Circadian Rhythm Sleep Disorders: Part I, Basic Principles, Shift Work and Jet Lag Disorders

An American Academy of Sleep Medicine Review

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

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

Objective: This the first 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. In this first part of this paper, the general principles of circadian biology that underlie clinical evaluation and treatment are reviewed. We then report on the accumulated evidence regarding the evaluation and treatment of shift work disorder (SWD) and jet lag disorder (JLD).

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 SWD and JLD. 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 the SWD and JLD, 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

Citation: Sack RL; Auckley D; Auger RR; Carskadon MA; Wright KP; Vitiello MV; Zhdanova IV. Circadian rhythm sleep disorders: Part I, basic principles, shift work and jet lag disorders. *SLEEP* 2007;30(11):1460-1483.

TABLE OF CONTENTS

Disclosure Statement

This is not an industry supported study. Dr. Sack has received research support from GlaxoSmithKline, Takeda, and Cephalon and has consulted for Minimitter Company. Dr. Auckley has received research support from Invacare and TAP Pharmaceuticals. Dr. Carskadon has received research support from Evotec and Cephalon and has participated in speaking engagements for World Class and Cephalon. Dr. Wright has received research support from and has participated in speaking engagements for Cephalon and Takeda, and has consulted for Takeda. Dr. Vitiello is on the speakers bureau for Takeda. Drs. Auger and Zhdanova 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 is the first 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), employing the methodology of evidence-based medicine. To this end, the Task Force formulated a set of specific questions relevant to clinical practice, extensively searched the medical literature, abstracted the core findings, and graded the quality of the evidence. From this process, an evidence table was constructed (available online at http://www.aasmnet.org/). In these two review articles, we provide a summary of the evidence gleaned through this process, and place the evidence regarding clinical issues in the context of current circadian science.

Because of the large volume of relevant scientific literature, the Task Force divided the report into two papers. In the first paper, we review the circadian science concepts and research strategies that have provided the framework for clinical investigation. We then report on the accumulated evidence regarding shift work disorder (SWD) and jet lag disorder (JLD). We grouped SWD and JLD together because, in both of these disorders, the circadian system functions adequately under usual circumstances, but when an imposed or voluntary shift in the timing of sleep exceeds the limits of circadian adaptation, misalignment occurs and generates a constellation of symptoms that characterize a disorder. However, this grouping of SWD and JLD together is not meant to imply that endogenous factors (such as individual differences in the ability to sleep at an unfavorable circadian phase) do not contribute to SWD and JLD.

The second paper will deal with disorders that are thought to be more intrinsic; that is, involving a problem with the circadian system itself (although these disorders may, in turn, be influenced by exogenous factors). Specifically, these disorders include advanced sleep phase disorder (ASPD), delayed sleep phase disorder (DSPD), free-running disorder (FRD), and irregular sleep-wake rhythm (ISWR). These reports will be accompanied by practice recommendations formulated by the AASM Standards of Practice Committee.

2.0 DEFINITION AND OVERVIEW OF CIRCADIAN RHYTHM SLEEP DISORDERS

2.1 Classification

Major progress is being made in understanding the biology of circadian rhythms, but in clinical practice, classification remains based primarily on criteria related to a constellation of symptoms, at times supplemented by standardized questionnaires and laboratory tests.

There are six distinct CRSDs currently recognized in the International Classification of Sleep Disorders (ICSD-2),[1] namely: 1) *delayed sleep phase type*, 2) *advanced sleep phase type,* 3) *irregular sleep-wake phase type*, 4) *free-running type*, 5) *jet lag type*, and 6) *shift work type*. The ICSD-2 also recognizes CRSDs *secondary to medical conditions* and *drug or substance abuse*, as well as a general category, CRSD *Not Otherwise Specified (NOS*). In order to be consistent with the *International Classification of Diseases*, the clinical entities are classified as *Type,* but are equivalent to the more commonly employed labeling as *disorders* or *syndromes* with the associated abbreviations; for example, *delayed sleep phase disorder (DSPD).*

According to the ICSD-2,[1] "The essential feature of CRSDs is a persistent or recurrent pattern of sleep disturbance due primarily to alterations in the circadian timekeeping system or a misalignment between the endogenous circadian rhythm and exogenous factors that affect the timing or duration of sleep." Thus, either exogenous or endogenous factors (and often both) can contribute to the misalignment between the timing of internal circadian rhythms and the desired (from the patient's perspective) or required (from the scheduling demands of society) time for sleep.

The diagnostic criteria include "impairment," e.g., "social, occupational, or other." While there may be a correlation between the degree of misalignment and the symptom burden, such is not always the case. Some individuals appear to have *phase tolerance*;[2] that is, their sleep is relatively unaffected by circadian misalignment; others may be very sensitive.

The diagnosis also requires that the disorder not be "better explained" by another primary sleep disorder. This criterion is very important clinically; for example, a complaint of sleepiness in a night shift worker should not overlook the possibility of obstructive sleep apnea or some other primary sleep disorder.

Table 1—Clinical Questions Addressed in the Review

Clinical Questions	Observations promoting questions
Risk Factors	
Is age a risk factor for developing a CRSD?	Basic research suggests that the circadian system undergoes major changes over the course of the life cycle.
Is gender a risk factor for developing a CRSD?	Gender may be a significant risk factor for CRSDs, given the interaction between the circadian and reproductive systems, including the menstrual cycle. Gender could be also an important risk factor because of employment patterns or childcare duties.
Is insufficient, excessive, or inappropriately timed light exposure a risk factor for developing a CRSD?	Because sunlight is the most important circadian time cue in humans, it is logical to ask whether the intensity, duration or timing of light exposure is a risk factor for CRSDs.
Is there a familial (genetic) predisposition for developing a CRSD?	Many patients with CRSDs report family members with similar problems. Furthermore, recent advances in molecular biology have identified "clock genes" that could be involved in the pathophysiology of CRSDs.
Assessment Tools	
How useful is a sleep log (diary)?	Sleep-wake diaries (sleep logs) are consistently recommended as a method for evaluating sleep schedules in CRSD patients.
How useful is actigraphy?	The ICSD-2 diagnostic criteria for most CRSDs require that abnormalities in the timing of the habitual sleep pattern be documented with either sleep logs or actigraphy for seven days or more.[1]
How useful is the MEQ in clinical practice?	The Morningness-Eveningness Questionnaire (MEQ) developed by Horne and Ostberg in 1976[7] has become a widely employed instrument to classify individuals with extreme circadian tendencies ("larks" and "owls").
Is a PSG necessary in the clinical management of a CRSD?	Polysomnography (PSG) is considered the "gold standard" for sleep assessment. In some of the research studies we reviewed, PSG, and in a few instances, multiple sleep latency tests (MSLTs) have been employed.
When might it be useful (or necessary) to assess circadian phase and/or amplitude using a marker such as core body temperature (CBT) or melatonin?	Methods have been refined that can determine circadian phase (circadian time [CT]) in humans.
Treatment	
Is prescribed sleep/wake scheduling safe and effective?	*Chronotherapy* was the first recognized treatment for a CRSD and can be considered an example of prescribed sleep scheduling, based on a hypothesized circadian mechanism. Another example is prescribed napping proposed as a countermeasure for night workers.
Is timed light exposure safe and effective? Is timed melatonin administration safe and effective?	Inasmuch as CRSDs involve a misalignment of the circadian system with the preferred sleep schedule, can this be corrected by circadian phase shifting?
Are sleep-promoting medications safe and effective? Are wakefulness-promoting medications safe and effective?	Insomnia can be one of the symptoms of a CRSD. Excessive sleepiness can be one of the symptoms of CRSDs.

It should be noted that an unconventional sleep schedule does not in itself qualify as a CRSD. If the timing of sleep is congruent with the timing of the circadian sleep propensity rhythm (the two rhythms are synchronized), and there is no symptomatic burden or disability, then there is no basis for a CRSD diagnosis. Likewise, if a patient has insomnia regardless of when he/she sleeps, then a diagnosis of insomnia and not a CRSD should be considered.

Although we have divided these reports into exogenous and endogenous disorders, we recognize that CRSDs can involve a mixture of etiological factors. For example, it has been suggested that the greater tendency for teenagers and young adults to have DSPD may be due to some alteration of the circadian system (such as a lengthening of the intrinsic circadian period—possibly secondary to hormonal influences), *as well as* peer-reinforced behavior patterns such as staying up late and "sleeping in." It is also possible that tolerance to shift work or jet travel may depend on a mixture of exogenous and endogenous factors; for example, it has been suggested that night work and westward flight may be easier for evening types ("owls") because of their stronger natural propensity to delay their circadian rhythms.

2.2 Prevalence

The prevalence of CRSDs is unknown, although, if one takes into account the large number of people who do shift work or fly, it must be high. There are very few community based epidemiological studies of CRSDs. According to the only study that combined formal diagnostic criteria with an epidemiologic sample

(using questionnaire data and not clinical evaluation), 32.1% of night workers and 26.1% of rotating workers met the minimal criteria for SWD.[3] There are almost no prevalence data for the other CRSDs. In one random telephone survey,[4] seven people out of 1525 contacted had sleep log patterns similar to DSPD, but just one actually met diagnostic criteria for DSPD after interview.

The proportion of patients who are diagnosed with a CRSD in current sleep disorders medicine clinics is quite small compared to other diagnostic categories.[5,6] In a review of one clinic's experience, Dagan[5] found that DSPD was the most common CRSD diagnosis (83%), followed by free-running disorder (12%). ASPD and ISWR were very rarely diagnosed, accounting for less than 2% of the CRSD patients. On the other hand, the number of patients presenting to a clinic may be quite different from the prevalence in the population. Patients with CRSDs may not recognize that their problem has a physiological basis, or may not know that medical help is available.

3.0 THE QUESTIONS ADDRESSED IN THIS REVIEW

In order to focus the review, the Task Force, in communication with the Standards of Practice Committee of the AASM, constructed questions drawn from common clinical concerns in the evaluation and treatment of CRSDs. Table 1 lists the specific questions (first column) followed by one or more considerations that prompted the question.

4.0 METHODS

4.1 Inclusion and Exclusion.

To address these questions, the medical literature was searched for studies of patients with a presumptive or diagnosed CRSD, and an evidence table constructed. Searches were limited to articles published in the English language involving human subjects. Abstracts, theoretical papers and editorials were excluded. Review articles were excluded from the evidence table, but have been incorporated into this report where appropriate for background. Because unequivocal cases of ASPD and FRD are quite rare, single case reports were accepted for these categories; otherwise, studies were required to include at least eight subjects. We did not include studies of disorders that may have a circadian component but are not considered CRSDs; e.g., restless legs syndrome, seasonal affective disorder (winter depression), and extended duty/acute sleep deprivation. Also, we did not review studies of treatments that might affect circadian rhythms if the study did not aim to correct a circadian abnormality (e.g., melatonin administration for psychophysiological insomnia). No age range was imposed; in other words, we included studies that involved children, young adults, and older adults. Some of the studies were used as evidence on more than one relevant question; i.e., risk, assessment, and treatment.

We also reviewed studies of simulated SWD or JLD and included them in the evidence table if they provided evidence for important principles that could be applied clinically. These studies recruited subjects without a clinical diagnosis who participated in a phase shifting protocol designed to simulate a clinical condition. Given the constraints of space, these studies are summarized in the text, and not described in detail.

Table 2—Search Strategy and Results

Search Term(s)	Number of Citations*
Sleep Disorders, Circadian Rhythm	436
Chronobiology Disorders	131
Work Schedule Tolerance, AND *Sleep*	687
Jet Lag Syndrome	119
Delayed Sleep Phase Syndrome	111
Advanced Sleep Phase Syndrome	26
Irregular Sleep-Wake Disorder	0
Non–24-Hour Sleep-Wake Disorder	2
Chronotherapy combined with *Sleep Disorders*	35
Phototherapy combined with *Sleep Disorders*	127
Melatonin combined with *Sleep Disorders*	254
Blindness combined with *Sleep Disorders*	44
Morningness Eveningness	89
Total	2084

*Found in an iterative search strategy (see text)

4.2 Literature Search

We searched MEDLINE through October 2006 (using the search terms listed in Table 2) to identify citations of potential relevance for this review. The most relevant search term, *Sleep Disorders, Circadian Rhythm*, became a MESH heading in the year 2000, and the search term, *Chronobiology Disorders*, became a MESH heading in 2001. Several CRSDs are not yet included in the MESH headings list. Consequently, to identify relevant articles, especially those published prior to 2000, the terms were searched both as MESH headings and as keywords. Also, broader search terms were used and then limited by including *sleep* as a search co-term. An iterative process was used to remove duplicates; that is, as each term was searched, only articles that had not been previously identified were added to the citation list. In addition, the bibliographies of review articles were examined by Task Force members in order to find articles that were missed in the initial search.

After this large set of potentially relevant citations was identified, the titles and abstracts were reviewed by at least two members of the task force who voted for or against inclusion in a final set of articles to be reviewed in more detail and scored (see below). When the two reviewers were in disagreement, the Chair of the Task Force (RLS) acted as a tiebreaker.

Each article was abstracted either by a task force member or a paid professional. Each abstract contained four essential items that were placed in a *PICO* evidence table; namely, 1) A description of the *P*atient or *P*roblem that was addressed, 2) The *I*ntervention that was made, 3) A *C*omparison intervention (if necessary) and 4) The *O*utcome(s). These abstracts are posted in an evidence table on the AASM website: www.aasmnet.org/

In addition to being abstracted, the studies were graded using the Oxford System for Evidence-Based Medicine[8] (http://www.cebm.net/index.aspx?o=1025). See Table 3.

Table 3—Levels of Evidence
Adapted from Oxford Centre for Evidence-Based Medicine (May 2001)

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.
The Oxford system defines four levels of evidence, and appends each level with an "a" if the evidence is based on a systematic review, or a "b" if it refers to a single study. Because we did not find any systematic reviews (only individual reports), we dropped the "b" and indicated only the numerical level of evidence. Papers that were considered important background citations are included in the bibliography without an evidence grade.

5.0 CIRCADIAN RHYTHM BIOLOGY

5.1 General Principles

In order to put the clinical research into the appropriate context, we felt it was important to review, more generally, the current concepts and experimental strategies used in human circadian rhythm research. A full introduction to circadian rhythm biology can be found in a recently published textbook[9] and is beyond the scope of this paper.

In the last decade, breakthroughs have been made in understanding the intracellular protein transcriptional feedback mechanisms that generate circadian rhythms. These discoveries are just beginning to reach the clinical arena as genetic mechanisms are being investigated as possible etiological factors in some CRSDs. These studies are reviewed in some detail in Part II of this report.

Before these advances at the molecular level, it was well documented that mammalian circadian rhythms were generated within the neurons of the suprachiasmatic nucleus (SCN) of the hypothalamus. Output signals (efferents) from the SCN not only modulate daily rhythms in sleep and alertness, but also the rhythms of core body temperature and the secretion of certain hormones such as melatonin and cortisol. It was also well established that, in most humans (reviewed by Dijk and Lockley),[10] the intrinsic rhythm of the clock is slightly longer than 24 hours, so that precise synchronization to a 24-hour day (entrainment) depends on exposure to environmental time signals (*zeitgebers*)—most importantly, the solar light/dark cycle. In the absence of timing signals (e.g., sighted subjects kept in temporal isolation), or light exposure (e.g., totally blind subjects), circadian rhythms typically "free-run" on a non–24-hour cycle, expressing the intrinsic circadian (*circa* meaning *about* and *dian* meaning *day*) period of the clock. Therefore, maintaining normal entrainment is a dynamic process that depends on regular adjustments of the circadian pacemaker via exposure to the relevant environmental time cues, most importantly the solar light-dark cycle.

Recently, non-rod, non-cone photoreceptors in the ganglion cells of the retina have been identified[11,12] as especially important for the entraining effects of light.[13,14] These novel nonvisual circadian photoreceptors, which contain the photopigment melanopsin, are most sensitive to blue wavelength light; thus blue light exposure may be the most efficient wavelength to shift the circadian system and suppress melatonin. Based on these discoveries, light treatment devices that are enriched with blue light are now being tested.[15] Although for the mammalian circadian system, blue light exposure of the ganglion cells is important, there appears to be some redundancy in the circadian photoreceptive system, such that the rods and cones also influence the circadian response to light. In any case, ordinary white light fixtures of sufficient intensity can produce phase shifts equal to blue light.

Nonphotic time cues (e.g., scheduled sleep and activity) may have some influence on circadian timing, but their potency, compared to the solar light/dark cycle, remains to be defined and appears to be relatively weak. Because people ordinarily sleep at night in a dark space with eyes closed, the sleep/wake schedule indirectly influences circadian rhythms. In fact, Burgess and Eastman[16] have recently shown that manipulations of sleep duration (*short nights* [6 h] or *long nights* [9 h]) can produce phase shifts, presumably by gating exposure to ambient light.

The effect of environmental time cues on the circadian system depends on the timing of their occurrence relative to the endogenous circadian cycle. For example, (in a normally entrained individual) light exposure in the morning around dawn resets the pacemaker to an earlier time, while light exposure in the evening around dusk resets the pacemaker to a later time. These time (phase) dependent effects of environmental cues on the circadian system can be plotted as a phase response curve (PRC).[17] The circadian system is most sensitive to light during the biological night, when humans normally sleep, and is least sensitive to light about midday recently (reviewed by Duffy and Wright).[18] Thus, in circadian rhythm biology, the timing of an intervention (for example, prescribed bright light exposure) can be as important (or more important) than the intensity (dose).

The interactions between the homeostatic and circadian mechanisms for sleep regulation are helpful in explaining much of the symptomatology of CRSDs. According to the opponent process model of sleep regulation,[19] the circadian system generates a

clock dependent alerting process during the waking hours. Consequently, attempting sleep at the "wrong circadian phase" (during the "circadian day") undermines sleep quality and shortens its duration because of the competing circadian arousal process. The shortened sleep duration may, in turn, lead to an accumulation of homeostatic sleep drive.

5.2 Assessment Strategies Based on Basic Circadian Science: Circadian Phase Markers

One of the important strategies useful in circadian science is to be able to know "what time it is in the brain": in other words, to determine, at various times, the phase of the circadian cycle. To that end, major efforts have been made to develop markers of circadian phase suitable for human investigation; for example, the phase and amplitude of the core body temperature (CBT) or the melatonin rhythm. These markers can be thought of as "the hands on the clock." Circadian phase markers are beginning to be used as assessment tools to detect circadian timing abnormalities clinically as the barriers of inconvenience and expense are being lowered. One can, in principle, employ any physiological variable that is modulated by SCN output, provided that the evoked influences on the rhythm (masking) are factored out. The sleep-wake cycle itself is a rough indicator of circadian phase, but it is strongly influenced by homeostatic sleep drive, as well as many other factors that obscure or "mask" the underlying circadian signal. Notwithstanding, it has been shown that wake up time provides a fair estimate of circadian phase in subjects who are allowed to sleep on a "free schedule," but entrained to a 24-h day.[20,21]

Historically, the core body temperature (CBT) rhythm has been used more extensively than any other circadian phase marker, but like sleep, the circadian signal from the CBT rhythm can be easily masked by activity, food intake, and sleep. Consequently, valid estimates of circadian phase derived from the CBT rhythm require that a subject be kept awake, at bed rest, and fed equally distributed small meals for at least 24 hours—the "constant routine protocol."[22] This technique has been useful for research, but seems unsuitable for clinical use. As an alternative to the constant routine, masking effects on CBT can be minimized by mathematical adjustments to the temperature rhythm,[23] but the magnitude of the adjustment varies according to circadian phase.[24]

The timing of melatonin secretion by the pineal gland has become an increasingly popular strategy for determining circadian phase. This technique has been facilitated by the availability of immunoassays that are sufficiently sensitive and specific so that concentrations of melatonin can be measured in plasma or saliva; or its metabolite, 6-sulphatoxy melatonin (aMT6s) in urine. The transition from low, daytime secretion to robust nocturnal secretion, the "melatonin onset" provides a high-resolution marker of circadian phase and is relatively convenient because serial sampling can be done in the evening, at least for subjects who are normally entrained;[25] however, the entire melatonin profile, or other points on it (e.g., midpoint of secretion) can also be used as phase markers. Melatonin secretion is suppressed by light exposure (a masking effect), so that samples need to be obtained under dim light conditions, and thus the procedure is often termed the *dim light melatonin onset* (DLMO). It has also been reported that posture[26,27] and drugs (such as beta-blockers, NSAIDS, and caffeine) may influence melatonin levels and thus may mask, to some degree, the melatonin rhythm. [28-31]

When both CBT (using constant routine conditions) and DLMO have been assessed concurrently as phase markers, the correlation is usually high.[32,33] For example, in a phase shifting study using bright light, Shanahan and Czeisler[33] found the correlation between the two phase markers to be 0.97 ($P < 0.0001$; $N = 23$). Klerman, et al.[34] measured circadian phase in a time-isolated environment in 13 subjects on three occasions, spaced five days apart, and found that the standard deviation, using CBT data, was 0.78 h; using cortisol data, 0.65 h; and using melatonin data, it ranged from 0.23 to 0.35 h (for the eight different analysis methods). In summary, melatonin was a much more stable phase marker than CBT. Benloucif et al.[35] also found melatonin to be a more stable phase marker than CBT, although the experimental conditions were not so rigidly controlled, and the CBT was estimated by mathematical de-masking, not a constant routine. These findings provide strong support for the melatonin profile as the most stable, and therefore presumably the most accurate, currently available marker for circadian phase. Because of its convenience, sensitivity, and validity, the DLMO appears to be on the threshold for clinical application. A consensus on the methodology of the procedure would facilitate its development as a clinical tool; for example, standardizing the minimum frequency of sampling, the lighting conditions required, and the definition of the "melatonin onset" for both plasma and saliva. Norms could then be developed.

Almost by definition, a circadian rhythm sleep disorder involves an abnormality in the timing of sleep relative to the optimal circadian phase for sleep. The relationship between the timing of sleep and the circadian phase (estimated by a circadian marker) can be quantified as the interval (*phase angle*) between the two rhythms. To date, only a few studies have attempted to measure phase angle abnormalities in CRSDs; for example, Uchiyama et al. found a delayed sleep propensity in DSPD patients relative to the phase of the circadian pacemaker as measured by the melatonin profile.[36]

5.3 Assessment Strategies Based on Behavioral Science

In addition to circadian biological science, circadian rhythm studies have utilized some behavioral assessment techniques, also used in other sleep disorders, but especially relevant to CRSDs.

5.3.1 Sleep Logs and Diaries

As mentioned above, sleep-wake diaries (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.

A recent large-scale clinical trial (described below)[37] used electronic diaries to assess sleepiness during the night shift (sleepiness, mistakes, unintentional and intentional sleep episodes, accidents, or near accidents), sleepiness during the commute home (unintentional sleep episodes, accidents, or near accidents) and sleep efficiency during the daytime following a night shift. Such diary techniques, if adapted for clinical practice, could help to document excessive sleepiness and clinical significance of the sleepiness reported by SWD patients.

Table 4—Aspects of Circadian Theory and the Correlation (r) between MEQ Score and Objective Phase Markers in Unaffected, Healthy Individuals

Aspect of Theory	Reference	Study Population	Study Type	Phase Marker	MEQ/Phase Circadian marker (r)
Simulated nightshift/ shift work	Baehr, 2000	172 adults (25.2 ± 5.3 yrs)	Other*	Tmin	-0.520
	Griefahn, 2002	34 males (22.3 ± 3.1 yrs)	Const. Rtn.	Tmin (main study)	-0.483
				DLMO (main study)	-0.686
	Martin, 1998	35 adults (26.3 ± 6.2 yrs)	Other	Tmin	-0.459
	Mitchel, 1997	32 adults (24.7 ± 4.6 yrs)	Other	Tmin	-0.650
Diurnal Preference/age	Duffy, 2002	13 adults (67.4 ± 3.2 yrs)	Const. Rtn.	Tmin (older adults)	-0.49
				Tmin (young adults, previously reported)	-0.76
Endogenous oscillator/ overt circadian rhythms	Griefahn, 2002	51 adults (21.8 ± 2.6 yrs)	Const. Rtn.	Tmin	-0.353
				DLMO	-0.607
	Martin, 2002	26 adults (18-38 yrs)	Other	DLMO	-0.48
	Roemer, 2003				
	Study 1:	34 men (22.2 ± 3.1 yrs)	Const. Rtn.	DLMO	-0.6818
		17 women (20.9 ± 1.1 yrs)	Const. Rtn.	DLMO	-0.5562
	Study 2:	57 adults (28.0 ± 10.3 yrs)	Other	DLMO	-0.3964
	Laberge, 2000	37 adolescents/adults (14-31 yrs)	Const. Rtn.	DLMO	-0.49
	Duffy, 2001	17 adults (23.5 ± 3 yrs)	Const. Rtn.	Tmin	-0.60

* Indicates a study design "Other" than Constant Routine

The Social Rhythms Metric (SRM), developed by Monk et al.[38] was designed to quantify daily social and occupational rhythms; in particular, gauging the regularity of everyday activities. The SRM has been used as a research tool to test hypotheses regarding the effect of social rhythmicity on sleep quantity and quality in affective disorders,[39,40] but we found no studies of its use in CRSDs.

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; therefore, we did not pursue our question of the utility of sleep logs and diaries further (except to mention examples of non-standard methods used in some studies).

5.3.2 Actigraphy

ICSD-2 diagnostic criteria for most CRSDs require that abnormalities in the timing of the habitual sleep pattern be documented with either sleep logs or actigraphy for seven days or more.[1] Actigraphy provides a reasonably accurate estimate of sleep and wakefulness that can be readily obtained over multiple sleep cycles and is thus very useful for the longitudinal assessment of sleep patterns. Indeed, the scientific literature addressing the role of actigraphy in the study of sleep and circadian rhythms was extensively reviewed by an AASM Task Force in 2003[41] with the subsequent development of Practice Parameters.[42] At that time, the Task Force concluded that:

> "The one area where actigraphy can be used for clinical diagnosis is in the evaluation of circadian rhythm disorders. Actigraphy has been shown to be very good for identifying rhythms. Results of actigraphic recordings correlate well with measurements of melatonin and of core body temperature rhythms. Activity records also show sleep disturbance when sleep is attempted at an unfavorable phase of the circadian cycle. Actigraphy, therefore, would be particularly good for aiding in the diagnosis of delayed or advanced sleep phase disorder, non-24-hour-sleep syndrome and in the evaluation of sleep disturbances in shift workers. It must be remembered, however, that overt rest-activity rhythms are susceptible to various masking effects, so they may not always show the underlying rhythm of the endogenous circadian pacemaker."

Updated Practice Parameters were recently developed (Morgenthaler et al., 2007), and provide further endorsement for actigraphy as a useful clinical tool in the evaluation and the assessment of treatment response in CRSDs.

Because actigraphy has been thoroughly addressed in two recent AASM reports, the task force did not systematically review actigraphy, and refers the reader to these published reports (Ancoli-Israel et al., 2003; Morgenthaler et al., 2007).

5.3.3 The "Morningness -Eveningness Questionnaire" (MEQ)

The MEQ, developed by Horne and Ostberg in 1976,[7] contains 19 questions aimed at determining when the respondent's natural propensity to be active lies during the daily temporal span. Most questions are framed in a preferential manner, in the sense that the respondent is asked to indicate when, for example, he/she would prefer to wake up or start sleep, rather than when he/she actually does. Questions are multiple choice, with each answer assigned a value from 0 to 6. Their sum gives a score ranging from 16 to 86, with lower values corresponding to evening types. More recently, another questionnaire—the Munich Chronotype Questionnaire—has been developed to assess morning and evening preferences[43,44]; that is, to separate putative "larks" from "owls."[45-48]

The MEQ has become a widely employed instrument to classify circadian tendencies in studies of normal (unaffected) subjects as well as (to some extent) patients. The MEQ score is often assumed to be correlated with core parameters of human circadian organization such as the timing of sleep[45,49,50] and possibly endogenous circadian period.[51] While mild to moderate preferences in morningness-eveningness may not have clinical significance, extremes of the spectrum may play a role in CRSDs and their associated functional and cognitive impairments.

Our search procedure provided a total of 28 studies using the MEQ as an assessment tool. Of these studies, 19 employed the MEQ in unaffected individuals (subjects without a CRSD diagnosis). The remaining nine studies used the MEQ in investigations involving CRSDs.

Of the 19 studies using the MEQ in unaffected individuals, 14 used the MEQ, in conjunction with an objective circadian phase marker (e.g., core body temperature, DLMO), in investigations of circadian adaptation to simulated nightshift/shift work,[52-54] age differences in diurnal preference,[55] and the impact of the endogenous circadian oscillator on overt circadian rhythms.[46,47,50-52,56-60] As predicted by circadian theory, all studies found a negative correlation between the MEQ score and the objective circadian phase marker; in other words, subjects with a later circadian phase generally scored lower on the MEQ (Table 4). However, Pearson's correlation coefficients (if available) covered a wide range ($r = -0.353$ to $r = -0.760$). While the wide range in correlation coefficients reported between different studies is likely a result of different study populations (e.g., young versus older adults) and different study conditions (e.g., lab versus naturalistic settings), overall, MEQ score appears to be a fair predictor of the endogenous circadian period or phase.Four studies in unaffected individuals used the MEQ with additional measures (e.g., actigraphy, sleep logs, questionnaires) to investigate circadian adaptation to simulated night shift work,[61] the effect of age on diurnal preference,[49,62] and the relevance of diurnal preference for specific sleep disturbances.[63] These studies showed the MEQ score to be correlated with: 1) the ability to adapt to night shift work,[61] 2) preferred time of exercise,[62] 3) age (increasing morningness),[49] and 4) characteristic sleep disturbances (e.g., difficulty in maintaining sleep in the early morning, morning sleepiness) relative to diurnal preference.[63] Studies using the MEQ in investigations involving specific CRSDs will be discussed later in this review.

5.4 Treatments for CRSDs Based on Circadian Rhythm Science

We next review the treatment strategies for CRSDs that have been developed based on circadian rhythm science. These interventions fall into three broad categories: 1) prescribed sleep scheduling, 2) circadian phase shifting ("resetting the clock"), and 3) medications that can promote sleep or wakefulness that are used to counteract the symptoms generated by the circadian misalignment and sleep deprivation associated with CRSDs.

5.4.1 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.[64] Devising an optimal schedule for shift workers, based on circadian principles, is another example of prescribed sleep scheduling. Planned napping has also been employed to counteract nighttime sleepiness in night shift workers.

5.4.2 Circadian Phase Shifting with Timed Light Exposure

It has been well established that the solar light-dark cycle is the primary environmental time cue for synchronizing the circadian system of most living organisms—plants, animals, and bacteria—to the 24-hour day. At one time it was thought that the human species, with more developed cognitive and social capacities, might be an exception. However, studies with bright light exposure demonstrated robust suppression of melatonin secretion[65] as well as phase resetting (shifting) effects on the human circadian system.[66,67] These discoveries gave rise to the proposed use of timed light exposure as a treatment for CRSDs. In addition, it was hypothesized that inappropriately timed exposure to natural and artificial light could underlie or exacerbate several CRSDs. In one manuscript, it was reported that light exposure to the skin behind the knee could phase shift the human circadian system,[68] but this finding has not been replicated.[69,70]

Light intensity or illumination levels are often reported in units of lux or watts. Lux is the International System unit of illumination based on the spectral characteristics of human visual photoreceptors, not circadian photoreceptors. One lux is equal to the light exposure received when gazing at a standard candle that is one meter away from the eye. Light intensity (lux) diminishes in proportion to the square of the distance from the source. Watts are the International System unit of power used to indicate the intensity of light in absolute energy units per meter squared.

Light of higher intensity generally produces larger effects on the circadian system. Although bright light exposure (3000-10,000 lux) has been shown to produce robust phase shifts, even modest intensities (50-600 lux) can produce substantial phase shifts if the light is presented to subjects who have been living in a dim light-dark environment.[71] Moreover, 3 cycles of exposure to just 12 lux for 6.5 h produced phase shifts.[18] In fact, the illuminance level reported to be sufficient to maintain synchronization of the human biological clock to the 24-hour day in these conditions [72] is less than one-thousandth of the intensity that was initially thought to be necessary.[73] Exposure history also appears to influence chronobiological responses to light.[74-76] Specifically, prior exposure to dim light appears to enhance subsequent melatonin suppression by light.

In general, light intensities of >1000 lux are needed to treat CRSDs, although under special circumstances low levels of light may be sufficient in resetting the circadian timekeeping system (see review by Duffy and Wright, 2005).[18] Conceivably, exposure to ordinary intensity artificial light at night may have a strong effect on the circadian system if an individual spends most of his/her time indoors.

Light exposure does not need to be continuous to influence the circadian system. In fact, alternating exposure to intermittent bright and dim light has been reported to produce almost as much phase shifting as continuous exposure.[77] This finding indicates that the phase resetting response to light is greatest in the beginning of the light exposure session, and this property of circadian photoreception may be able to be used to more easily implement light treatment.

In summary, there are a number of parameters of light exposure that are important for its phase-shifting effect: intensity, duration,

wavelength, pattern of exposure (continuous vs. intermittent), circadian phase of the light exposure, as well as light exposure history (reviewed by Duffy and Wright, 2005).[18] The precise contribution of each of these variables to the overall phase-shifting effect of light on the circadian timekeeping systems remains to be elucidated.

Questions have been raised about the safety of bright light exposure for humans, especially concerning the potential phototoxic effects on the lens and/or the retina. Some early experiments involved "full-spectrum" light sources that included UV spectra, but there is now a consensus that UV spectra are unnecessary for the phase shifting effect of light and should be avoided.[78] It has been argued that light sources used for treatment, are less intense than ordinary sunlight and therefore should be safe. However, the use of light treatment in patients using photosensitizing drugs or who have ongoing ocular or retinal pathology may be contraindicated.[79]

If the goal is to synchronize the circadian system to the desired (or required) sleep schedule, properly timed light exposure, in principle, should be a useful intervention for most of the CRSDs. Also, eliminating (or reducing) the unwanted effects of light on the circadian system, for example wearing goggles to prevent light-induced phase shifting, has been demonstrated in several simulated shift work studies to be effective.[80,81]

Buxton et al.[82] conducted an experiment to gather evidence for a darkness PRC. Except for the scheduled sleep/dark periods, subjects remained awake under constant routine conditions for 64 hours. Circadian phase was determined by serial sampling of melatonin and TSH, and sleep was monitored with PSG. Exposure to sleep and darkness in the morning (09:00–15:00) resulted in phase delays, whereas exposure in the evening (19:00–01:00) resulted in phase advances relative to controls. However, afternoon naps (14:00–20:00) did not affect circadian phase. In other words, not only is the timing of light exposure important, but it appears that the timing of darkness (and/or sleep) may be important as well.

One of the biggest drawbacks to timed light exposure (or light avoidance) is the associated inconvenience or expense. To overcome these problems, attempts have been made to integrate bright lights into the work environment or to develop light sources that can be worn like spectacles. Clinical trials of light therapy are discussed later in this report in relation to the specific CRSDs

5.4.3 Circadian Phase Shifting with Timed Melatonin Administration

Redman, Armstrong, and Ng[83] were the first to show that melatonin administration to animals could entrain free-running rhythms. Subsequently Lewy et al.[84] showed that melatonin could shift circadian rhythms in humans in a phase dependent manner. Investigations of the human PRC show that melatonin administration in the morning shifts rhythms later while melatonin administration in the evening shifts rhythms earlier. Thus, the melatonin PRC is about 180 degrees out of phase with the light PRC,[85] and therefore can be thought of, in a sense, as a "darkness signal." It is tempting to speculate that endogenous melatonin secretion at night has some role in the sleep promotion or circadian stability, but its function in humans (if any) remains to be clearly demonstrated.

A variety of doses of melatonin have been given to subjects for phase shifting, and the threshold for a chronobiological effect occurs at physiological blood levels (about or below 50 pg/mL). The dose-response curve for doses above 3 to 5 mg remains unclear. Recent studies suggest that timing is more important than dose. In fact, one study indicated that a high dose was less effective than a low dose to entrain the circadian system of a blind individual to the 24-h day, possibly because the high dose was active on both the advance and delay portions of the melatonin PRC.[86] The phase shifting potency of melatonin relative to light exposure when these two agents are promoting shifts in opposite directions has received little attention. In one study, the combination of evening melatonin (5 mg) and evening bright light (5,000 lux) resulted in no shift; apparently, the phase advance shift by melatonin and the phase delay shift of light canceled each other out.[87]

There may be some synergistic effect when light and melatonin are used to promote shifts in the same direction. Recently Revell et al.[88] demonstrated that a combination of a gradual advancement of the sleep schedule (wake time one hour earlier each morning) combined with bright light upon awakening and melatonin (0.5 or 5 mg) in the afternoon, induced a maximal phase advance while maintaining circadian alignment, suggesting a synergistic effect of the treatments.

In addition to its phase shifting effects, melatonin may have some direct soporific effects, especially at higher doses, and especially when administered during the usual wake period.[89] This effect could account for some of its benefit in the treatment of SWD and JLD.

Although melatonin has not been approved by the FDA as a drug, it is widely available in the United States as a nutritional supplement. Concerns have been raised about the purity of the available preparations, as well as the reliability of stated doses. However, no serious adverse reactions have been attributed to melatonin use to date. Generally available formulations (3 mg) produce blood levels that are "pharmacologic;" that is, typically peaking at a 10-fold higher concentration than physiological blood levels. Formulations that have a GLP (good laboratory practice) stamp can be considered to be the most reliable.

Recently, a specific melatonin receptor agonist, ramelteon, has been licensed as a hypnotic in the United States. Animal studies suggest that it has phase shifting effects that are analogous to melatonin,[90] but no studies have been reported in humans.

Clinical trials of melatonin administration are discussed later in this report in relation to the specific CRSDs

5.4.4 Other Phase-Shifting Treatments

Physical activity has been reported to phase shift the circadian clock in animals.[91] Timed vigorous exercise has also been tested for its phase shifting effects in humans; the available data suggest that nocturnal exercise prior to the body temperature minimum can induce circadian phase delay shifts[92-94] and that timed exercise in the evening can induce circadian phase advance shifts.[93] In addition, a combination of morning and afternoon exercise has been reported to advance the circadian clock when subjects were exposed to a shorter than 24-hour day.[95]

Early studies using daily vitamin B12 administration as a treatment for CRSDs were promising,[96,97] suggesting that it had a chronobiologic effect; but a review of clinical response in a larger cohort of patients with a mixture of CRSD diagnoses[98] indicated only modest benefit that may have been due to a placebo effect. A double-blind, placebo-controlled, multicenter clinical trial of vitamin B12 for DSPD[99] found no difference from placebo.

5.4.5 Symptomatic Treatment: Counteracting Insomnia

In CRSDs, there is a mismatch so that the circadian alerting signal occurs during the desired (or required) time for sleep, thereby generating insomnia, usually manifest as foreshortened sleep. Hypnotic drugs have been tested to counteract unwelcome clock-dependent alerting in patients with CRSDs, and examples will be addressed in regard to specific disorders.

5.4.6 Symptomatic Treatment: Counteracting Excessive Sleepiness

The symptom of excessive sleepiness in CRSDs can be explained in two ways: 1) If circadian misalignment persists, foreshortened or inefficient sleep causes a build up of homeostatic sleep drive. 2) Because of the circadian mismatch, clock dependent alerting does not occur when the person is awake. Sleepiness can be counteracted with stimulant medications, and this strategy will be discussed later in this review in regard to specific disorders.

In the remainder of this report, we turn to the applications derived from circadian and behavioral science, described above, to address our list of questions regarding two of the specific CRSDs; shift work disorder (SWD) and jet lag disorder (JLD). As indicated above, a subsequent report will address the remaining CSRDs (DSPD, ASPD, FRD, and ISWR).

6.0 SHIFT WORK DISORDER

6.1 Diagnostic issues

Shift work is a term that applies to a broad spectrum of nonstandard work schedules ranging from occasional on-call overnight duty, to rotating schedules, to steady, permanent night work. It can also apply to schedules demanding an early awakening from nocturnal sleep. The heterogeneity of work schedules makes it very difficult to generalize about shift work. Shift work is very common; in fact, about one in five workers in the United States do some form of shift work, women more than men.[100]

The diagnosis of *Shift Work Disorder* (SWD) presumably applies to a subset of shift workers who meet ICSD-2 diagnostic criteria, but the boundary between a "normal response" to the rigors of night work, and a diagnosable disorder is not sharp; consequently the prevalence of the disorder is unclear. As mentioned above, Drake, et al (level 3),[3] using questionnaire data from an epidemiologic survey, found that 32.1% of night workers and 26.1% of rotating workers met the minimal criteria for SWD; however, the methodology has significant limitations. In our literature search, we found that a formal diagnosis of SWD was rarely used to describe subjects in shift work research studies.

It is likely that people are intolerant of shift work for a variety of reasons, and that the diagnosis is applicable to a large and heterogeneous population. In addition to circadian arousal processes, attempted sleep at unusual times can be interrupted by noise, social obligations, and other factors. Finally, there is an inevitable degree of sleep deprivation associated with sudden transitions in sleep schedule. For example, a night worker who stays awake for 24 hours on the first night of a tour of duty is acutely sleep deprived in the morning. In some patients with a CRSD, it may be appropriate to make a dual diagnosis, including Behaviorally Induced Insufficient Sleep Syndrome.

Conclusion: The formal diagnosis of SWD has rarely been used in research studies. The validity and reproducibility of the AASM diagnostic criteria need testing. The boundary between a normal and a pathological response to the circadian stress of the unnatural sleep schedule associated with shift work remains unclear.

6.2 Risk Factors

6.2.1 Age

It has frequently been suggested that shift work becomes more difficult with aging. This hypothesis has been addressed in several ways. Harma, et al (level 4)[101] initially found no effect of age on CBT phase-shifting or nighttime sleepiness, but in a later study, found that, after three nights, older workers showed less circadian adaptation and were more sleepy (level 2).[102] More recently, Monk et al (level 2),[103] in a laboratory study, found that older subjects (67–87 years old) phase-shifted more readily in a delay direction than in an advance direction; in this regard, older subjects were similar to younger subjects.

In one large survey, done by the French government, age was associated with a higher frequency of sleep disturbances and hypnotic use which peaked at 52 years (level 4),[104] suggesting a "selection effect" (intolerant workers quit their jobs), and then decreased at 62 years (level 2),[105] suggesting a "retirement effect;" in other words, senior workers who were intolerant left the work force. A survey of police officers (N=286) supported the suggestion that older shift workers had more difficulty with sleep quality and on-duty sleepiness, however many of the measures failed to reach statistical significance (level 4).[106]

Conclusion: More data are needed, but the current evidence indicates that advancing age is a risk factor for shift work intolerance.

6.2.2 Gender

Female night workers tend to sleep less than men, possibly because of social obligations that increase their vulnerability to SWD. Using questionnaires and self-reports, Oginska et al (level 3)[107] found that female crane operators got less sleep, and were more likely to be drowsy on the job than males. A recent epidemiologic study on the prevalence of SWD did not break down the data by gender (level 3).[3]

Conclusion: There may be a tendency for female workers to get less sleep and to be more drowsy on the job that males, but the evidence is weak (one level 3 study).

6.2.3 Timed Light Exposure

Eastman et al.[81] initially suggested that night workers rarely shift their circadian rhythms to match their daytime sleep schedule because of continued exposure to the solar light dark cycle. Subsequently, they showed, in shift work simulation studies, that wearing dark goggles during the morning commute improves adaptation (level 2).[108]

Five field studies have examined the impact of natural light on circadian adaptation in night workers. Dumont et al (level 3)[109] monitored 24-hour light exposure with ambulatory wrist monitors for 3 consecutive nights in 30 permanent night workers and assessed the degree of adaptation by measuring urinary aMT6s

every two hours as a phase marker. They found a strong association between sleeping in a darker bedroom during the day and circadian adaptation.

Using a photometer mounted on spectacles, Koller, et al. (level 3)[110] showed that successful permanent night workers avoided bright light on their days off. In a subsequent study (level 3),[111] this group (using a similar technique) showed an inverse correlation between morning light exposure and adaptive phase shifting.

In a study exploring sunlight exposure related to seasonality, offshore oil drill crews were found to adapt less well to night work in March than in November, presumably because of greater morning light exposure in the spring (level 3).[112] Night workers living in the sunless Antarctic winter had difficulty returning to a conventional day-active schedule (level 4).[113,114]

Conclusion: Shift work simulation studies (level 2) and a few field studies (level 3) indicate that daylight (or bright light) exposure in the early morning can inhibit adaptative circadian phase resetting. In the simulation studies, the inhibition of phase resetting was successfully countered by wearing dark goggles.

6.2.4 Familial (Genetic) Predisposition

We found no studies relevant to this question.

6.3 Assessment Tools

6.3.1 Sleep Logs and Diaries.

To reiterate, sleep-wake diaries (sleep logs) have face validity for the evaluation of the timing, quantity, and quality of sleep, and their clinical utility for the evaluation of suspected SWD seems clear.

6.3.2 The Morningness-Eveningness Questionnaire(MEQ)

According to the diagnostic manual,[1] individuals described as morning types are thought to obtain shorter daytime sleep after a night shift than those described as evening types. As such, MEQ score might have predictive value in assessing adaptability to shift work. The current literature search found five reports (two level 2)[115,116] and three level 3[61,117,118] that used the MEQ in studies of night shift work. Four of these studies evaluated the phase-shifting effect of judicious light and darkness exposure, and its value in adapting to night shift work. Of the four studies, however, only one assessed the MEQ score in relation to predicting adaptability to shift work; that is, Stewart et al. (level 3)[117] reported the MEQ score to have little predictive power.

A fifth study (level 3),[61] investigated the influence of morningness-eveningness as determined by the MEQ on sleepiness during simulated night shifts. MSLT data analysis revealed the morning-tendency (MT) group to have significantly shorter sleep latencies between 00:30 and 04:30 hours ($P < 0.05$) and to rate themselves as significantly sleepier on the Stanford Sleepiness Scale than the non-morning-tendency (non-MT) group.

Conclusion: One level 3 study suggests that morning types may be significantly sleepier than evening-types during night shift work. However, the validity and reliability of the MEQ score in predicting adaptability to night shift work requires further research.

6.3.3 Actigraphy

Conclusion: Actigraphy is a useful adjunct for the evaluation of shiftworker sleep-wake patterns. Refer to the recent AASM Standards of Practice.[42]

6.3.4 Polysomnography

In the research literature, PSGs have been primarily used to assess the effectiveness of such interventions as hypnotic medications for daytime sleep, or alerting medications for nighttime alertness (see treatment section to follow). In principle, MSLT or maintenance of wakefulness tests (MWTs) might be useful in documenting shift work intolerance, but no field studies have been done to test this hypothesis.

Conclusion: No studies have determined the specific utility of PSG in assessing SWD. It appears that the primary value of PSG is to rule out other sleep disorders.

6.3.5 Phase Markers

The diagnostic criteria for SWD stipulate that patients manifest circadian and sleep time misalignment. The prevailing belief has been that most night shift workers do not shift their endogenous rhythms to match their required sleep schedule. However, some field studies, using standard circadian phase makers, have documented phase resetting without treatment, at least in some people (level 2),[109,111,119,120] so not all shift workers suffer circadian misalignment. Furthermore, it has been suggested that there are individual differences in tolerance to circadian misalignment, termed *phase tolerance* (level 2);[121] thus, some individuals may be relatively asymptomatic even though their underlying rhythms are not appropriately synchronized with sleep.

6.3.5.1 Core Body Temperature Rhythm

Core temperature monitoring employing a mathematical algorithm for de-masking has been used to assess phase shifts in simulated shift work studies,[23,46,81,122,123] but this technique is difficult to carry out in the field.

6.3.5.2 Melatonin Rhythm

There are a few field studies in which the melatonin rhythm was used to assess phase in actual night workers. Roden et al. (level 3)[124] found that night workers with a high degree of work satisfaction did not usually lose the diurnal orientation of their melatonin rhythms, indicating that factors other than reorientation of the circadian system may be important for high tolerance to shift work. Similarly, a study that measured aMT6s in urine collected every 2 hours for 24 hours to determine circadian phase in 15 night workers, unexpectedly found no correlation of phase with sleep quality (level 3).[125] In another study of hospital night workers, the DLMO was used to assess the degree of phase resetting after seven nights of work and after seven days off (level 2).[126] After the week off, on a conventional schedule, the DLMO was in the typical phase, but after the week of night work, the phase ranged from no shift to complete adaptation. In a study of light treatment, salivary melatonin was successfully employed to document the phase shifting effects of timed light exposure (level 3).[118]

Conclusion: The limited research employing circadian phase markers has shown that night workers are quite variable in their circadian adaptation. If the DLMO were to become an available clinical tool, the degree of circadian adaptation could be objectively assessed in individual patients and phase shifting treatments (if indicated) could be evaluated for their effectiveness. On the other hand, some studies have found a lack of correlation between circadian phase alignment and other measures of adaptation to shift work (such as self-reports of sleep and overall satisfaction with employment), suggesting that, in addition to phase incongruence, other variables may be important to the disorder of SWD.

6.4 Treatment

6.4.1 Prescribed Sleep/Wake Scheduling

There has been considerable interest in the possibility that certain work schedules are more conducive to circadian adaptation than others; for example, Czeisler et al.[127] found that a clockwise rotation, rather than counterclockwise rotation, was favored by workers, consistent with the understanding that delaying sleep times should be easier than advancing. Another proposed shift work schedule involves gradual phase shifts that are consistent with the principle that the circadian pacemaker can only be reset an hour or two per day.[128] On the other hand, some experts have argued that a rapidly rotating schedule is more rational since it minimizes the time spent in a desynchronized state,[129] while others could argue for longer runs (more consecutive days) of shift work that provide an opportunity to achieve a degree of synchronization. Another issue in shift work scheduling is the length of the shift. Extended duty shifts (10-12 h) have become more popular because they maximize time off from work. As shift work scheduling is a highly specialized occupational consulting activity, and includes questions of safety and productivity, it is usually beyond the scope of clinical practice, and we did not formally review the scientific literature on this topic.

Planned napping is another form of prescribed sleep/wake scheduling, and more likely to be utilized as a clinical intervention. In a shift work laboratory simulation study (using experienced shift workers), Sallinen et al. (level 2)[130] compared four naps strategies (50 or 30 minutes at 01:00 or 04:00) to no naps (the control condition). Napping resulted in improved reaction times in the second half of the night. The early naps produced increased alertness (assessed by PSG sleep latency).

In an uncontrolled trial, planned napping for up to one hour was shown to counteract sleepiness on the job, and did not undermine the main sleep bout (level 4).[131] In a retrospective survey of police officers, napping before night shift duty was associated with fewer accidents (level 3).[132] Purnell et al. (level 2)[133] showed that a 20-minute nap at 03:00 resulted in improved performance, with no significant sleep inertia and no effect on daytime sleep. In both a laboratory and field study, Schweitzer et al. (level 1)[134] showed that napping before the night shift, especially when combined with caffeine, improved alertness as assessed with MSLT and psychomotor vigilance testing.

Conclusion: The evidence for planned napping before, or on the job, to counteract shift work sleepiness is limited but consistent in demonstrating an increase in alertness on the job.

6.4.2 Circadian Phase Shifting

Assuming that the primary pathophysiology of SWD relates to circadian misalignment, it follows that corrective phase shifting is a rational treatment, with the caveat that some workers would prefer to align their rhythms to their *days off* rather than to their work schedule. Most studies of phase shifting have involved shift work simulations; field trials are much less common.

6.4.2.1 Timed Light Exposure

There is a sizable literature investigating the effects of bright light exposure on recruited research subjects who simulate a night shift sleep-wake schedule (level 2)[54,80,108,121,123,135-137], (level 3).[53] In some studies, the effect of restricting light exposure in the morning was also investigated (level 2).[80,81] These studies provide compelling evidence that, in a controlled setting, appropriately timed bright light treatment (or avoidance) can shift circadian rhythms as predicted from a light PRC.

Altering the timing of sleep can also shift rhythms, possibly by altering the exposure to light. For example, Santhi, et al.(level 3)[138] showed in a simulation study that a pre-nightshift sleep episode (14:00-22:00) advanced circadian phase (DLMO) by nearly an hour while post-night shift sleep episode (08:00-14:00) delayed circadian phase.

Because of the limitations of space, simulation studies are not reviewed in detail, but are listed in the posted evidence table. Simulation studies provide important principles that can underlie rational treatment; but in order to confine our evidence review to clinical data, we focused our review on six field studies that involved actual shift workers.

Using a within-subject design, Costa et al.[139] (Level 3) exposed 15 night duty nurses, working on a fast-rotating schedule, to bright light (2350 lux) for four 20-minute periods throughout their shift, for the two days they were on night duty. There was substantial subjective improvement in self-ratings and in psychomotor performance tests, but no shift in the rhythms of cortisol, CBT, or aMT6s.

In the study by Budnick et al.(level 3),[140] 13 rotating shift workers were exposed for three months of bright light (6000 to 12,000 lux) on the job for at least 50% of their shift. Compared to ordinary light, circadian phase resetting and subjective improvements in work time alertness were reported with bright light treatment, but the effects on sleep were mixed.

In a small but controlled study, Stewart et al. (level 3)[117] exposed eight night workers to bright light (8800-10,670 lux) during the first half of their shift. Compared to the eight control subjects, self-reported daytime sleep was improved, as were other subjective measures, but no objective assessments of sleep or circadian phase were performed.

In the study conducted by Boivin et al. (level 3),[118] nine nurses were instructed to remain under a bright light (2500 lux), as much as their shift allowed, for the 12 consecutive nights they were on duty. They were also given goggles to wear during the morning commute, and they were instructed to attempt sleep and remain in absolute darkness for eight hours after they got home. Nine untreated nurses served as controls. The treatment produced a robust shift in phase markers (CBT, salivary melatonin), but the effects on sleep and alertness were not reported.

Using a repeated measures, crossover design Yoon et al. (level 2)[141] administered three different light treatments to 12 night nurses for four consecutive nights: 1) room light (control), 2) bright light (4000-6000 lux from 01:00 to 05:00), and 3) bright light with sunglasses for the morning commute. Self-rated alertness and performance were most improved with the third (combined) treatment.

Using a crossover design (level 3), Lowden et al.[142] exposed 18 factory production workers to bright light (2500 lux) for 20 minutes (during their break) for four weeks, mostly between 03:00 and 04:00. Self-reported alertness and mood were significantly improved. Baseline salivary melatonin concentrations correlated with sleepiness, and bright light suppressed melatonin secretion.

Night workers at an oil platform in the North Sea were treated with bright light for 30 minutes per exposure during the first four nights of their 14-day work period (applied to promote a phase delay) and then for the first four days after returning home. Subjective adaptation to night work was moderately improved with bright light, however, the adaption was more pronounced during the re-adaption to home phase (level 4).[143]

Conclusion: It is difficult to devise a credible placebo control for light treatment studies, and no placebo-controlled trials of light therapy of shift workers have been conducted. The intensity and timing of the light exposure in field studies has been quite variable. All of the studies involved relatively few subjects. The limitations of these studies illustrate some of the difficulties incorporating bright light treatment into the workplace. Nevertheless, bright light treatment has clearly been shown, in simulated shift work studies, to promote phase shifting and circadian realignment. If bright light can be accommodated in the work environment, and if it is timed appropriately, the evidence indicates that it could be an effective treatment.

6.4.2.2 Timed Melatonin Administration

We found two shift work simulation studies that were relevant. Using a crossover design Sharkey et al. (level 1)[144] treated 21 normal subjects with melatonin (1.8 mg, controlled-release) prior to daytime sleep after two nights of simulated shift work. Melatonin improved daytime sleep only on the first daytime sleep, but did not improve alertness at night. In a randomized, placebo-controlled, cross-over design, Sharkey and Eastman (level 1)[116] treated 32 subjects with melatonin (0.5 mg or 3.0 mg) or placebo prior to sleep in the afternoons/evenings (a 7-h advance of the sleep schedule) for seven days of simulated night work, and circadian phase was assessed by DLMO and CBT. Melatonin treatment produced a significantly enhanced phase advance.

We found four level 2 studies and one level 3 study conducted in the field using melatonin prior to day sleep in night workers; none of the subjects were formally diagnosed with SWD.[126,145-148]

In the earliest study, using a randomized crossover design Folkard el al. (level 3)[145] treated 17 police officers on a rotating schedule with melatonin (5 mg) prior to day sleep for six days (although only seven subjects completed the placebo arm). Melatonin treatment produced an increase in self-rated sleep quality and duration. It was unclear whether this was a direct hypnotic effect or a phase shifting effect.

In a randomized, crossover study, James et al. (level 2)[147] treated 22 paramedics with melatonin (6 mg) or placebo prior to daysleep for 4 to 6 days, on four occasions (two blocks of each treatment). There were no differences between melatonin and placebo treatment in self-ratings of sleep and alertness.

In a randomized, crossover study Jorgensen and Witting (level 2)[146] treated 18 emergency room physicians with melatonin (10 mg, sublingual) or placebo prior to day sleep for two to five nights. There were no significant differences between melatonin and placebo on measures of sleep or nighttime alertness.

Using a repeated measures crossover design, Yoon et al. (level 2)[148] treated 12 night shift nurses for two days prior to daytime sleep with melatonin (6 mg), melatonin (6 mg) combined with morning light avoidance, or placebo. Melatonin, either alone, or in combination with light avoidance, resulted in a significant increase in total sleep time (TST) as estimated from sleep logs. Morning light avoidance did not enhance the effect.

In a randomized, crossover study Sack et al.(level 1)[126] treated 24 nurses working seven consecutive 10-h night shifts alternating with seven days off, with melatonin (0.5 mg) taken prior to sleep in all conditions. Circadian phase (DLMO) was measured at the end of each week. Although nine of the subjects inverted their DLMO almost completely on placebo, and eight failed to shift on either treatment, there was a subgroup of seven subjects who shifted with melatonin treatment but not placebo.

Conclusion: The evidence of benefit for melatonin administration prior to daytime sleep is mixed. The variability in shift schedules, as well as melatonin dosage and timing, makes it is difficult to draw firm conclusions. There are good theoretical reasons why melatonin (or melatonin agonists) might benefit daytime sleep in night workers, and more research is needed. Observed improvement in day sleep may be related to a hypnotic effect as well as a phase shifting effect.

6.4.2.3 Promoting Sleep with Hypnotic Medication

We found three night work simulation studies that used hypnotics to promote daytime sleep and potentially night (waketime) alertness.[149-151] Both studies by Walsh et al. (level 1)[149,151] employed a crossover design to test triazolam 0.5 mg[149] and 0.25 mg[151] vs. placebo prior to daytime sleep after five days of simulated night work. Although the duration and quality of daytime sleep improved with triazolam, there was no significant improvement in alertness (assessed by MSLT) during the night. The 0.5 mg dose was higher than the currently prescribed standard.

In another simulation study, Porcu et al. (level 2)[150] treated eight subjects with temazepam (20 mg) for a single day sleep (14:30 to 22:00) that was followed by a night of testing, including MSLTs and MWTs. Treatment, compared with the control, lengthened sleep by about two hours. Although the night MSLT was not affected by treatment, the MWT improved, suggesting that the two dimensions of sleepiness are differentially affected by treatment.

We found just two field studies involving hypnotics given to improve daytime sleep in night workers. In a well-designed randomized, double-blind, placebo-controlled trial Monchesky et al. (level 1)[152] treated 25 assembly line workers with zopiclone 7.5 mg at bedtime and 25 control subjects with placebo for 13 days. Self-rated sleep quality and duration were significantly improved by hypnotic treatment.

Using a crossover design, Moon et al. (level 2)[153] treated 12 air force radar personnel on a rotating two-night, two-day work schedule with zopiclone (7.5 mg) or placebo for two cycles. Self-

rated sleep was improved without any apparent impairment of psychomotor performance while awake.

A small (N = 15) non-blind study tested triazolam 0.25 mg in night workers complaining of disturbed sleep (level 3)[154] and found improvement in self-rated sleep and quality of life.

Conclusion: Night shift simulation studies have consistently demonstrated that hypnotics increase daytime sleep; however, some studies raise doubts that treatment improves nighttime alertness. There are only two double-blind field studies, and both employed a hypnotic drug (zopiclone) that is not available in the United States; also, they did not employ objective outcome measures of sleep. Even though field trials for shift work related insomnia are scarce, the abundant clinical trials carried out for other types of insomnia are probably relevant to shift work-related insomnia. However, hypnotic treatment for daytime sleep in night shift workers raises some distinctive issues regarding nighttime performance and safety. Given the array of currently available hypnotic drugs, with varying pharmacokinetic profiles, additional studies are needed.

6.4.2.4 Promoting Alertness with Stimulant Medication

In a double-blind, crossover, placebo-controlled trial Hart et al. (level 2)[155] assessed the effects of the stimulant methamphetamine (10 mg) given prior to night duty, and zolpidem (10 mg) prior to daytime sleep—as well as a combination of the two treatments—on performance, mood, and sleep, in eight healthy normal adults undergoing a simulated, rotating shift schedule across 21 days in a residential lab context. They concluded that methamphetamine reversed most of the adverse consequences of night work, but that zolpidem alone, or the combination, had mixed effects.

In a double-blind, parallel group design study (level 1), Walsh et al.[156] tested modafinil (200 mg) vs. placebo given an hour prior to four consecutive simulated night shifts. Modafinil significantly improved alertness (assessed by MWT) and psychomotor performance.

In the largest double-blind, placebo-controlled shift work field study to date, Czeisler et al. (level 1)[37] tested modafinil as a treatment to counteract excessive sleepiness during night work. A total of 209 subjects diagnosed with SWD were randomized to either modafinil 200 mg (N = 96) or placebo (N= 108) administered at the start of each shift. At baseline, and then on three occasions one month apart (after three or more nights of work), the subjects reported to a laboratory setting for a night of simulated shift work involving laboratory testing. Outcome measures included MSLTs, clinical symptom ratings, and simple reaction time performance testing. Modafinil produced a modest but highly significant lengthening of MSLT assessed sleep latency (1.7 ± 0.4 vs. 0.3 ± 0.3 minutes; P = 0.002), indicating decreased sleepiness. Self-rated symptom improvement occurred in 74 % of those treated vs. 36 % on placebo. There were concomitant improvements in performance measures.

It is notable that in this study, both treated and untreated patients manifested sleepiness during the night shift that was comparable to patients with a primary sleep disorder (e.g., narcolepsy); although modafinil counteracted the sleepiness, it did not restore alertness to daytime levels. It is unknown whether a higher dose would have produced a more robust effect.

In a number of studies (see evidence table), caffeine has been shown to be an effective countermeasure for sleepiness during experimentally induced sleep deprivation.[157-164] Although acute sleep deprivation can be an aspect of SWD, these studies were not primarily focused on shift work and were not abstracted nor graded.

We found just one field trial of caffeine given alone (4 mg/kg 30 minutes prior to the night shift), and in combination with napping (level 1).[134] Caffeine was shown to counteract nighttime sleepiness, but the combination was shown to be more effective.

Conclusion: There is compelling evidence that modafinil can improve nighttime alertness in shift workers (and has received FDA approval for that indication). Caffeine is not considered a drug, but has been demonstrated to improve alertness in simulation studies and in one well-controlled field study. One study found that methamphetamine improved alertness, but this drug has serious abuse potential.

7.0 JET LAG DISORDER

7.1 Diagnostic Issues

The symptoms of jet lag disorder (JLD) are generated by circadian misalignment, the inevitable consequence of crossing time zones too rapidly for the circadian system to keep pace. Depending on the number and direction of time zones crossed, it may take days for the circadian system to resynchronize. The intensity and duration of the disorder are related to: 1) the number of time zones crossed, 2) the direction of travel, 3) the ability to sleep while traveling, 4) the availability and intensity of local circadian time cues, and 5) individual differences in phase tolerance. Jet lag is usually benign and self-limited, but can occasionally have serious consequences (an aircraft pilot error or misjudged business negotiation). Also, travel time is precious, and therefore treatment, if safe and effective, is justified.

7.2 Risk Factors

7.2.1 Age

While there are no large systematic studies addressing the role of age as a potential risk factor for the development of jet lag, there are some data to suggest that older individuals may be less prone to experiencing the symptoms of jet lag. In a case series of 85 athletes, academics, and coaches traveling eastward across 10 time zones, multiple regression analysis revealed that older subjects experienced fewer jet lag symptoms than younger subjects, though the effect was quite modest (1 unit less on a 10 unit scale) (level 4).[165] However, this is consistent with data from a smaller study of 33 pilots crossing 7 to 8 time zones (both eastward and westward) that found that those over the age of 50 experienced lower levels of anxiety and tiredness following travel than the pilots younger than 50 years old (level 2).[166] In contrast to these field study findings, a small simulation study of 14 men found that those in a "middle-aged" group (ages 37-52 years old, n = 8) did not tolerate a six-hour time advance as well as those in the "young" group (ages 18-25 years old, n = 6) (level 4).[167] In particular, the middle-aged group had more fragmented sleep (as measured by PSG) and reported feeling less alert following the shift than the younger group. Interestingly, while the middle-aged individuals had larger swings in other mood parameters with the time shift, they were, on average, less "weary," happier, and reported a greater sense of well

being than the younger group. Some of the seemingly different findings from these studies may be, explained in part, by the differences in the age groups studied as well as the issues surrounding field vs. simulation methods.

Conclusion: Limited available data suggests that older individuals may experience fewer jet lag symptoms compared to younger individuals. However, the quality of the data is rather poor and further research is needed to better define the relationship between age and the development of JLD.

7.2.2 Gender

Gender as a potential risk factor for the development of JLD has not been adequately studied and no firm conclusions can be drawn. Many studies have included only male subjects, and only one case series has sought to analyze gender as a risk factor. Using multiple regression analysis, males were found to go to sleep later and experience less subjective fatigue in the first two days after arrival following a flight across 10 time zones in an eastward direction (n = 85, males = 54) (level 4).[165]

Conclusion: The data are insufficient to allow any conclusions regarding gender as a risk factor for JLD.

7.2.3. Light Exposure

It might be more difficult to adapt to local time in the short days of winter when less ambient light is available to resynchronize the internal clock. However, no studies have been conducted to address this specifically. Utilizing variable light intensities for 3.5 hours in the morning of the 3 days preceding prospective eastward travel, one simulation study found slower phase advances and more jet lag symptoms in those exposed to dim light versus continuous bright light (level 2).[168] This study will be further discussed in the section on light therapy as a treatment of jet lag.

Exposure to the local light-dark cycle usually accelerates adaptation after jet travel between 2 to 10 time zones. However, as Daan and Lewy have pointed out exposure to morning light after an eastward flight of more than eight time zones could retard adaptation to local time because it would be "hitting" the wrong area of the light PRC. Likewise, late evening light following a westward flight could retard adaptation for the same reason. Although this suggestion is congruent with current circadian models, the supporting data are very limited.

Conclusion: Light exposure as a risk factor for the development of JLD has been inadequately studied and thus no conclusions can be drawn.

7.2.4 Familial (Genetic) Predisposition

We found no studies bearing on this question.

7.2.5 Miscellaneous Risk Factors

Numerous potential risk factors for the development of jet lag have been mentioned in the literature, though most have not been studied in any type of controlled fashion. Some of these factors include: sleep deprivation preceding travel, air pressure and quality, excessive caffeine intake, excessive alcohol use, and the time of destination arrival. While most of these factors have theoretic underpinnings for why they might promote jet lag, only the time of destination arrival has been evaluated, and this is only in a case series. Following eastward travel across 10 time zones, midday arrivals experienced fewer jet lag symptoms than morning arrivals in a case series of 85 subjects (level 4).[165] This could be related to the timing of light exposure at the destination, as theorized by Daan and Lewy.[169] Further work would be required to clarify this as well as the risk posed by the other factors mentioned.

Conclusion: A number of additional risk factors for the development of JLD have been proposed, though data are lacking to support any conclusions.

7.3 Assessment Tools

7.3.1 Questionnaires

In a simulation study of eastward traveling subjects, continuous morning bright light exposure in the days preceding travel advanced the circadian rhythm and reduced jet lag symptoms more effectively than dim light (level 2).[168] In this study, there were no significant differences among the subjects for the different light groups in MEQ score (average was 52.1 ± 8.5) at baseline. Potentially, knowledge of the MEQ score could be used as a convenient means of assessing the endogenous circadian phase and thus the optimum time for bright light exposure (pre- or post-flight) to reduce jet lag symptoms. However, the current search criteria did not find any such studies evaluating the use of the questionnaire in this manner. In addition, no other questionnaires have been tested at present as tools to risk stratify individuals for the development of jet lag symptoms.

The diagnostic criteria for jet lag as established by the ICSD-2 rely on subjective complaints in the appropriate setting. In research studies, a variety of questionnaires have been utilized to assess for the presence and severity of jet lag. Only one of these, the Columbian Jet Lag Scale, has been validated (level 1).[170] This questionnaire rates 9 symptoms associated with jet lag, each on a four-point scale, and has a high internal consistency (Cronbach's alpha = 0.78-0.94). However, given the transient nature of jet lag, routine use of questionnaires to establish the diagnosis has not been actively pursued in the clinical arena.

Conclusion: No study has examined the utility of the MEQ in assessing risk for the development of JLD. The Columbian Jet Lag Scale has been validated as a tool for measuring the symptoms of JLD in a standardized fashion, though likely has no role outside the research setting.

7.3.2 Actigraphy

Actigraphy has been utilized in numerous jet lag studies as part of the assessment of rest-activity. Only one study attempted to validate this as an adequate tool for assessing jet lag-related changes in the rest-activity cycle (level 1).[171] In this study, actigraphically measured rest-activity shifts correlated well with the number of time zones traversed in both eastward (approximately 34 minutes for every time zone crossed) and westward (approximately 1 hour for every time zone crossed). Unfortunately, these findings were not correlated with other measures of circadian rhythms or sleep, and thus further validation in the setting of jet lag is still needed.

Conclusion: Actigraphy appears to have face validity for assessing rest-activity patterns in the setting of JLD, though corre-

lation with circadian markers has not been demonstrated. Its role in the evaluation and management of JLD in clinical practice has not been established.

7.3.3 Polysomnography

PSGs have been performed as part of the treatment response assessment for jet jag, though primarily in the laboratory setting of simulated jet lag (level 2).[172,173] Only one study to date utilized PSG as well as a limited sleep latency test (2 nap opportunities) to assess sleep and sleepiness in a field study of 27 subjects undergoing a 7-hour eastward flight (level 2).[174] Compared to a baseline night of PSG recording, subjects in the placebo arm of this study (n = 9) had no change in their total nocturnal sleep time or sleep efficiency during the 9 nights following the trip. However, prolongation of the sleep latency was noticed by night 4 during recovery and persisted through night 8. Increased slow wave sleep and decreased REM sleep time were seen on the first night post-travel, but these changes normalized on subsequent nights. The limited sleep latency testing in the placebo group suggested significant daytime sleepiness with sleep latencies always <10 minutes during 10 days of recovery testing. These findings, coupled with the logistical practicality of PSG field testing, limit this tool to research endeavors only.

Conclusion: The transient nature of JLD coupled with the impracticality of performing portable PSGs limit this tool to the research setting only.

7.3.4 Phase Markers

A number of circadian phase markers have been utilized in the study of jet lag, mostly in terms of phase response to treatments. Circadian phase markers that have been studied include both skin temperature (level 2)[175], CBT readings (level 2);[176-178] salivary melatonin (level 2),[179] salivary dim light melatonin onset (level 2),[168,180] and urinary melatonin (level 2)[166] (level 4);[181] salivary cortisol (level 2),[179] urinary cortisol (level 2),[166,182] and plasma cortisol (level 2),[172] plasma growth hormone (level 2);[172] and plasma TSH (level 2).[173] However, in terms of clinical practice, circadian markers are of limited value for assessing or treating jet lag.

In one study, circadian phase markers (urinary melatonin and cortisol) were examined in the assessment of jet lag in pilots flying across 7 or 8 time zones in both directions (level 2).[166.] The endogenous circadian rhythms were found to be out of phase with the local time, as expected, though the rhythms were also out of phase with one another (internal desynchronization). Of perhaps even greater importance, following a 2-day layover, the pilots were noted to be flying the return flight home during their circadian trough in terms of alertness and near their peak melatonin level.

Conclusion: While a number of circadian phase markers have been examined in JLD, these have been utilized to assess the phase response to treatment interventions. In terms of clinical practice, this would be of little value. Determining an individuals underlying circadian rhythm by phase marker analysis prior to travel could theoretically have some utility in assessing risk and treatment strategies for JLD. This approach has not been investigated yet.

7.4 Treatment

7.4.1 Prescribed Sleep Scheduling

While it makes sense for travelers to attempt to adopt the sleep schedule of their destination upon arrival in hopes that this will speed up entrainment, the impact of this has not, in fact, been well-studied. In a balanced crossover field study, investigators examined adapting to destination sleep hours vs. keeping home-base sleep hours during a two-day layover after a 9-h westward flight (level 2).[183] The group that kept home-based sleep hours experienced reduced sleepiness and global jet lag ratings compared to the group that adopted destination sleep hours, in part related to longer and better quality sleep during the layover. However, the home-based sleep hours group had a longer awake period from the last layover sleep to first recovery sleep following the return flight (37.5 hours vs. 30.6 hours for the destination sleep group). In addition, one third of the subjects in the study expressed a preference for adopting destination sleep hours in order to be in synch with local social activities and eating schedules.

Another approach has been to adjust the sleep schedule (and thus the circadian rhythms) in the days preceding flight to more closely match destination sleep hours. One such study successfully phase advanced the sleep schedule prior to simulated eastward travel using light therapy (level 2).[168] This study was primarily designed to determine the effects of light exposure (see below) and did not include a non-phase advanced control group. Likewise, in a follow-up study by this same group, advancing the sleep schedule by 2 hours per day vs. 1 hour per day via morning intermittent bright light coupled with advancing wakeup time was more successful at advancing the circadian rhythms by the day of simulated eastward travel, though only marginally (DLMO advanced by 1.8 h vs. 1.5 h respectively) (level 2).[184] Of interest, the 2-h advancing group did not show an increase in sleepiness over the three treatment days, while the 1-h advancing group did. However, jet lag symptom scores were only different between the groups on treatment day two. As in the previous study, a non-phase advanced control group was not included. No studies have been performed using this approach for westward travel.

Conclusion: One level 2 study supports staying on a home-based sleep schedule when time at destination is planned to be brief (i.e., two days or less) in order to limit jet lag symptoms. There are some data (level 2) from simulated jet lag studies to support altering the scheduled timing of sleep prior to eastward travel to help with entrainment, though the impact of this on jet lag symptoms is not entirely clear.

7.4.2 Circadian Phase Shifting

7.4.2.1 Timed Light Exposure

Current circadian theory would suggest that, after rapid travel across multiple time zones, the amount and timing of light exposure on arrival should have important consequences in determining the speed and direction of re-entrainment.

An early field trial provided a suggestion of benefit from timed light exposure (as well as light avoidance at the "wrong" circadian time) but the study involved only two subjects.[169] This report subsequently led to numerous studies evaluating the impact of timed light exposure on sleep in phase-shifting experiments.

These studies were nicely reviewed by Boulos et al. in 1995[185] and will not be reviewed here.

In the most recent simulation experiment to test whether timed light exposure could be a potential treatment for jet lag, 28 subjects were phase-shifted in the laboratory in anticipation of an eastward flight (level 2).[168] Their sleep schedule was shifted earlier by one hour per day for three days. Each morning, upon awakening, they were exposed to 3.5 hours of light presented as either continuous bright light (>3000 lux, n = 8), intermittent bright light (>3000 lux alternating 0.5 hours on with 0.5 hours off, n = 11) or "ordinary" dim indoor light (<60 lux, n = 9). The average DLMO phase advances in the continuous bright light, intermittent bright light and dim light groups were 2.1, 1.5, and 0.6 hours, respectively ($P < 0.01$ for the continuous and intermittent vs. the dim light group). No increase, as compared with baseline, was seen in the jet lag symptom score in the continuous light group, while a significant increase was noted in the intermittent and dim light groups.

We found only one published controlled field study of light treatment for jet lag (level 2).[180] In this small, randomized, controlled trial, subjects received either 3 hours of bright (3000 lux) light exposure from head-mounted goggles or 3 hours of dim (10 lux) red light at 19:00 local time for two evenings following a westward flight from Zurich to New York. A greater phase delay (1 hour) in the salivary melatonin-determined DLMO was seen in the bright light group ($P < 0.02$), but there were no significant differences in sleep or other performance measures (jet lag scale, psychomotor performance, or mood).

Conclusion: In a jet lag simulation study (level 2), appropriately timed bright light exposure prior to travel was able to shift circadian rhythms in the desired direction but would require high motivation and strict compliance with the prescribed light-dark schedule if prescribed clinically. One field trial (level 2) with artificial light exposure upon arrival produced equivocal results.

7.4.2.2 Timed Melatonin Administration

We found 12 double blind, placebo-controlled field trials of melatonin for jet lag published as full manuscripts—five level 1 studies[170,186-189] and seven level 2 studies.[174,176,179,182,190-192] Melatonin was administered in doses ranging from 0.5 to 10 mg, typically at local bedtime, for up to 3 days prior to departure and up to 5 days upon arrival at the destination. A variety of outcome measures were employed including subjective ratings scales of jet lag symptoms, sleep logs, and standardized mood scales as well as, in a few studies, objective measures of sleep (PSG and modified sleep latency testing)(level 2)[174] and actigraphy (level 2 and 1).[174,186] The quality of the studies was generally high, although only a few utilized circadian markers as objective indicators of circadian phase (level 2).[174,179]

In the studies that specifically examined symptoms of jet lag, the majority found an improvement in jet lag symptoms with melatonin (level 1),[187,188](level 2).[182,190-192] In the two studies that failed to show an improvement in jet lag scores, one (level 2)[176] found that although melatonin was more effective than placebo during the first thee days post-travel, a significant improvement was not seen as the data were analyzed by the first six days after travel. In the other negative study (level 1)[170] the subjects may not have been at their circadian baseline preceding travel, and this likely impacted the results.

The remaining studies examined the effect of melatonin on either sleep (not daytime jet lag symptoms) or circadian entrainment following travel. These (level 1 and 2) studies consistently found that melatonin improved the duration and quality of sleep as measured both subjectively and objectively.[174,186-189] Aside from this hypnotic effect, melatonin treatment may well accelerate circadian phase resetting to the new time zone, but evidence from field studies using circadian markers is limited. The strongest data supporting the impact of melatonin on entrainment comes from a study that examined the effect of melatonin on cortisol rhythms in subjects crossing 7 time zones in an eastward direction (level 2).[179] Compared to placebo, melatonin accelerated entrainment 4 days faster (6 days for melatonin vs. 10 days for placebo). This improvement mirrors that found in another study that used oral temperature as a circadian phase marker (level 2)[174] and noted signs of entrainment three days earlier in those on melatonin compared to placebo.

It is of interest that most studies have tested melatonin for eastward flight, for which taking melatonin at bedtime could involve benefits from both soporific and phase-resetting mechanisms. With westward flight, melatonin taken at bedtime could, in theory, inhibit phase resetting. However, in two randomized, controlled trials exploring the use of melatonin following westward travel (level 2)[191,192] improvements in jet lag scores and sleep were seen. It should be noted that in both of these studies, subjects crossed 12 or more time zones.

There is no strong evidence for a dose response for melatonin treatment, but larger doses may have a stronger hypnotic action. In a dose comparison study, 5 mg immediate-release melatonin was found to be much more effective at relieving symptoms of jet lag than a 2 mg slow-release formulation, though only marginally more effective than a 0.5 mg immediate-release formulation (level 1).[187] Thus, the timing of release and not the actual dosage appears relevant. Only one study has looked at using melatonin in combination with another agent for the management of jet lag (level 1).[188] This study, described in detail in the section below, did not find benefit for the combination of melatonin and zolpidem.

Adverse effects resulting from taking melatonin were, by and large, not evaluated in most of the studies. In the few studies where potential side effects are mentioned, they were not found to be different between active treatment and placebo groups. Differentiating adverse effects of melatonin vs. symptoms of jet lag may be difficult and limit accurate reporting. Thirty eight percent of subjects taking melatonin in one study[176] developed a "rocking" sensation and one subject developed difficulty breathing and swallowing 20 minutes after taking melatonin.[170]

Conclusion: Although two of the studies were negative (level 1 and level 2), the evidence is overall quite supportive that melatonin, administered at the appropriate time, can reduce the symptoms of jet lag and improve sleep following travel across multiple time zones (4 level 1 studies and 6 level 2 studies). Immediate-release formulations in doses of 0.5 to 5 mg appear effective (one level 1 study).

7.4.2.3 Promoting Sleep with Hypnotic Medication

We found nine field trials utilizing hypnotic agents to alleviate jet lag induced insomnia. Five of these studies examined the newer (non-benzodiazepine hypnotics) class of hypnotics (level

1),[188,189,193] (level 2)[173,178], while four evaluated the effect of a traditional benzodiazepine on jet lag (level 2).[172,177,194,195]

Of the studies utilizing traditional benzodiazepines, all had 20 or less subjects. In a small (n =17) nonrandomized study (level 2)[177] involving westward flight across five time zones, temazepam 10 mg had little effect on jet lag symptoms, sleep quality, or circadian entrainment, though the dose was much lower than is typically prescribed for sleep. At a higher dose of 20 mg given at bedtime, temazepam improved subjective sleep quality in another small study of 20 subjects traveling across 10 time zones eastward (level 2).[195] However, other sleep and circadian parameters did not improve. A study with midazolam (level 2)[194] yielded similar subjective findings following eastward travel. In a simulation study (level 2)[172] designed to mimic crossing 8 time zones to the west (8 hour phase delay), triazolam was no different than placebo for PSG measured sleep efficiency or total sleep time.

Like the traditional benzodiazepines, the non-benzodiazepine hypnotics appear to improve subjective sleep quality and duration. Zolpidem 10 mg at bedtime for 3-4 nights following eastward travel across 5 to 9 time zones was found to significantly improve total sleep time and sleep quality while reducing awakenings from sleep in a large (n=133) randomized placebo-controlled trial (level 1).[193] However, all outcomes were self-reported and no objective measures of sleep were assessed. Daytime symptoms of jet lag were not reported. In a smaller randomized placebo-controlled trial of 24 subjects, zopiclone 7.5 mg. given at bedtime was found to improve sleep duration (measured by actigraphy) for the four post-flight days following a 5-h. westward flight (level 2).[178] Daytime activity appeared greater as well, though subjective jet-lag scores were no different compared to placebo.

Two of the studies with non-benzodiazepine hypnotics compared the effects of these newer hypnotic agents to that of melatonin. In the first study (n = 137), zolpidem (10 mg) administered during a night flight and for 4 days after arrival was found to be significantly better than placebo or melatonin (5 mg) in counteracting jet lag symptoms (less confusion, lower jet lag scores on visual analog scales) following eastward travel across 6-9 time zones (level 1).[188] Subjects also reported better sleep duration and sleep quality on zolpidem, though this was not verified by actigraphic assessment. Of interest, this study also included a treatment arm that received both melatonin and zolpidem. This group did not report better sleep or better jet lag scores than the zolpidem alone group. In the other study (level 1),[189] zopiclone (5 mg) was compared to melatonin (2 mg) or placebo in 30 subjects traveling eastward across 5 time zones. Each subject served as his/her own control (they repeated the trip x 3), though the treatment was administered for only one night (after arrival). Zopiclone and melatonin were equally effective at improving both subjective and objective (measured by actigraphy) sleep duration and quality as compared to placebo. Other symptoms of jet lag were not assessed.

One additional study compared the non-benzodiazepine hypnotic zolpidem to bright light exposure in a simulated 8-hour eastward time shift (level 2).[173] In this study, 8 subjects underwent 3 separate 8-hour phase advances. In one arm, they took a placebo pill at the advanced bedtime on the day of the advance and the following day, in another they took zolpidem 10 mg at the advanced bedtime on the day of the advance and the following day, and in the final arm, they were exposed to continuous bright light (as opposed to dim light in the other arms) upon awakening on the day of the advance and the following day. Total sleep times (by PSG) did not differ between the treatments, though sleep efficiency improved significantly with zolpidem (night of shift only) and bright light (night after shift only). No other symptoms of jet leg were recorded. Of interest, both zolpidem and bright light appeared to attenuate the rebound rise in TSH that usually accompanies sudden phase advances.

Adverse effects of hypnotic agents for jet lag have been reported. For example, triazolam was implicated in several dramatic cases of global amnesia following its use to promote sleep during jet travel.[196] More commonly, nausea/vomiting, headaches, and confusion are reported. In the study comparing a combination of zolpidem plus melatonin to zolpidem, melatonin, or placebo, there was a much higher rate of adverse events in the zolpidem group than the other treatment groups.[188] The author termed the adverse events as not being "serious," though 14 subjects dropped out of the study as a result. In addition, when zolpidem and melatonin were combined, the high rate of adverse events persisted (and was comparable to the zolpidem alone group). Immobility associated with hypnotic use might increase the risk for deep vein thrombosis, known to be a risk of jet travel. This hypothetical risk has not been documented though.

Conclusion: Although the number of studies is limited (three level 1, six level 2), the use of hypnotic agents for jet lag-induced insomnia is a rational treatment and consistent with the standard recommendations for the treatment of short-term insomnia. However, the effects of hypnotics on daytime symptoms of jet lag have not been well-studied and are unknown. In addition, any benefits to using hypnotics must be weighed against the risk for side effects. Because alcohol intake is often high during international travel, the risk of interaction with hypnotics should be emphasized with patients.

7.4.2.4 Promoting Alertness with Stimulant Medication

Increased coffee consumption is the first countermeasure many travelers use to combat sleepiness. This strategy has not been studied in a controlled fashion and there remains concern that the resulting increased caffeine levels may exacerbate jet-lag induced insomnia. There are two controlled field trials in which slow-release caffeine (SRC) was evaluated for its effects on alertness and jet lag symptoms. The first study compared placebo to SRC 300 mg daily for 5 days after flight or melatonin 5 mg daily starting on the day of travel to 3 days post flight (level 2).[179] There were nine subjects in each group and the study was double-blinded. Following eastward flight across seven time zones, both the SRC and melatonin groups had a faster entrainment of their circadian rhythms (by day 5 vs. day 9 for placebo) as measured by salivary cortisol levels. Symptoms of alertness and jet lag were not assessed in this study. Utilizing the same protocol and number of subjects, the same group reported a follow-up study examining the impact of these treatments on both objective (PSG) and subjective measures of sleep and daytime sleepiness (two-nap sleep latency test) (level 2).[174] While subjects in the SRC treatment arm experienced less daytime sleepiness than with either melatonin or placebo (by objective measures as there was no significant difference in subjective sleepiness), they reported longer sleep onsets and more awakenings at night than the other groups. This was confirmed by PSG, which also documented a delay in recovery slow wave sleep in the SRC group.

Conclusion: The use of caffeine to counteract jet lag induced sleepiness seems rational, but the evidence is very limited (two level 2 studies). The alerting effects of these agents must be weighed against their propensity to disrupt sleep. One level 2 study suggested that a slow-release caffeine formulation may enhance the rapidity of circadian entrainment following eastward travel.

7.4.2.5 Miscellaneous

Diet modification has been proposed as a potential modality to prevent and reduce the symptoms of jet lag. Only one field study addressing this issue was found (level 4).[197] In this study, the "Argonne diet" was assessed in a 186 soldiers undergoing a 9-h westward flight followed by a return flight. The Argonne diet consists of alternating days of "feasting" with high carbohydrate dinners and "fasting" with small, low calorie meals. The authors found a significant reduction in self-reported jet lag symptoms in those utilizing the diet. However, the study had several limitations, including self-selection of diet with unclear oversight, self-reporting of symptoms, and non-validated outcome measures. In addition, fewer subjects chose the diet on the return flight than utilized it on the outbound flight.

Conclusions: Diet modification as a means to prevent jet lag is unproven at this time (one level 4 study).

8.0 DISCUSSION

Sound clinical practice is based on both a scientific understanding of pathophysiology as well as empirical evidence derived from clinical application, ideally from well-designed clinical trials. In regard to SWD and JLD, a foundation for understanding of the pathophysiology of these disorders has been built by the discipline of circadian rhythm science that now extends from molecular biology to behavior. One of the most important conclusions from human circadian rhythm research is that the anatomy, physiology, and even the molecular biology of the human circadian system are homologous to the animal models that have been so thoroughly investigated in recent years.

Circadian rhythm science has also pointed the way to rational interventions for the CRSDs, and these treatments have been introduced into the practice of sleep medicine with varying degrees of success, but with many practical matters unresolved. The use of timed light exposure for clock resetting provides an example: How bright? How long? What color spectrum? From what light source? For what disorders? Are there contraindications for light treatment, such as ocular pathology, or the risk of bright light falling on the "wrong" portion of the light PRC? The use of melatonin administration for phase resetting can generate an analogous array of questions.

In addition to clock resetting, the current understanding of the interaction between the homeostatic and circadian regulation of sleep and alertness provides a good explanation of the symptoms of sleepiness and insomnia inherent to the CRSDs. However, with the exception of the large modafinil trial,[37] there have been no large multicenter trials focusing on pharmacological countermeasures. When double-blind clinical trials have been conducted, the number of subjects is often small.

Also, much of the human research has been done with normal subjects tested in conditions that simulate a CRSD (such as shift work disorder or jet lag disorder). While these studies are valuable, they need to be followed up, as much as possible, with clinical trials in the field. Although the data from clinical research is limited, it can be generally concluded that the clinical outcomes have not been at odds with hypotheses based on principles derived from circadian science.

EVIDENCE TABLE

The Evidence Table for parts I and II of the CRSD Review Papers are located on the SLEEP website www.journalsleep.org.

REFERENCES

1. American Academy of Sleep Medicine. The international classification of sleep disorders : diagnostic & coding manual (2nd ed). Westchester, IL: American Academy of Sleep Medicine, 2005.
2. Campbell, SS, and Dawson, D. Aging young sleep: a test of the phase advance hypothesis of sleep disturbance in the elderly. J Sleep Res 1992;1:205-10.
3. Drake, CL, Roehrs, T, Richardson, G, Walsh, JK, and Roth, T. Shift work sleep disorder: prevalence and consequences beyond that of symptomatic day workers. Sleep 2004;27:1453-62.
4. Yazaki, M, Shirakawa, S, Okawa, M, and Takahashi, K. Demography of sleep disturbances associated with circadian rhythm disorders in Japan. Psychiatry & Clinical Neurosciences 1999;53:267-8.
5. Dagan, Y, and Eisenstein, M. Circadian rhythm sleep disorders: toward a more precise definition and diagnosis. Chronobiology International 1999;16:213-22.
6. Kamei, Y, Urata, J, Uchiyaya, M, Hayakawa, T, Ozaki, S, Shibui, K, and Okawa, M. Clinical characteristics of circadian rhythm sleep disorders. Psychiatry & Clinical Neurosciences 1998;52:234-5.
7. Horne, JA, and Ostberg, O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol 1976;4:97-110.
8. Medicine., CfEB (2007) Levels of Evidence In Vol. 2007 p. Oxford, EN
9. Dunlap, J, Loros, J, and DeCoursey, P. Chronobiology, Biological Timekeepinged). Sunderland, Massachusetts, USA: Sinauer Associates, Inc., 2004.:
10. Dijk, DJ, and Lockley, SW. Integration of human sleep-wake regulation and circadian rhythmicity. J Appl Physiol 2002;92:852-62.
11. Berson, DM, Dunn, FA, and Takao, M. Phototransduction by retinal ganglion cells that set the circadian clock. Science 2002;295:1070-3.
12. Hattar, S, Liao, HW, Takao, M, Berson, DM, and Yau, KW. Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. Science 2002;295:1065-70.
13. Brainard, GC, and Hanifin, JP. Photons, clocks, and consciousness. J Biol Rhythms 2005;20:314-25.
14. Lockley, SW, Brainard, GC, and Czeisler, CA. High sensitivity of the human circadian melatonin rhythm to resetting by short wavelength light. J Clin Endocrinol Metab 2003;88:4502-5.
15. Glickman, G, Byrne, B, Pineda, C, Hauck, WW, and Brainard, GC. Light therapy for seasonal affective disorder with blue narrow-band light-emitting diodes (LEDs). Biol Psychiatry 2006;59:502-7.
16. Burgess, HJ, and Eastman, CI. A late wake time phase delays the human dim light melatonin rhythm. Neuroscience Letters 2006;395:191-5.
17. Czeisler, C, and Wright Jr., K (1999) Influence of light on circadian rhythmicity in humans. In Regulation of Sleep and Circadian Rhythms, (Turek, F, et al. ed) pp. 149-80.
18. Duffy, JF, and Wright, KP, Jr. Entrainment of the human circadian system by light. J Biol Rhythms 2005;20:326-38.
19. Edgar, DM, Dement, WC, and Fuller, CA. Effect of SCN lesions on sleep in squirrel monkeys: evidence for opponent processes in sleep-wake regulation. J Neurosci 1993;13:1065-79.

20. Burgess, HJ, and Eastman, CI. The dim light melatonin onset following fixed and free sleep schedules. J Sleep Res 2005;14:229-37.
21. Burgess, HJ, Savic, N, Sletten, T, Roach, G, Gilbert, SS, and Dawson, D. The relationship between the dim light melatonin onset and sleep on a regular schedule in young healthy adults. Behavioral Sleep Medicine 2003;1:102-14
22. Minors, DS, and Waterhouse, JM. Does 'anchor sleep' entrain circadian rhythms? Evidence from constant routine studies. J Physiol 1983;345:451-67.
23. 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.
24. Waterhouse, J, Weinert, D, Minors, D, et al. The effect of activity on the waking temperature rhythm in humans. Chronobiol Int 1999;16:343-57.
25. Lewy, AJ, and Sack, RL. The dim light melatonin onset as a marker for circadian phase position. Chronobiol Int 1989;6:93-102.
26. Deacon, S, and Arendt, J. Posture influences melatonin concentrations in plasma and saliva in humans. Neurosci Lett 1994;167:191-4.
27. Nathan, PJ, Jeyaseelan, AS, Burrows, GD, and Norman, TR. Modulation of plasma melatonin concentrations by changes in posture. J Pineal Res 1998;24:219-23.
28. Murphy, PJ, Myers, BL, and Badia, P. Nonsteroidal anti-inflammatory drugs alter body temperature and suppress melatonin in humans. Physiol Behav 1996;59:133-9.
29. Shilo, L, Sabbah, H, Hadari, R, et al. The effects of coffee consumption on sleep and melatonin secretion. Sleep Medicine 2002;3:271-73.
30. Stoschitzky, K, Sakotnik, A, Lercher, P, Zweiker, R, Maier, R, Liebmann, P, and Lindner, W. Influence of beta-blockers on melatonin release. Eur J Clin Pharmacol 1999;55:111-5.
31. Wright, KP, Jr., Badia, P, Myers, BL, Plenzler, SC, and Hakel, M. Caffeine and light effects on nighttime melatonin and temperature levels in sleep-deprived humans. Brain Research 1997;747:78-84.
32. Boivin, DB, Duffy, JF, Kronauer, RE, and Czeisler, CA. Dose-response relationships for resetting of human circadian clock by light. Nature 1996;379:540-2.
33. Shanahan, TL, and Czeisler, CA. Light exposure induces equivalent phase shifts of the endogenous circadian rhythms of circulating plasma melatonin and core body temperature in men. Journal of Clinical Endocrinology & Metabolism 1991;73:227-35.
34. Klerman, EB, Gershengorn, HB, Duffy, JF, and Kronauer, RE. Comparisons of the variability of three markers of the human circadian pacemaker. Journal of Biological Rhythms 2002;17:181-93.
35. Benloucif, S, Guico, MJ, Reid, KJ, Wolfe, LF, L'Hermite-Baleriaux, M, and Zee, PC. Stability of melatonin and temperature as circadian phase markers and their relation to sleep times in humans. J Biol Rhythms 2005;20:178-88.
36. 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;25:83-8.
37. Czeisler, CA, Walsh, JK, Roth, T, et al. Modafinil for excessive sleepiness associated with shift-work sleep disorder. New England Journal of Medicine 2005;353:476-86.
38. Monk, TH, Flaherty, JF, Frank, E, Hoskinson, K, and Kupfer, DJ. The Social Rhythm Metric. An instrument to quantify the daily rhythms of life. Journal of Nervous & Mental Disease 1990;178:120-26.
39. Carney, CE, Edinger, JD, Meyer, B, Lindman, L, and Istre, T. Daily activities and sleep quality in college students. Chronobiology International 2006;23:623-37.
40. Monk, TH, Reynolds, CF, 3rd, Machen, MA, and Kupfer, DJ. Daily social rhythms in the elderly and their relation to objectively recorded sleep. Sleep 1992;15:322-9.
41. Ancoli-Israel, S, Cole, R, Alessi, C, Chambers, M, Moorcroft, W, and Pollak, CP. The role of actigraphy in the study of sleep and circadian rhythms. Sleep 2003;26:342-92.
42. 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;30:519-29.
43. Roenneberg, T, Wirz-Justice, A, and Merrow, M. Life between clocks: daily temporal patterns of human chronotypes. J Biol Rhythms 2003;18:80-90.
44. Zavada, A, Gordijn, MC, Beersma, DG, Daan, S, and Roenneberg, T. Comparison of the Munich Chronotype Questionnaire with the Horne-Ostberg's Morningness-Eveningness Score. Chronobiology International 2005;22:267-78.
45. Andrade, MM, Benedito-Silva, AA, and Menna-Barreto, L. Correlations between morningness-eveningness character, sleep habits and temperature rhythm in adolescents. Braz J Med Biol Res 1992;25:835-9.
46. 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;9:117-27.
47. Bailey, SL, and Heitkemper, MM. Circadian rhythmicity of cortisol and body temperature: morningness-eveningness effects. Chronobiology International 2001;18:249-61.
48. Duffy, JF, Dijk, DJ, Hall, EF, and Czeisler, CA. Relationship of endogenous circadian melatonin and temperature rhythms to self-reported preference for morning or evening activity in young and older people. Journal of Investigative Medicine 1999;47:141-50.
49. Carrier, J, Monk, TH, Buysse, DJ, and Kupfer, DJ. Sleep and morningness-eveningness in the 'middle' years of life (20-59 y). Journal of Sleep Research 1997;6:230-7.
50. Laberge, L, Carrier, J, Lesperance, P, Lambert, C, Vitaro, F, Tremblay, RE, and Montplaisi, J. Sleep and circadian phase characteristics of adolescent and young adult males in a naturalistic summertime condition. Chronobiology International 2000;17:489-501.
51. Duffy, JF, Rimmer, DW, and Czeisler, CA. Association of intrinsic circadian period with morningness-eveningness, usual wake time, and circadian phase. Behavioral Neuroscience 2001;115:895-9.
52. Griefahn, B, Kunemund, C, Golka, K, Thier, R, and Degen, G. Melatonin synthesis: a possible indicator of intolerance to shiftwork. American Journal of Industrial Medicine 2002;42:427-36.
53. Martin, SK, and Eastman, CI. Medium-intensity light produces circadian rhythm adaptation to simulated night-shift work. Sleep 1998;21:154-65.
54. Mitchell, PJ, Hoese, EK, Liu, L, Fogg, LF, and Eastman, CI. Conflicting bright light exposure during night shifts impedes circadian adaptation. Journal of Biological Rhythms 1997;12:5-15.
55. Duffy, JF, and Czeisler, CA. Age-related change in the relationship between circadian period, circadian phase, and diurnal preference in humans. Neuroscience Letters 2002;318:117-20.
56. Kerkhof, GA, and Van Dongen, HP. Morning-type and evening-type individuals differ in the phase position of their endogenous circadian oscillator. Neuroscience Letters 1996;218:153-6.
57. Martin, SK, and Eastman, CI. Sleep logs of young adults with self-selected sleep times predict the dim light melatonin onset. Chronobiology International 2002;19:695-707.
58. Mongrain, V, Lavoie, S, Selmaoui, B, Paquet, J, and Dumont, M. Phase relationships between sleep-wake cycle and underlying circadian rhythms in Morningness-Eveningness. Journal of Biological Rhythms 2004;19:248-57.
59. Roemer, HC, Griefahn, B, Kuenemund, C, Blaszkewicz, M, and Gerngross, H. The reliability of melatonin synthesis as an indicator of the individual circadian phase position. Military Medicine 2003;168:674-8.
60. Waterhouse, J, Folkard, S, Van Dongen, H, et al. Temperature profiles, and the effect of sleep on them, in relation to morningness-

eveningness in healthy female subjects. Chronobiology International 2001;18:227-47.
61. Hilliker, NA, Muehlbach, MJ, Schweitzer, PK, and Walsh, JK. Sleepiness/alertness on a simulated night shift schedule and morningness-eveningness tendency. Sleep 1992;15:430-3.
62. Ceolim, MF, and Menna-Barreto, L. Sleep/wake cycle and physical activity in healthy elderly people. Sleep Res Online 2000;3:87-95.
63. Taillard, J, Philip, P, Chastang, JF, Diefenbach, K, and Bioulac, B. Is self-reported morbidity related to the circadian clock? Journal of Biological Rhythms 2001;16:183-90.
64. 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.
65. Lewy, AJ, Wehr, TA, Goodwin, FK, Newsome, DA, and Markey, SP. Light suppresses melatonin secretion in humans. Science 1980;210:1267-9.
66. Czeisler, CA, Allan, JS, Strogatz, SH, et al. Bright light resets the human circadian pacemaker independent of the timing of the sleep-wake cycle. Science 1986;233:667-71.
67. Lewy, AJ, Sack, RL, Miller, LS, and Hoban, TM. Antidepressant and circadian phase-shifting effects of light. Science 1987;235:352-4.
68. Campbell, SS, and Murphy, PJ. Extraocular circadian phototransduction in humans. Science 1998;279:396-9.
69. Eastman, CI, Martin, SK, and Hebert, M. Failure of extraocular light to facilitate circadian rhythm reentrainment in humans. Chronobiology International 2000;17:807-26.
70. Wright, KP, Jr., and Czeisler, CA. Absence of circadian phase resetting in response to bright light behind the knees. Science 2002;297:571.
71. Zeitzer, JM, Dijk, DJ, Kronauer, R, Brown, E, and Czeisler, C. Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression. J Physiol 2000;526 Pt 3:695-702.
72. Wright, KP, Jr., Hughes, RJ, Kronauer, RE, Dijk, DJ, and Czeisler, CA. Intrinsic near-24-h pacemaker period determines limits of circadian entrainment to a weak synchronizer in humans. Proc Natl Acad Sci U S A 2001;98:14027-32.
73. Wever, RA. Light effects on human circadian rhythms: a review of recent Andechs experiments. J Biol Rhythms 1989;4:161-85.
74. Hebert, M, Martin, SK, Lee, C, and Eastman, CI. The effects of prior light history on the suppression of melatonin by light in humans. J Pineal Res 2002;33:198-203.
75. Jasser, SA, Hanifin, JP, Rollag, MD, and Brainard, GC. Dim light adaptation attenuates acute melatonin suppression in humans. J Biol Rhythms 2006;21:394-404.
76. Smith, KA, Schoen, MW, and Czeisler, CA. Adaptation of human pineal melatonin suppression by recent photic history. Journal of Clinical Endocrinology & Metabolism 2004;89:3610-4.
77. Gronfier, C, Wright, KP, Jr., Kronauer, RE, Jewett, ME, and Czeisler, CA. Efficacy of a single sequence of intermittent bright light pulses for delaying circadian phase in humans. American Journal of Physiology - Endocrinology & Metabolism 2004;287:E174-81.
78. Reme, CE, Rol, P, Grothmann, K, Kaase, H, and Terman, M. Bright light therapy in focus: lamp emission spectra and ocular safety. Technol Health Care 1996;4:403-13.
79. Roberts, JE. Screening for ocular phototoxicity. Int J Toxicol 2002;21:491-500.
80. Crowley, SJ, Lee, C, Tseng, CY, Fogg, LF, and Eastman, CI. Combinations of bright light, scheduled dark, sunglasses, and melatonin to facilitate circadian entrainment to night shift work. Journal of Biological Rhythms 2003;18:513-23.
81. 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;17:535-43.
82. Buxton, OM, L'Hermite-Baleriaux, M, Turek, FW, and van Cauter, E. Daytime naps in darkness phase shift the human circadian rhythms of melatonin and thyrotropin secretion. Am J Physiol Regul Integr Comp Physiol 2000;278:R373-82.
83. Redman, J, Armstrong, S, and Ng, KT. Free-running activity rhythms in the rat: entrainment by melatonin. Science 1983;219:1089-91.
84. Lewy, AJ, Ahmed, S, Jackson, JM, and Sack, RL. Melatonin shifts human circadian rhythms according to a phase-response curve. Chronobiol Int 1992;9:380-92.
85. Lewy, A. J., V. K. Bauer, et al. The human phase response curve (PRC) to melatonin is about 12 hours out of phase with the PRC to light. Chronobiology International 1998 15:71-83.
86. 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;19:649-58.
87. Wirz-Justice, A, Krauchi, K, Cajochen, C, Danilenko, KV, Renz, C, and Weber, JM. Evening melatonin and bright light administration induce additive phase shifts in dim light melatonin onset. J Pineal Res 2004;36:192-4.
88. Revell, VL, Burgess, HJ, Gazda, CJ, Smith, MR, Fogg, LF, and Eastman, CI. Advancing human circadian rhythms with afternoon melatonin and morning intermittent bright light. Journal of Clinical Endocrinology & Metabolism 2006;91:54-9.
89. 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;20:908-15.
90. Hirai, K, Kita, M, Ohta, H, Nishikawa, H, Fujiwara, Y, Ohkawa, S, and Miyamoto, M. Ramelteon (TAK-375) accelerates reentrainment of circadian rhythm after a phase advance of the light-dark cycle in rats. J Biol Rhythms 2005;20:27-37.
91. Reebs, SG, and Mrosovsky, N. Effects of induced wheel running on the circadian activity rhythms of Syrian hamsters: entrainment and phase response curve. J Biol Rhythms 1989;4:39-48.
92. Van Reeth, O, Sturis, J, Byrne, MM, et al. Nocturnal exercise phase delays circadian rhythms of melatonin and thyrotropin secretion in normal men. American Journal of Physiology 1994;266:E964-74.
93. Buxton, OM, Lee, CW, L'Hermite-Baleriaux, M, Turek, FW, and Van Cauter, E. Exercise elicits phase shifts and acute alterations of melatonin that vary with circadian phase. Am J Physiol Regul Integr Comp Physiol 2003;284:R714-24.
94. Barger, LK, Wright, KP, Jr., Hughes, RJ, and Czeisler, CA. Daily exercise facilitates phase delays of circadian melatonin rhythm in very dim light. Am J Physiol Regul Integr Comp Physiol 2004;286: R1077-84.
95. Miyazaki, T, Hashimoto, S, Masubuchi, S, Honma, S, and Honma, KI. Phase-advance shifts of human circadian pacemaker are accelerated by daytime physical exercise. American Journal of Physiology - Regulatory Integrative & Comparative Physiology 2001;281: R197-205.
96. 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;47:563-67.
97. Okawa, M, Uchiyama, M, Ozaki, S, Shibui, K, and Ichikawa, H. Circadian rhythm sleep disorders in adolescents: clinical trials of combined treatments based on chronobiology. Psychiatry & Clinical Neurosciences 1998;52:483-90.
98. Yamadera, W, Sasaki, M, Itoh, H, Ozone, M, and Ushijima, S. Clinical features of circadian rhythm sleep disorders in outpatients. Psychiatry & Clinical Neurosciences 1998;52:311-6.
99. 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;51:275-79.
100. Presser, HB. Job, family, and gender: determinants of nonstandard work schedules among employed Americans in 1991. Demography 1995;32:577-98.
101. Harma, M, Knauth, P, Ilmarinen, J, and Ollila, H. The relation of age to

the adjustment of the circadian rhythms of oral temperature and sleepiness to shift work. Chronobiology International 1990;7:227-33.
102. Harma, MI, Hakola, T, Akerstedt, T, and Laitinen, JT. Age and adjustment to night work. Occupational & Environmental Medicine 1994;51:568-73.
103. Monk, TH, Buysse, DJ, Carrier, J, and Kupfer, DJ. Inducing jet-lag in older people: directional asymmetry. Journal of Sleep Research 2000;9:101-16.
104. Marquie, JC, Foret, J, and Queinnec, Y. Effects of age, working hours, and job content on sleep: a pilot study. Experimental aging research 1999;25:421-7.
105. Marquie, JC, and Foret, J. Sleep, age, and shiftwork experience. Journal of Sleep Research 1999;8:297-304.
106. Smith, L, and Mason, C. Reducing night shift exposure: a pilot study of rota, night shift and age effects on sleepiness and fatigue. Journal of human ergology 2001;30:83-7.
107. Oginska, H, Pokorski, J, and Oginski, A. Gender, ageing, and shiftwork intolerance. Ergonomics 1993;36:161-8.
108. Crowley, SJ, Lee, C, Tseng, CY, Fogg, LF, and Eastman, CI. Complete or partial circadian re-entrainment improves performance, alertness, and mood during night-shift work. Sleep 2004;27:1077-8.
109. Dumont, M, Benhaberou-Brun, D, and Paquet, J. Profile of 24-h light exposure and circadian phase of melatonin secretion in night workers. Journal of Biological Rhythms 2001;16:502-11.
110. Koller, M, Kundi, M, Stidl, HG, Zidek, T, and Haider, M. Personal light dosimetry in permanent night and day workers. Chronobiology International 1993;10:143-55.
111. Koller, M, Harma, M, Laitinen, JT, Kundi, M, Piegler, B, and Haider, M. Different patterns of light exposure in relation to melatonin and cortisol rhythms and sleep of night workers. Journal of pineal research 1994;16:127-35.
112. Barnes, RG, Forbes, MJ, and Arendt, J. Shift type and season affect adaptation of the 6-sulphatoxymelatonin rhythm in offshore oil rig workers. Neuroscience Letters 1998;252:179-82.
113. Midwinter, MJ, and Arendt, J. Adaptation of the melatonin rhythm in human subjects following night-shift work in Antarctica. Neurosci Lett 1991;122:195-8.
114. Ross, JK, Arendt, J, Horne, J, and Haston, W. Night-shift work in Antarctica: sleep characteristics and bright light treatment. Physiol Behav 1995;57:1169-74.
115. Quera-Salva, MA, Guilleminault, C, Claustrat, B, Defrance, R, Gajdos, P, McCann, CC, and De Lattre, J. Rapid shift in peak melatonin secretion associated with improved performance in short shift work schedule. Sleep 1997;20:1145-50.
116. 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.
117. Stewart, KT, Hayes, BC, and Eastman, CI. Light treatment for NASA shiftworkers. Chronobiology International 1995;12:141-51.
118. Boivin, DB, and James, FO. Circadian adaptation to night-shift work by judicious light and darkness exposure. Journal of Biological Rhythms 2002;17:556-67.
119. Quera-Salva, MA, Defrance, R, Claustrat, B, De Lattre, J, and Guilleminault, C. Rapid shift in sleep time and acrophase of melatonin secretion in short shift work schedule. Sleep 1996;19:539-43.
120. Weibel, L, Spiegel, K, Gronfier, C, Follenius, M, and Brandenberger, G. Twenty-four-hour melatonin and core body temperature rhythms: their adaptation in night workers. American Journal of Physiology 1997;272:R948.
121. Dawson, D, and Campbell, SS. Timed exposure to bright light improves sleep and alertness during simulated night shifts. Sleep 1991;14:511-6.
122. 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.
123. 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.
124. 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:R261-7.
125. Benhaberou-Brun, D, Lambert, C, and Dumont, M. Association between melatonin secretion and daytime sleep complaints in night nurses. Sleep 1999;22:877-85.
126. 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.
127. Czeisler, CA, Moore-Ede, MC, and Coleman, RH. Rotating shift work schedules that disrupt sleep are improved by applying circadian principles. Science 1982;217:460-3.
128. Gallo, LC, and Eastman, CI. Circadian rhythms during gradually delaying and advancing sleep and light schedules. Physiology & behavior 1993;53:119-26.
129. Hakola, T, and Harma, M. Evaluation of a fast forward rotating shift schedule in the steel industry with a special focus on ageing and sleep. Journal of human ergology 2001;30:315-9.
130. 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;7:240-7.
131. 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;44:937-45.
132. Garbarino, S, Mascialino, B, Penco, MA, et al. Professional shiftwork drivers who adopt prophylactic naps can reduce the risk of car accidents during night work. Sleep 2004;27:1295-1302.
133. 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;11:219-27.
134. 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.
135. Foret, J, Daurat, A, and Tirilly, G. Effect of bright light at night on core temperature, subjective alertness and performance as a function of exposure time. Scandinavian Journal of Work, Environment & Health 1998;24:115-20.
136. Horowitz, TS, Cade, BE, Wolfe, JM, and Czeisler, CA. Efficacy of bright light and sleep/darkness scheduling in alleviating circadian maladaptation to night work. American Journal of Physiology - Endocrinology & Metabolism 2001;281:E384.
137. Reid, K, and Dawson, D. Comparing performance on a simulated 12 hour shift rotation in young and older subjects. Occupational & Environmental Medicine 2001;58:58-62.
138. Santhi, N, Duffy, JF, Horowitz, TS, and Czeisler, CA. Scheduling of sleep/darkness affects the circadian phase of night shift workers. Neuroscience Letters 2005;384:316-20.
139. 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;19:414-20.
140. 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;27:771-8.
141. 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;25:351-56.
142. 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.
143. 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;8:105-12.
144. Sharkey, KM, Fogg, LF, and Eastman, CI. Effects of melatonin administration on daytime sleep after simulated night shift work. Journal of Sleep Research 2001;10:181-92.
145. Folkard, S, Arendt, J, and Clark, M. Can melatonin improve shift workers' tolerance of the night shift? Some preliminary findings. Chronobiology International 1993;10:315-20.
146. 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.
147. James, M, Tremea, MO, Jones, JS, and Krohmer, JR. Can melatonin improve adaptation to night shift? American Journal of Emergency Medicine 1998;16:367-70.
148. 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;19:903-13.
149. Walsh, JK, Sugerman, JL, Muehlbach, MJ, and Schweitzer, PK. Physiological sleep tendency on a simulated night shift: adaptation and effects of triazolam. Sleep 1988;11:251-64.
150. 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;20:535-41.
151. 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;14:140-6.
152. Monchesky, TC, Billings, BJ, Phillips, R, and Bourgouin, 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;61:255-9.
153. 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.
154. Puca, FM, Perrucci, S, Prudenzano, MP, et al. Quality of life in shift work syndrome. Functional neurology 1996;11:261-8.
155. 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;81:559-68.
156. 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.
157. Bonnet, MH, and Arand, DL. Impact of naps and caffeine on extended nocturnal performance. Physiology & behavior 1994;56:103-9.
158. Bonnet, MH, and Arand, DL. The use of prophylactic naps and caffeine to maintain performance during a continuous operation. Ergonomics 1994;37:1009-20.
159. De Valck, E, and Cluydts, RB. Slow-release caffeine as a countermeasure to driver sleepiness induced by partial sleep deprivation. Journal of Sleep Research 2001;10:203-9.
160. De Valck, E, De Groot, E, and Cluydts, R. Effects of slow-release caffeine and a nap on driving simulator performance after partial sleep deprivation. Perceptual & Motor Skills 2003;96:67-78.
161. McLellan, TM, Bell, DG, and Kamimori, GH. Caffeine improves physical performance during 24 h of active wakefulness. Aviation Space & Environmental Medicine 2004;75:666-72.
162. Walsh, JK, Muehlbach, MJ, Humm, TM, Dickins, QS, Sugerman, JL, and Schweitzer, PK. Effect of caffeine on physiological sleep tendency and ability to sustain wakefulness at night. Psychopharmacology 1990;101:271-3.
163. Muehlbach, MJ, and Walsh, JK. The effects of caffeine on simulated night-shift work and subsequent daytime sleep. Sleep 1995;18:22-9.
164. Wyatt, JK, Cajochen, C, Ritz-De Cecco, A, Czeisler, CA, and Dijk, DJ. Low-dose repeated caffeine administration for circadian-phase-dependent performance degradation during extended wakefulness. Sleep 2004;27:374-81.
165. Waterhouse, J, Edwards, B, Nevill, A, et al. Identifying some determinants of "jet lag" and its symptoms: a study of athletes and other travellers. British journal of sports medicine 2002;36:54-60.
166. Tresguerres, JA, Ariznavarreta, C, Granados, B, Martin, M, Villanua, MA, Golombek, DA, and Cardinali, DP. Circadian urinary 6-sulphatoxymelatonin, cortisol excretion and locomotor activity in airline pilots during transmeridian flights. Journal of pineal research 2001;31:16-22.
167. Moline, ML, Pollak, CP, Monk, TH, et al. Age-related differences in recovery from simulated jet lag. Sleep 1992;15:28-40.
168. 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;18:318-28.
169. Daan, S, and Lewy, AJ. Scheduled exposure to daylight: a potential strategy to reduce "jet lag" following transmeridian flight. Psychopharmacol Bull 1984;20:566-8.
170. 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;156:1392-6.
171. 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;20:1039-43.
172. 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;23:915-27.
173. 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;81:3270-7.
174. 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;96:50-8.
175. Ariznavarreta, C, Cardinali, DP, Villanua, MA, et al. Circadian rhythms in airline pilots submitted to long-haul transmeridian flights. Aviation Space & Environmental Medicine 2002;73:445-55.
176. 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;43:1501-13.
177. 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;22:166-74.
178. 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;149:241-5.
179. Pierard, C, Beaumont, M, Enslen, 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;85:144-50.
180. 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;73:953-63.
181. Cardinali, DP, Bortman, GP, Liotta, G, et al. A multifactorial approach employing melatonin to accelerate resynchronization of sleep-wake cycle after a 12 time-zone westerly transmeridian flight in elite soccer athletes. Journal of pineal research 2002;32:41-6.
182. 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.

183. 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
184. Eastman, CI, Gazda, CJ, Burgess, HJ, Crowley, SJ, and Fogg, LF. Advancing circadian rhythms before eastward flight: a strategy to prevent or reduce jet lag. Sleep 2005;28:33-44.
185. Boulos, Z, Campbell, SS, Lewy, AJ, Terman, M, Dijk, DJ, and Eastman, CI. Light treatment for sleep disorders: consensus report. VII. Jet lag. J Biol Rhythms 1995;10:167-76.
186. 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;67:520-4.
187. 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;15:655-66.
188. 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;72:638-46.
189. 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;75:439-43.
190. Claustrat, B, Brun, J, David, M, Sassolas, G, and Chazot, G. Melatonin and jet lag: confirmatory result using a simplified protocol. Biol Psychiatry 1992;32:705-11.
191. Petrie, K, Conaglen, JV, Thompson, L, and Chamberlain, K. Effect of melatonin on jet lag after long haul flights. BMJ 1989;298:705-7.
192. 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;33:526-30.
193. Jamieson, AO, Zammit, GK, Rosenberg, RS, Davis, JR, and Walsh, JK. Zolpidem reduces the sleep disturbance of jet lag. Sleep Medicine 2001;2:423-30.
194. Lavie, P. Effects of midazolam on sleep disturbances associated with westward and eastward flights: evidence for directional effects. Psychopharmacology (Berl) 1990;101:250-4.
195. 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;62:654-60.
196. Morris, HH, 3rd, and Estes, ML. Traveler's amnesia. Transient global amnesia secondary to triazolam. Jama 1987;258:945-6.
197. Reynolds, NC, Jr., and Montgomery, R. Using the Argonne diet in jet lag prevention: deployment of troops across nine time zones. Military Medicine 2002;167:451-3.