmental Medicine* 2001;72:638-646.
53. Suhner, A, Schlagenhauf, P, Johnson, R, Tschopp, A, and Steffen, R. Comparative study to determine the optimal melatonin dosage form for the alleviation of jet lag. *Chronobiol Int* 1998;15:655-666.
54. Arendt, J, Aldhous, M, and Marks, V. Alleviation of jet lag by melatonin: preliminary results of controlled double blind trial. *Br Med J (Clin Res Ed)* 1986;292:1170.
55. Claustrat, B, Brun, J, David, M, Sassolas, G, and Chazot, G. Melatonin and jet lag: confirmatory result using a simplified protocol. *Biol Psychiatry* 1992;32:705-711.
56. Petrie, K, Conaglen, JV, Thompson, L, and Chamberlain, K. Effect of melatonin on jet lag after long haul flights. *BMJ* 1989;298:705-707.
57. Petrie, K, Dawson, AG, Thompson, L, and Brook, R. A double-blind trial of melatonin as a treatment for jet lag in international cabin crew. *Biological psychiatry* 1993;33:526-530.
58. Edwards, BJ, Atkinson, G, Waterhouse, J, Reilly, T, Godfrey, R, and Budgett, R. Use of melatonin in recovery from jet-lag following an eastward flight across 10 time-zones. *Ergonomics* 2000;43:1501-1513.
59. Comperatore, CA, Lieberman, HR, Kirby, AW, Adams, B, and Crowley, JS. Melatonin efficacy in aviation missions requiring rapid deployment and night operations. *Aviat Space Environ Med* 1996;67:520-524.
60. Paul, MA, Gray, G, Sardana, TM, and Pigeau, RA. Melatonin and zopiclone as facilitators of early circadian sleep in operational air transport crews. *Aviation Space & Environmental Medicine* 2004;75:439-443.
61. Beaumont, M, Batejat, D, Pierard, C, et al. Caffeine or melatonin effects on sleep and sleepiness after rapid eastward transmeridian travel. *Journal of applied physiology* 2004;96:50-58.
62. Pierard, C, Beaumont, M, Enslin, M, et al. Resynchronization of hormonal rhythms after an eastbound flight in humans: effects of slow-release caffeine and melatonin. *European journal of applied physiology* 2001;85:144-150.
63. Jamieson, AO, Zammit, GK, Rosenberg, RS, Davis, JR, and Walsh, JK. Zolpidem reduces the sleep disturbance of jet lag. *Sleep Medicine* 2001;2:423-430.
64. Buxton, OM, Copinschi, G, Van Onderbergen, A, Karrison, TG, and Van Cauter, E. A benzodiazepine hypnotic facilitates adaptation of circadian rhythms and sleep-wake homeostasis to an eight hour delay shift simulating westward jet lag. *Sleep* 2000;23:915-927.
65. Daurat, A, Benoit, O, and Buguet, A. Effects of zopiclone on the rest/activity rhythm after a westward flight across five time zones. *Psychopharmacology* 2000;149:241-245.
66. Donaldson, E, and Kennaway, DJ. Effects of temazepam on sleep, performance, and rhythmic 6-sulphatoxymelatonin and cortisol excretion after transmeridian travel. *Aviat Space Environ Med* 1991;62:654-660.
67. Hirschfeld, U, Moreno-Reyes, R, Akseki, E, L'Hermite-Baleriaux, M, Leproult, R, Copinschi, G, and Van Cauter, E. Progressive elevation of plasma thyrotropin during adaptation to simulated jet lag: effects of treatment with bright light or zolpidem. *Journal of Clinical Endocrinology & Metabolism* 1996;81:3270-3277.
68. Lavie, P. Effects of midazolam on sleep disturbances associated with westward and eastward flights: evidence for directional effects. *Psychopharmacology (Berl)* 1990;101:250-254.
69. Reilly, T, Atkinson, G, and Budgett, R. Effect of low-dose temazepam on physiological variables and performance tests following a westerly flight across five time zones. *International Journal of Sports Medicine* 2001;22:166-174.
70. Morris, HH, 3rd, and Estes, ML. Traveler's amnesia. Transient global amnesia secondary to triazolam. *Jama* 1987;258:945-946.
71. Satoh, K, Mishima, K, Inoue, Y, Ebisawa, T, and Shimizu, T. Two pedigrees of familial advanced sleep phase syndrome in Japan. *Sleep* 2003;26:416-417.
72. Jones, CR, Campbell, SS, Zone, SE, et al. Familial advanced sleep-phase syndrome: A short-period circadian rhythm variant in humans. *Nature Medicine* 1999;5:1062.
73. Palmer, CR, Kripke, DF, Savage, HC, Jr., Cindrich, LA, Loving, RT, and Elliott, JA. Efficacy of enhanced evening light for advanced sleep phase syndrome. *Behavioral Sleep Medicine* 2003;1:213-226.
74. Campbell, SS, Dawson, D, and Anderson, MW. Alleviation of sleep maintenance insomnia with timed exposure to bright light. *J Am Geriatr Soc* 1993;41:829-836.
75. Suhner, AG, Murphy, PJ, and Campbell, SS. Failure of timed bright light exposure to alleviate age-related sleep maintenance insomnia. *Journal of the American Geriatrics Society* 2002;50:617-623.
76. Lack, L, Wright, H, Kemp, K, and Gibbon, S. The treatment of early-morning awakening insomnia with 2 evenings of bright light. *Sleep* 2005;28:616-623.
77. Lack, L, and Wright, H. The effect of evening bright light in delaying the circadian rhythms and lengthening the sleep of early morning awakening insomniacs. *Sleep* 1993;16:436-443.
78. Moldofsky, H, Musisi, S, and Phillipson, EA. Treatment of a case of advanced sleep phase syndrome by phase advance chronotherapy. *Sleep* 1986;9:61-65.
79. Pallesen, S, Nordhus, IH, Skelton, SH, Bjorvatn, B, and Skjerve, A. Bright light treatment has limited effect in subjects over 55 years with mild early morning awakening. *Perceptual & Motor Skills* 2005;101:759-770.
80. Cole, RJ, Smith, JS, Alcala, YC, Elliott, JA, and Kripke, DF. Bright-light mask treatment of delayed sleep phase syndrome. *Journal of Biological Rhythms* 2002;17:89-101.
81. Rosenthal, NE, Joseph-Vanderpool, JR, Levendosky, AA, et al. Phase-shifting effects of bright morning light as treatment for delayed sleep phase syndrome. *Sleep* 1990;13:354-361.
82. Czeisler, CA, Richardson, GS, Coleman, RM, Zimmerman, JC, Moore-Ede, MC, Dement, WC, and Weitzman, ED. Chronotherapy: resetting the circadian clocks of patients with delayed sleep phase insomnia. *Sleep* 1981;4:1-21.
83. Ito, A, Ando, K, Hayakawa, T, Iwata, T, Kayukawa, Y, Ohta, T, and Kasahara, Y. Long-term course of adult patients with delayed sleep phase syndrome. *Japanese Journal of Psychiatry & Neurology* 1993;47:563-567.

84. Kayumov, L, Brown, G, Jindal, R, Buttoo, K, and Shapiro, CM. A randomized, double-blind, placebo-controlled crossover study of the effect of exogenous melatonin on delayed sleep phase syndrome. *Psychosomatic medicine* 2001;63:40-48.
85. Dahlitz, M, Alvarez, B, Vignau, J, English, J, Arendt, J, and Parkes, JD. Delayed sleep phase syndrome response to melatonin. *Lancet* 1991;337:1121-1124.
86. Munday, K, Benloucif, S, Harsanyi, K, Dubocovich, ML, and Zee, PC. Phase-dependent treatment of delayed sleep phase syndrome with melatonin. *Sleep* 2005;28:1271-1278.
87. Dagan, Y, Yovel, I, Hallis, D, Eisenstein, M, and Raichik, I. Evaluating the role of melatonin in the long-term treatment of delayed sleep phase syndrome (DSPS). *Chronobiology International* 1998;15:181-190.
88. Okawa, M, Takahashi, K, Egashira, K, et al. Vitamin B12 treatment for delayed sleep phase syndrome: a multi-center double-blind study. *Psychiatry & Clinical Neurosciences* 1997;51:275-279.
89. Uchiyama, M, Shibui, K, Hayakawa, T, et al. Larger phase angle between sleep propensity and melatonin rhythms in sighted humans with non-24-hour sleep-wake syndrome. *Sleep* 2002;25:83-88.
90. Boivin, DB, James, FO, Santo, JB, Caliyurt, O, and Chalk, C. Non-24-hour sleep-wake syndrome following a car accident. *Neurology* 2003;60:1841-1843.
91. Oren, DA, Giesen, HA, and Wehr, TA. Restoration of detectable melatonin after entrainment to a 24-hour schedule in a 'free-running' man. *Psychoneuroendocrinology* 1997;22:39-52.
92. Hashimoto, S, Nakamura, K, Honma, S, and Honma, K. Free-running of plasma melatonin rhythm prior to full manifestation of a non-24 hour sleep-wake syndrome. *Psychiatry & Clinical Neurosciences* 1998;52:264-265.
93. Hayakawa, T, Kamei, Y, Urata, J, Shibui, K, Ozaki, S, Uchiyama, M, and Okawa, M. Trials of bright light exposure and melatonin administration in a patient with non-24 hour sleep-wake syndrome. *Psychiatry & Clinical Neurosciences* 1998;52:261-262.
94. Kamei, Y, Hayakawa, T, Urata, J, et al. Melatonin treatment for circadian rhythm sleep disorders. *Psychiatry & Clinical Neurosciences* 2000;54:381-382.
95. McArthur, AJ, Lewy, AJ, and Sack, RL. Non-24-hour sleep-wake syndrome in a sighted man: circadian rhythm studies and efficacy of melatonin treatment. *Sleep* 1996;19:544-553.
96. Dagan, Y, and Ayalon, L. Case study: psychiatric misdiagnosis of non-24-hours sleep-wake schedule disorder resolved by melatonin. *J Am Acad Child Adolesc Psychiatry* 2005;44:1271-1275.
97. Sack, RL, Lewy, AJ, Blood, ML, Keith, LD, and Nakagawa, H. Circadian rhythm abnormalities in totally blind people: incidence and clinical significance. *J Clin Endocrinol Metab* 1992;75:127-134.
98. Lockley, SW, Skene, DJ, James, K, Thapan, K, Wright, J, and Arendt, J. Melatonin administration can entrain the free-running circadian system of blind subjects. *Journal of Endocrinology* 2000;164:R1-6.
99. Sack, RL, Brandes, RW, Kendall, AR, and Lewy, AJ. Entrainment of free-running circadian rhythms by melatonin in blind people. *N Engl J Med* 2000;343:1070-1077.
100. Hack, LM, Lockley, SW, Arendt, J, and Skene, DJ. The effects of low-dose 0.5-mg melatonin on the free-running circadian rhythms of blind subjects. *J Biol Rhythms* 2003;18:420-429.
101. Lewy, AJ, Hasler, BP, Emens, JS, and Sack, RL. Pretreatment circadian period in free-running blind people may predict the phase angle of entrainment to melatonin. *Neuroscience Letters* 2001;313:158-160.
102. Lewy, AJ, Bauer, VK, Hasler, BP, Kendall, AR, Pires, ML, and Sack, RL. Capturing the circadian rhythms of free-running blind people with 0.5 mg melatonin. *Brain Research* 2001;918:96.
103. Lewy, AJ, Emens, JS, Sack, RL, Hasler, BP, and Bernert, RA. Low, but not high, doses of melatonin entrained a free-running blind person with a long circadian period. *Chronobiology International* 2002;19:649-658.
104. Lewy, AJ, Emens, JS, Bernert, RA, and Lefler, BJ. Eventual entrainment of the human circadian pacemaker by melatonin is independent of the circadian phase of treatment initiation: clinical implications. *Journal of Biological Rhythms* 2004;19:68-75.
105. Klein, T, Martens, H, Dijk, DJ, Kronauer, RE, Seely, EW, and Czeisler, CA. Circadian sleep regulation in the absence of light perception: chronic non-24-hour circadian rhythm sleep disorder in a blind man with a regular 24-hour sleep-wake schedule. *Sleep* 1993;16:333-343.
106. Hoban, TM, Sack, RL, Lewy, AJ, Miller, LS, and Singer, CM. Entrainment of a free-running human with bright light? *Chronobiology International* 1989;6:347-353.
107. Okawa, M, Uchiyama, M, Ozaki, S, Shibui, K, Kamei, Y, Hayakawa, T, and Urata, J. Melatonin treatment for circadian rhythm sleep disorders. *Psychiatry & Clinical Neurosciences* 1998;52:259-260.
108. Watanabe, T, Kajimura, N, Kato, M, Sekimoto, M, Hori, T, and Takahashi, K. Case of a non-24 h sleep-wake syndrome patient improved by phototherapy. *Psychiatry & Clinical Neurosciences* 2000;54:369-370.
109. Siebler, M, Steinmetz, H, and Freund, HJ. Therapeutic entrainment of circadian rhythm disorder by melatonin in a non-blind patient. *Journal of Neurology* 1998;245:327-328.
110. Arendt, J, Aldhous, M, and Wright, J. Synchronisation of a disturbed sleep-wake cycle in a blind man by melatonin treatment. *Lancet* 1988;1:772-773.
111. Folkard, S, Arendt, J, Aldhous, M, and Kennett, H. Melatonin stabilises sleep onset time in a blind man without entrainment of cortisol or temperature rhythms. *Neuroscience Letters* 1990;113:193-198.
112. Lapiere, O, and Dumont, M. Melatonin treatment of a non-24-hour sleep-wake cycle in a blind retarded child. *Biological psychiatry* 1995;38:119-122.
113. Tzischinsky, O, Pal, I, Epstein, R, Dagan, Y, and Lavie, P. The importance of timing in melatonin administration in a blind man. *Journal of pineal research* 1992;12:105-108.
114. Okawa, M, Mishima, K, Nanami, T, Shimizu, T, Iijima, S, Hishikawa, Y, and Takahashi, K. Vitamin B12 treatment for sleep-wake rhythm disorders. *Sleep* 1990;13:15-23.
115. Ohta, T, Ando, K, Iwata, T, et al. Treatment of persistent sleep-wake schedule disorders in adolescents with methylcobalamin (vitamin B12). *Sleep* 1991;14:414-418.
116. McCurry, SM, Gibbons, LE, Logsdon, RG, Vitiello, MV, and Teri, L. Nighttime insomnia treatment and education for Alzheimer's disease: a randomized, controlled trial. *Journal of the American Geriatrics Society* 2005;53:793-802.
117. Singer, C, Tractenberg, RE, Kaye, J, et al. A multicenter, placebo-controlled trial of melatonin for sleep disturbance in Alzheimer's disease. *Sleep* 2003;26:893-901.
118. Alessi, CA, Martin, JL, Webber, AP, Cynthia Kim, E, Harker, JO, and Josephson, KR. Randomized, controlled trial of a nonpharmacological intervention to improve abnormal sleep/wake patterns in nursing home residents. *J Am Geriatr Soc* 2005;53:803-810.
119. Ancoli-Israel, S, Gehrman, P, Martin, JL, Shochat, T, Marler, M, Corey-Bloom, J, and Levi, L. Increased light exposure consolidates sleep and strengthens circadian rhythms in severe Alzheimer's disease patients. *Behavioral Sleep Medicine* 2003;1:22-36.
120. Ancoli-Israel, S, Martin, JL, Kripke, DF, Marler, M, and Klauber, MR. Effect of light treatment on sleep and circadian rhythms in demented nursing home patients. *Journal of the American Geriatrics Society* 2002;50:2829.
121. Dowling, GA, Hubbard, EM, Mastick, J, Luxenberg, JS, Burr, RL, and Van Someren, EJ. Effect of morning bright light treatment for rest-activity disruption in institutionalized patients with severe Alzheimer's disease. *Int Psychogeriatr* 2005;17:221-236.
122. Hatfield, CF, Herbert, J, van Someren, EJ, Hodges, JR, and Hastings, MH. Disrupted daily activity/rest cycles in relation to daily cortisol rhythms of home-dwelling patients with early Alzheimer's dementia. *Brain* 2004;127:1061-1074.

123. Van Someren, EJ, Kessler, A, Mirmiran, M, and Swaab, DF. Indirect bright light improves circadian rest-activity rhythm disturbances in demented patients. *Biol Psychiatry* 1997;41:955-963.
124. Fetveit, A, Skjerve, A, and Bjorvatn, B. Bright light treatment improves sleep in institutionalised elderly--an open trial. *International journal of geriatric psychiatry* 2003;18:520-526.
125. Mishima, K, Okawa, M, Hishikawa, Y, Hozumi, S, Hori, H, and Takahashi, K. Morning bright light therapy for sleep and behavior disorders in elderly patients with dementia. *Acta Psychiatrica Scandinavica* 1994;89:1-7.
126. Fetveit, A, and Bjorvatn, B. The effects of bright-light therapy on actigraphical measured sleep last for several weeks post-treatment. A study in a nursing home population. *Journal of Sleep Research* 2004;13:153-8.
127. Satlin, A, Volicer, L, Ross, V, Herz, L, and Campbell, S. Bright light treatment of behavioral and sleep disturbances in patients with Alzheimer's disease. *American Journal of Psychiatry* 1992;149:1028-1032.
128. Serfaty, M, Kennell-Webb, S, Warner, J, Blizard, R, and Raven, P. Double blind randomised placebo controlled trial of low dose melatonin for sleep disorders in dementia. *International journal of geriatric psychiatry* 2002;17:1120-1127.
129. Pillar, G, Shahar, E, Peled, N, Ravid, S, Lavie, P, and Etzioni, A. Melatonin improves sleep-wake patterns in psychomotor retarded children. *Pediatric Neurology* 2000;23:225-228.
130. Jan, JE, Espezel, H, and Appleton, RE. The treatment of sleep disorders with melatonin. *Developmental Medicine & Child Neurology* 1994;36:97-107.
131. Jan, JE, Hamilton, D, Seward, N, Fast, DK, Freeman, RD, and Laudon, M. Clinical trials of controlled-release melatonin in children with sleep-wake cycle disorders. *J Pineal Res* 2000;29:34-39.
132. McArthur, AJ, and Budden, SS. Sleep dysfunction in Rett syndrome: a trial of exogenous melatonin treatment. *Developmental Medicine & Child Neurology* 1998;40:186-192.
133. Guilleminault, C, McCann, CC, Quera-Salva, M, and Cetel, M. Light therapy as treatment of dyschronosis in brain impaired children. *European journal of pediatrics* 1993;152:754-759.