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

An American Academy of Sleep Medicine Review

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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

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TABLE OF CONTENTS

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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.

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Author/Year/ Citation #	Evidence Grade	Condition (CRSD type or Normal)	Intervention / Intervention Duration	Intervention Timing	Study Description	Total # Participants	Mean Age ± SD (range)	Comparison (Placebo, other test group, etc.)	Primary Outcome
{Adan, 2002 #1888}	2	Unaffected Controls	NA / NA	NA	University students completed the MEQ and results were evaluated for both reliability of the Questionnaire and a gender difference in morningness-eveningness.	2135	22	MEQ	Gendered effect found. Men are more evening-type; women are more morning-type. Highly significant statistically ($p < 0.0001$) but the average difference was small (MEQ = 46.81 + 10.34 vs. 49.61 + 9.71). ~16% of total participants found to be morning-type; ~25% found to be evening-type. High Internal consistency indicates reliability.
{Akaboshi, S, 2000 1889}	4	Non-24hr	Melatonin (0.75 mg) / 7 months	1800 to 1900 for one month, then 2100h for 6 months	Case report of a 5-year old boy with developmental delay of unknown etiology (without blindness) who manifest a non-24-h sleep/wake rhythm (24.9 hr.) for 16 weeks prior to evaluation and treatment.	1	5	Pretreatment and washout (8 days)	Entrainment to a normal schedule.
{Alessi, 2005 #1642}	2	Nursing Home residents w/ EDS diagnosed by daytime observations of eyes closed w/ no purposeful activity for 15% or more of the day and for nighttime sleep disruption by wrist activity (<80% of the night spent in sleep).	5 combined, behavioral strategies – 1) decr in-bed time during the day; 2) 30-mis or more of daily sunlight exposure (>10K lux); 3) structured daytime physical activity; 4) structured bedtime routine; & 5) nighttime noise and light minimization / 5-days	Structured Behavioral Observations at Baseline & at f/u were every 15-mins from 0600 to 2200hrs and hourly from 2200 to 0600hrs for 72-hrs x2 time pts. Behavioral Interventions were from 0800 to 2000hrs; 30-mins of >10K lux sunlight in the AM.	A randomized, controlled clinical trial designed to test the effectiveness of a multidimensional behavioral regimen for improving sleep patterns in nursing home residents w/ daytime sleepiness and nighttime sleep impairment.	Enroll: 62 Compl: 58 (54 w/ valid actigraph data	87.8 +/- 7.8 yrs – Interv group 85.9 +/-10.1yrs - contr	"Usual care" - NS	The combined behavioral regimen produced a small, but sign, improvement in sleep (by shortening nighttime wake episodes) and a 46% decr in observed daytime sleeping at f/u in intervent Ps compared to controls ($p<.001$).
{Alvarez, 1992 #1022}	4	DSPS diagnosed from modified Weitzman and ICSD criteria	Investigations: Sleep logs PSG Actigraphy Treatment: Progressive Phase Delays Phase Advances Melatonin 5 mg/ 4 weeks (Mel)	2200 for melatonin	This case series describes a sample of DSPS patients in terms of their sleep logs, PSG sleep, rest-activity cycle, plasma melatonin and urinary aMT6s. Treatment consisted of progressive phase delays (n=5), phase advances (n=9), and oral melatonin (n=8).	Enroll: 14 Compl: 14 (only 12 consented to extended assessments)	33.2 (18.9) (14-71)	Placebo (for melatonin treatment)	Patients showed varied patterns of sleep-wake times characterized by stable delay (n=10), progressive delay (n=1), or irregular rhythms (n=3). Mean bedtime and sleep latency on sleep logs were 1:21 and 1:50. On PSG sleep latency was 89 minutes. Plasma melatonin and aMT6 were in the normal range.
Ancoli-Israel, 2001	4	DSPS	Administration of MEQ	Single administration	A pedigree of one extended family with symptoms suggestive of DSPS was studied. MEQ 's were administered to all first- and second-degree relatives of a proband identified with DSPS.	51	Proband: 41 y.o. woman. Ages of other subjects not stated.		A total of 51 questionnaires returned, 6 adult biological relatives of 27 showed a preference for eveningness, which is much higher than repor ted in the general population. Both the paternal and maternal branches contained affected individuals, suggesting incomplete penetrance or a multifactorial mode of inheritance.
{Ancoli-Israel, 2002 #1891}	2	Dementia (MMSE=12.8 +/- 8.8)	AM or PM Bright Light (2500 lux) / 2-hrs (Patients averaged 107.8 mins in front of light box) x 10 days	0930-1130 hrs (AM) or 1730-1930 hrs (PM)	Would fragmented sleep in nursing home patients improve bright light. Dementia patients were randomly assigned by block stratification to 1 of 4 tx groups: AM or PM Bright Light, PM Dim Red Light, or Daytime sleep restriction.	Enroll: 118 Compl: 77	85.7 +/- 7.3 yrs (60-100 yrs	Dim Red Light (<50 lux) Daytime Sleep Restriction (for staff interaction)	No actigraphic improvements occurred in nighttime sleep or daytime alertness in any of the tx groups. AM bright light delayed the acrophase of the activity rhythm by 1hr46mins ($p=.022$) and incr the mesor from baseline to tx

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{Ancoli-Israel, 2003 #1890}	2	Alzheimer's Disease (MMSE=5.7ave;4 median; Neuro exam)	AM or PM Bright Light (2500 lux) / 2 hrs	0930-1130 hrs or 1730-1930 hrs	To improve sleep, Alzheimer's patients were randomly assigned by block stratification (morning, evening, or all-day agitation) to 1 of 3 treatment groups: AM (0930-1130 hrs) Bright, AM Dim Red or Evening (1730-1930 hrs) Bright Light.	Enroll: 92 Compl: 83 (Data available on 72)	82.3 +/- 7.6 (61 – 99 yrs)	Dim Red Light (<300 lux) Control	Bright Light (BL) exposure consolidated nighttime sleep by lengthening max sleep bouts across the night compared to baseline. Nighttime sleep increased >30-mins under AM BL and >20-mins for PM BL. PM BL also strengthened the circadian activity rhythm.
{Ando, K, et al. 2002 #2049}	4	Telephone survey	Retrospective sleep questionnaires w/24-hr actigraphy and light input in a random, stratified cohort / ~3-days for sleep logs actigraphy/ light cohort	NA	A telephone survey of sleep complaints in a larger sleep apnea study, with a secondary analysis to examine the prevalence of circadian rhythm disorders (by DSM-IV) in a population aged 40-64 y.o. A stratified cohort (age, gender and ethnicity) was then interviewed in person and completed 3 days of sleep diarys and actigraphy.	Enroll: 417 Compl: 350	51 +/- 7 yrs (40-60)	NA	While 7.4% and 3.1% complained of symptoms suggestive of ASPS and DSPS respectively, only 1-2 subjects, out of 350 surveyed, would have met definitions of ASPS or DSPS by combining complaints w/ actigraphic estimates of sleep timing.
{Archer, 2003 #1893}	3	DSPS diagnosed by MEQ	Assessment of diurnal preference by MEQ / one time	NA	The prevalence of a Per3 polymorphism in subjects identified as having extreme morningness or eveningness by the MEQ as well as additional DSPS patients was studied.	Enroll: 210 Compl: 210 16 additional DSPS subjects	NS for groups other than DSPS (range 16-27)	Volunteers found to be in the upper or lower 7% on the MEQ of 484 screened. An equal number of Ss with an intermediate score were used.	Morningness was correlated with a Per3 polymorphism in the longer allele (5/5) while eveningness correlated with the shorter allele (4/4). 75% of DSPS patients were homozygous for the shorter allele.
{Arendt, 1986 #1392}	2	Jet Lag by event itself – 8-time zone shift west and then east (only eastward direction tested)	Melatonin, 5 mg (in gelatin lactose) / 7 days total - 3-days prior to eastward flight (8 time zones) back home and 4 days post- flight	1800 hrs (local time) prior to eastward travel; 2200-2400hrs (local time) following eastward travel	To determine whether Melatonin is effective in the adaptation to an eastward 8-time-zone transition, healthy adult volunteers were randomly assigned in a double-blind, placebo-controlled study to receive either Melatonin or placebo starting on Day 12 (of	Enroll: 8 (drug) Compl: 8	29-68 yrs old	Placebo	Melatonin was effective in facilitating a subjective adaptation to an eastward advance of 8-time zones in healthy volunteers. None of the 8 Ss taking Melatonin rated their "jet lag" above 17, while 6 of the 9 Ss on placebo rated their jet lag >50 (p=0.009
{Arendt, 1988 #1170}	4	Clinical assessment	Oral mel 5 mg / Trial 1: 14 days placebo, 14 days treatment Trial 2: 30 days placebo, 30 days treatment	2100 - 2400 2300	Two brief clinical trials of mel to a totally blind man with recurrent insomnia, found to have apparent free-running rhythm (24 hr. 41 min.). Sleep logs were kept throughout, and during Trial 2, phase assessment were made with urinary aMT6s.	Enroll:1 Compl:1	59	Single blind, placebo crossover design.	Daytime naps during placebo but no daytime naps while on active treatment.

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{Arizna-varreta, 2002 #947}	2	Jet Lag by intervention	7 time-zones to the west and 8 time-zones to the east by Age: <50 yrs and >50 yrs / 6 days – pre-during, post-(2days before flight, flight itself, 2 days layover, return flight and day after)	Continuous 24-hr recordings	To study the desynchronization betw body rhythms and the environment involved in jet lag, 24-hr activity, skin temp, and heart rate, were monitored continuously over a 6 day protocol in male, trans-meridian airline pilots, where age (<50yrs or >50 yrs), fl	Enroll: 33 Compl: 33 (12 going 7 time-zones west- 5<50 yrs & 7>50yrs; 21 going 8 time-zones east-11<50yrs & 10>50yrs)	38.6 +/- 5.7yrs (31-47yrs); 58 +/- 1yrs (57-59yr) – Westward route 38.7 +/-2.1yrs(35-42-yrs); 55.1 +/- 2.2yrs (53-58yrs)-Eastward route	10 Non-flying control Ss in Madrid throughout study	Westward flights gave clear phase results while eastward flights were more complex. Desynchronization occurred betw the activity-rest cycle and skin temp rhythms w/ a rapid 7hr phase delay going west and a rapid 8hr phase advance going east in the activit
{Baehr, 1999 #1894}	2	Healthy normals	Intermittent Bright Light (IBL) Exposure (5,000 lx) Exercise / IBL=40min alternating with dim light (500 lx, 20 min) Exercise-15 minutes each hour	IBL-1rst 6 hours of first 3 nights Exercise-1rst 6 hours of first 3 nights	Between subjects 2x2 design investigating whether intermittent bright light, intermittent exercise, and a combination of the two can help entrain human circadian rhythms to a night-work, day-sleep schedule.	Enroll: 33 Compl: 33	23.8 + 4.6 y	4 groups: Bright light and exercise Bright light and no exercise Dim light and exercise Dim light and no exercise	The subjects in the bright-light groups had larger phase shifts than the subjects in the dim-light groups, and more bright-light subjects had Tmins that reached daytime S/D. Exercise had no significant effect on the phase shifts. ANOVA on the magnitude of phase shifts revealed a main effect of light [F(1,29) = 8.14, P < 0.01]. There was no main effect of exercise [F(1,29) = 0.16] and no interaction [F(1,29) = 0.35].
{Barnes, 1998 #406}	3	Shift Work	12-hr. Swing Shift Schedule (1 week days, 24-hr changeover, then 1 week nights) Late Fall vs. Spring seasons / 2-weeks in November or 2-weeks in March	1200-2400hrs.-Day shift (control); changeover of 2400-0800hrs.-sleep; 0800-1600hrs.-work; 1600-2400hrs.-sleep; then 2400-1200hrs.-Night shift	To assess the effect of seasonality on adaptation to a night shift associated with differences in both the duration and intensity of natural light exposure, 2 offshore oil drill crews on the same floating rig in the North Sea were studied across an identical 2-week, swing shift regimen at 2 different times of the year – either in November (1 crew) or in March (the other crew).	Enroll: 18 Compl: 18 (11 in November; 7 in March)	(25-48 y.o.) =entire group; 34.6 ± 2.1 y.o.-Nov group; 32.6 ± 1.8 y.o.March group	Day Shift	Both the type of shift and the scotoperiod of the season influenced the degree and direction of circadian adaptation to night shifts in offshore oil workers. Early natural sunlight exposure during the advance portion of the light phase response curve in the March group advanced the acrophase of the aMT6 rhythm by ~5hrs (to 0051hrs. ± 1.7hrs.) on the night shift from a day shift phase position of 0544hrs. ± 0.47hrs. (p<.05). However, the Nov crew showed no phase change in the acrophase of the aMT6 rhythm on the night shift. The aMT6 acrophases for both the Nov and March crews remained in the work period across the night shift. Only subjective sleep duration was different between groups with a shorter subjective sleep duration on the night shift vs the day shift in the Nov group (p=.005). This shorter subjective sleep duration in the Nov group was likely due to a failure in circadian adaptation as the same reported sleep loss was absent in the March group who had aMT6 acrophases that were more in phase with the free time and sleep periods of these subjects.
{Beaumont, 2004 #1896}	2	Jet Lag	Slow release caffeine 300 mg Melatonin 5 mg / SRC – D1-D5 Mlt – D-1 –D3	SRC 0800 Mlt 1600 (D-1), 2300 (D1-D3)	Eastward across 6 time zones	9-SRC 9 - Mlt	35.3 +/- 8.1	Placebo	On N1, Caffeine alleviated objective/subjective-daytime sleepiness but increased Stage 1 sleep and subjective nocturnal awakenings Melatonin improved subjective sleep and subjective daytime sleepiness but not objective daytime sleepiness measures

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{Benhaberou-Brun, 1999 #1897}	3		Urinary melatonin (aMT6s) / 3 days sleep logs 24 hours urine collection	Urine collected every 2 hours	This study examined the relationship between melatonin secretion and sleep quality in nightworkers. Subjects were classified as good or poor sleepers based on questionnaires. Subjects kept 3 days of sleep logs and had aMT6s measured in urine collected every 2 hours for 24 hours. The relationship between sleep questionnaires and logs and melatonin was examined.	Enroll: 15 Compl: 15	34.0 (7.8) (26-55) poor slprs 38.0 (8.9) (26-52) good slprs	Good Sleepers	There was no significant difference in circadian phase of melatonin onset or acrophase in night workers who were poor vs. good sleepers. More of the period of melatonin secretion occurred during the day in good vs. poor sleepers. Sleep difficulties were significantly associated with the proportion of the melatonin period that occurred during the day (r=-.40) and the quantity of UaMT6s excreted during the day (r=-.37). Better sleepers had more daytime melatonin secretion. Those with more daytime secretion also napped less at work and slept longer during the day.
{Bjorvatn, 1999 #2679}	4	No diagnosis	Bright light, 10,000 lux/30 min. per day for 4 days	Individually timed to promote phase delay. Timing delayed 1 hour per day.	Trial of bright light treatment (30 min for first four nights) on adaptation to 14 days consecutive night work on oil platform, and subsequent re-adaptation to day life at home. Outcome measure: Karolinska Sleepiness Scale and Sleep Diary.	Enroll:7 Compl:7	38.9	Cross over design	Modest improvement in subjective adaptation to night work. More pronounced effect on re-adaptation to conventional schedule.
{Boivin, 2002 #421}	3	Shift Work by history of night shift work	Intermittent Bright Light (2000lux) and avoidance of bright light (3243lux) / Light exposure=6hrs. Light avoidance=10 hrs.	First 6 hrs. of 8 hr. night shift After completion of shift	Combined field and laboratory study investigating the efficacy of an intermittent bright light intervention in assisting a group of nurses in their adaptation to night shift work.	Enroll: 9 Compl: 9	C= 42.0±7.2 E= 41.7±8.8	Habitual lighting environments	In the presence of the intervention, circadian rhythms of CBT and salivary Mel cycles were delayed by an average (± SEM) of –9.32 ± 1.06 h and –11.31 ± 1.13 h, respectively. These were significantly greater than the phase delays of –4.09 ± 1.94 h and –5.08 ± 2.32 h displayed by the control group ($p = 0.03$ and $p = 0.02$, respectively). The phase angle between circadian markers and the shifted schedule was reestablished to its baseline position only in the treatment group of workers. These results support the efficacy of a practical intervention for promoting circadian adaptation to night-shift work under field conditions.
{Boivin, 2003 #31}	4	Non-24hr	Brain injury / Followed for 6 months		Case report 39 y.yo woman with a non-24-h rhythm following an automobile accident causing a concussion. Free-running rhythm confirmed with diary, actigraphy and urinary 6-OH melatonin. Possible premorbid schizoid personality . Initiated sleep on the d	1	39	None	Free-running rhythm confirmed with diary, actigraphy and urinary 6-OH melatonin
{Bonnefond, 2001 #422}	4	Shift workers with a mean of 11.3 years of night shift work	Consisted of taking a short rest period during the night shift whenever possible / 1 hour per night shift for 1 year	23:30 to 03:30 hrs.	The purpose of the present study was to test, in a real working environment, whether napping during night work could be acceptable to shift workers, and would not be disruptive of the work demand and the general life quality of the workers.	Enroll: 12 Compl: 12	(30-46)	Naps vs. no naps	A short nap during the night shift can be considered as a positive way to counteract the low level of vigilance that normally occurs during the late part of the night.

Author/Year/ Citation #	Evidence Grade	Condition (CRSD type or Normal)	Intervention / Intervention Duration	Intervention Timing	Study Description	Total # Participants	Mean Age ± SD (range)	Comparison (Placebo, other test group, etc.)	Primary Outcome
{Bonnet, 1994 #426}	3	Healthy Normals	Prophylactic naps Caffeine / 4 hours 200mg	1600-2000h 0130 &0730	The study investigated the ability of a prophylactic nap and caffeine to assist on-call workers to maintain baseline levels of alertness and performance across the night. It hypothesized that naps during the night would permit normal circadian drops in temperature, alertness, & performance, whereas napping prior to the nightshift may prevent this from occurring.	Enroll: 12 Compl: 12	(18-30)	Counterbalanced continuous work periods. Primary IV was compared to 4 1-hour evening naps. Secondary IV (caffeine) was compared to placebo.	Study suggests that individuals who take a prophylactic nap prior to their work shift and use caffeine during their work shift have significantly increased objective alertness according to MSLT results [F(9,99)=3.48, p=.001] and subjective alertness. They also showed increased oral temperature [F(8,88)=3.27, p=.003] and increased performance on complex tasks and on general productivity. Results suggest that taking a nap prepares individuals to deal with the sleep loss that occurs during nocturnal work periods and that caffeine probably reverses some of the normal circadian decline in nocturnal alertness.
{Boulos, 2002 #1899}	2	Jet Lag	3000 lux / 3 hours for 2 nights after trip	1900 D1 and D2	Westward travel x 6 hours with either 3000 lux white light or 10 lux dim red light on D1 and D2. Measure circadian outcomes (by salivary melatonin) and subjective outcomes.	10	27 ± 3.68 (tx) 24.9 ± 2.85 (control)	Dim light (10 lux)	Phase delay of DLMO with bright light > dim light. Other measures (actigraphy, POMS, psychomotor performance, subjective sleepiness, Columbia jet lag scale) not changed
{Budnick, 1995 #441}	3	Shift Workers	Scheduled bright light of 6000-12000 lux and ambient light of 1200-1500lux / At least half of a 12 hr. night shift	Variable	Non-randomized, clinical crossover intervention trial evaluating the use of precisely timed bright light technology in the work environment and darkness at home. The objective was to determine its effectiveness to alter the circadian pacemaker of workers on rotating shiftwork in order to improve sleep patterns and performance. aMT6 measurements for phase assessment.	Enroll: 13 Compl: 13	(24-52) Median=35	Light vs. no light	All 10 workers evaluated with aMT6 had morning melatonin suppression on the night shift and 50% had a statistically significant (p<.05) circadian change. Most findings concerning self-perceived alertness and performance at work and sleep patterns were mixed and inconsistent.
{Burgess, 2003 #956}	2	Normals were used to determine if a treatment could be used to prevent jet lag.	Continuous Bright Light (>3000lux) Intermittent Bright Light (>3000lux, .5 hr on, .5 hr off, etc.) Ordinary Dim indoor light (<60 lux) / Light exposure for 3.5 hours for 3 days.	1st 3.5 hours after awakening	Study was a between-subjects design with 3 groups defined according to the morning light exposure received during an advancing sleep schedule: continuous light, intermittent light, and dim light.	Enroll: 32 Compl: 28 (8 in continuous light group, 11 in intermittent light group, and 9 in dim light group)	Overall = 27.7 + 5.0 (22-43) Dim=25.4+2.6 Int=26.7+4.0 Cont=32.5+6.4	All treatments included phase advancing each subjects sleep schedule by 1 hour/day for 3 days. Treatments differed in their morning light exposure: ordinary indoor light, intermittent bright light, or continuous bright light.	The mean DLMO phase advances in the dim, intermittent, and continuous light groups were .6, 1.5, and 2.1 hours, respectively. The intermittent and continuous light groups advanced significantly more than the dim light group (p<.01) but were not significantly different from each other.
{Buxton, 2000 #1901}	2	Screening Interview – normal Ss by hx	8-hr delay to the sleep schedule and light/dark cycle w/ triazolam, 0.5 mg or placebo given / 5 days	Acute 8-hr delay of sleep schedule to 0700-1500 hrs w/ scheduled meals at 1600hrs, 2030hrs & 0300hrs; triazolam or placebo at 0400hrs prior to the 1st shifted sleep per and at 0700hrs (bedtime) daily thereafter	Two, double-blind, placebo-controlled studies used a 9-day, in-lab protocol (2 mos apart) w/ an 8-hr delay of the sleep-wake and light-dark cycles to determine whether appropriately timed administration of triazolam facilitates adaptation of circadian rhy	Enroll: 6 Compl: 6	24-31 yrs	Placebo	Triazolam was more efficacious than placebo in 6 of 6 Ss on Day 1 (p=.031) and Day 3 (p=.031) of the 8-hr delay, but by Day 5, the effects of triazolam were no longer diff from placebo. Day 1 of the shift showed a sign Circadian improvement (p=.031) on tr

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{Cardinali, 2002 #957}	4	Jet Lag by event itself – 12-time zone shift to the west	Melatonin, , 3 mg (in gelatin), and daily physical exercise/outdoor light exposure / 8-days of daily Melatonin (starting on the plane, in-flight to Tokyo),; Physical exercise outdoors x2 for 5-days (after arrival in Tokyo)	Melatonin - 30-mins prior to bedtime (Tokyo time – 12 hrs delayd from Buenos Aires home time); Physical exercise outdoors - from 0800-1100hrs and from 1300-1600 hrs	To test the efficacy of oral Melatonin and timed physical exercise in outdoor sunlight to speed up the resynchronization of circadian rhythms in soccer players and their coaches after a westward transmeridian flight of 12-time zones.	Enroll: 22 Compl: 22	29.7 +/- 8.7 yrs	NA	Daily melatonin w/ timed physical exercise outdoors resulted in a mean resynchronization rate of reported sleep log parameters that was ~3-times faster (2.13 +/- 0.88 days) than the expected, minimal resynchronization rate of 6-days after a 12-hr eastward.
{Carrier, 1997 #1904}	2	Normal	MEQ sleep logs PSG/Lab study: 2 weeks of sleep logs and \MEQ: 1 administration, Sleep Diary: 2 weeks, Lab Study with PSG: 3 nights	Diary: 2 weeks before lab study	This study examined the relationships beteween M/E, age and sleep. Subjects completed 2 weeks of sleep diaries and the MEQ. Goal: to evaluate four separate issues related to morningness-eveningness (M/E) and sleep quality in the "middle-years" of life: Effect of age on sleep quality, effect of age on M/E, effect of M/E on sleep quality, and the role of M/E in terms of age and sleep. Participants completed a sleep diary and screening before taking the HO-MEQ and getting evaluated for 3 nights of lab study.	Enroll: 110 Compl: 110	(20-59)	Sleep logs --3 groups:: 20's vs 30's vs 40-60's groups	Morningness was significantly associated with earlier habitual bedtime and waketime on sleep logs. Increasing age was correlated with increasing M-type tendencies. Older age was associatied with an increased number of awakenings and decreased sleep efficiency, but was unrelated to sleep latency. Older age resulted in lower amounts of SWS and REM sleep. M/E was significantly correlated with age ($r = .37$, $p<.001$), showing earlier waketime, bedtime, and M-type characteristics on PSG in older participants compared to younger.
{Carskadon, 1998 #1714}	2	School grade- exclusionary criteria were hx of sleep disorders, chronic or current illness, learning disability, psychopathol, or drug use	A 1-hr Advance of school start time from 0825hrs (9th grade) to 0720hrs (10th grade) / 2 weeks of 24-hr home actigraphy and sleep logs followed by 24-hrs in the lab x 2 time pts	2nd half of 9th grade (Spring) and 1st half of 10th grade (Fall). Subgroup of 12 Ss repeated the salivary melatonin component ~5 mos later	Field and laboratory measures examined the premise that puberty is associated w/ a circadian delay and that this delay adversely interferes (less sleep time at night and greater daytime sleepiness) w/ the ability of 9th grade adolescents to phase advance	Enroll: 40 Compl: 32 completed study in 9th grade; 25 completed study in 10th grade	15 +/- 0.5yrs (14- 16.2yrs)	NA	Actigraphic estimate of Sleep Offset in 10th grade was ~15 mins earlier in the boys and ~30 mins earlier in the girls. Across the sexes, TST decr by ~20-mins in 10th compared to 9th grade. A delay of ~40-mins occurred in the sDLMO from 9th to 10th grade.
{Carvalho Bos, 2003 #1906}	2- Studies 1 and 2 Validity/ Reliability 1-Study 3	Jet Lag/Shift Work/Sleep Deprivation (type of work)	Work/Sleep schedule around a night shift (Study 1) and across time zone transitions (Studies 2 and 3) / 2-3 mos – Study 1 4 days – Study 2 4-5 days – Study 3	24 hours	Three field studies were designed to determine whether 24-hr actigraphy can be used to estimate the sleep and circadian system disruption caused by shift work or time-zone transitions and the process of adjustment. Studies 1 and 2 served as validity pilot	Enroll: 8-Study 1; 12-Study 2; 117-Study 3 Compl: 7-Study 1; 12-Study 2; 117-Study 3	NS –Study 1 (22-58 yrs) – Study 2 NS – Study 3	Only Study 2 had a non-traveling control group	24-hr Actigraphy data can be used in field studies as a partial substitute for "gold standard" markers of sleep and the body clock, e.g. PSG, core temperature, and melatonin. The rest-activity cycle shifted 1h for north-south flights consistent w/ the 1
{Claustrat, 1992 #1907}	2	Jet Lag	Melatonin 8 mg / 1 pre, 3 post	Bedtime	Eastward travel (6 time zones) Symptom self rating	15	36.3 +/- 8 35.7+/- 6	Placebo	Global treatment efficacy (self report) improved in Mlt tx group at D8

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{Cole, 2002 #50}	1	DSPS	Bright Light (2700 lux) vs. Dim Light (red light 0.1 lux) - both delivered via a mask / 26 days at home	Phototherapy began 4 hrs prior to and up until wake time.	Randomized parallel clinical trial comparing BL to dim light for DSPS. Study design was 1 baseline week, 4 week treatment phase, and then followed by 4 week follow-up phase. Random assignment to treatment but both treatments included instruction to advance sleep/wake schedule ~1 hr / week, avoid napping, and avoid bright light after 1700.	Enroll: 78 Randomized: 59 Compl: 54 (28 BL; 26 dim light)	25 +/- 6 years, (18-40)	Dim light (0.1 lux red light)	Only in patients with greater delayed phase at baseline did the aMT6 acrophase and sleep onset advance significantly. Morning sleepiness also decreased in this group. The overall treatment was felt to be more effective with BL.
{Comperatore, 1996 #1397}	1	Event – eastward flight across 8-time zones then Even/Night shift (duty – 2100-2400hrs to 0400-0600hrs) at destination	Melatonin, 10 mg Daylight exposure Sleep/Rest Schedule Noise Attenuation/masking During sleep/rest pers / Melatonin - 9 days total (Started 3-days prior to travel, travel day & for 5 days at destination) 5-days for daylight exposure, sleep schedule	30-min prior to bedtime (in-flight dose=1930-2000hrs origination time); After arrival in Middle East – 0400hrs nightly Daylight exposure from 1200hrs to sunset (all other times UVEX sunglasses) Sleep schedule – 0400-0600hrs to 1300 hrs (consistent lunch	In a double-blind placebo-controlled, randomly assigned study, the efficacy of Melatonin and behavioral countermeasures were tested for preventing sleep loss and cognitive degradation in volunteer aircrew men during a rapid- deployment training mission.	Enroll: 29 Compl: 27 (cognitive data); 23 (actigraphy data)	24-41 yrs	Placebo (cellulose)	Melatonin and behavioral countermeasures improved phase, sleep, and cognitive performance/daytime altertness post-deploy compared w/ placebo. Post-deploy, bedtimes demonstrated an ave phase advance of 3.07hrs w/ an ave phase advance of 2.65hr in rise-time
{Crowley, 2003 #472}	2	Healthy Normals	Normal sunglasses (15% transmission); Dark sunglasses (2% transmission); BL (5000lux); M (1.8mg) / Variable Variable 20 min on, 40 min off N/A	In daylight; In daylight; 4-5 light pulses/night); 0830	This study tested the relative contribution and the combined effectiveness of various circadian interventions, namely, bright light (BL), sunglasses (SG), and melatonin (M) to phase-delay circadian rhythms.	Enroll: 67 Compl: 67	23.9+6.2	The 6 groups were (1) D/S + N SG (n = 15), (2)D/S+DSG(n = 12), (3) D/S+DSG+M(n = 13), (4)D/S +NSG+ BL(n = 11), (5) D/S +DSG + BL(n = 9), (6) D/S + D SG + M + BL (n = 7).	Degree of re-entrainment depended upon circadian interventaions in earlier participants. Darker SG helped to increase the phase delay of night-shift participants while M did not.

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{Crowley, 2004 #54}	2	Normal Ss w/ no obvious med, psych, or sleep disorders by clinical interview; MMPI-2; sleep & health questionnaires	5 simulated night shifts/5 day sleep episodes; Oral Melatonin, 1.8 mg/sustained release or placebo; Intermittent Bright Light pulses (~5K lux) across the night shift vs ordinary room lighting (~150 lux); Dark (2% light transmission) vs Normal (15%) Sunglasses / 5, 24-hr periods	Night shifts from 2300hr to 0700hrs in the lab; Day sleep episodes from 0830hrs to 1530hrs; Oral Melatonin or placebo at 0830hrs just prior to day bedtime; Intermittent Bright Light pulses of 20-min duration in a "moving pattern" (NS) across the night shift vs continuous room light; sunglasses on "commute home" (betw 0700-0800hrs)	Data from a previous 14-day study that tested 6 combinations of interventions and 24-hr patterns of light exposure to phase delay circadian rhythms were analyzed to determine how much the phase delay (re-entrainment) improved performance, sleepiness, and mood, during a simulated night shift (x5) in the lab, and increased the duration of day sleep episodes (x5) in the home. Salivary melatonin was collected nightly (starting at 1830hrs or 1900hrs) with a phase assessment (DLMO) on the last night of baseline (Night 8) and the last shift night (Night 14).	Enroll: 67 Compl: 67	23.9 +/- 6.2yrs (18-43 yrs)	Placebo (for melatonin prior to day bedtime); ordinary room light (for bright light pulses across night shift); 5000lux Normal Sunglasses (for the Dark Sunglasses)	The data suggested that those Ss whose final DLMO (5th night of the work shift) occurred after 0130hrs - presumably due to an inferred Temp-min occurring somewhere in the Day sleep episode (~7-hrs after the DLMO) - demonstrated improved alertness, mood, and better performance, across the night shift compared to the Ss whose final DLMO occurred before 0130hrs (putting the estimated Temp-min ahead of the Day sleep episode). The later the estimated T-min in Ss, the later the final wake-up time from day sleep ($p=.003$) and the longer the daytime sleep duration ($p=.023$). Ss who did not re-entrain (phase delay the DLMO) reported ~30-mins less day sleep on the night shift compared to either the partially or fully re-entrained groups, although all 3 groups slept less during the day compared to Baseline night sleep.
{Czeisler, 1981 #2017}	4	DSPS diagnosed clinically and verified by 1-2 months of sleep/wake diaries and 1 night of PSG.	Chronotherapy – 3 hour daily delay of sleep/wake cycle during inpatient study / 5-6 days	Intervention took place following 1-2 months of baseline sleep/wake diaries and 4-7 days of baseline recording/adaption.	Screening included a daily sleep diary for 1-2 months, a screening PSG, a 3+ yr history of DSPS, and discontinuation of all medications Pre-Post study investigating the capability of a non-drug treatment (chronotherapy) to effectively shift the timing of the sleep-wake schedule. The therapy was a progressive daily 3 hour delay in sleep onset over 5-6 days.	Enroll: 5 Compl: 5	NS (range 24-37)	Pre-Post	Chronotherapy was successful in shifting the sleep schedules of all 5 subjects with minimal impact on other sleep parameters. The group average of reported sleep onsets before and after chronotherapy advanced from 4:50 AM to 12:20 AM; wake times from 1:00 PM to 07:55 AM.
{Czeisler, 2005 #1908}	1	Shift Workers – at least 5night shifts/mo of 12hrs. or less; Shift Work Sleep Disorder by ICSD; chronic EDS ≥3-months during night shifts; CGIS rating of at least moderately ill for sleepiness on work nights, Mean MSLT SOL of 6-mins. or less & Daytime PSG SE of 87.5% or less	Modafinil, 200 mg or placebo / 3-months	30-60 mins. prior to the start of each night work shift	In a randomized, stratified by center (28-centers total participating) with the use of permuted blocks of 2, a double-blind, placebo-controlled study of the effectiveness of modafinil in improving alertness across the night was carried out in patients with SWSD over a 3-month period. In-lab 24-hr. admissions occurred pre- (Baseline) and during drug or placebo administration at monthly intervals. Patients with shift-work sleep disorder were given modafinil or placebo to treat SWSD symptoms. Monthly assessments were performed with MSLT, Clinical global impression of change, psychomotor vigilance test, diaries, and daytime PSG.	Enroll: 99 Compl: 72 (completed all 3 months of treatment)	37.5 ± 9.2 yrs-Modafinil; 38.8 +/- 9.1yrs-placebo	Placebo	Electronic Sleep log data showed that 200mg of modafinil reduced the max level of sleepiness across the night shift ($p<.001$) and the level of sleepiness reported on the commute home ($p=.01$) compared to placebo, w/ 25% fewer patients on modafinil reporting accidents or near-accidents ($p<.001$). 74% of the patients on modafinil were rated as at least minimally improved at the final assessment (Clinical Global Impression of Change test) compared to 36% in the placebo group ($p<.001$). However, those on modafinil continued to remain pathologically sleepy w/ a mean MSLT SOL of 3.8-mins. during monthly in-lab assessments (up from 2.1-mins. at baseline, $p<.001$). Overall, modafinil resulted in very modest improvements in nighttime SOL (1.7 vs. 0.3 mins. in baseline vs. treatment), clinical symptoms, lapses of attention, and accidents or near-accidents.

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Daan, 1984	4	Jet Jag	Scheduled light exposure	Subject 1: Light exposure on arrival from 7 to 10 am Subject 1: Light avoidance on arrival from 7 to 10 am	This was a pilot study to test the hypothesis that early morning light should be avoided in the treatment of JLD for eastward travel over 6 – 12 time zones, because light at that time would fall on the phase delay portion of the PRC rather than the desired phase advance portion. Two subjects recorded oral temperatures and maintained sleep diaries before and after a eastward flight involved a 9 h. phase advance.	2	Not stated	Light avoidance vs. light exposure.	Light avoidance in the morning appeared to facilitate re-entrainment to the destination time zone.
{Dagan, 1998 #1029}	4	DSPS diagnosed by an ? unvalidated, sleep-wake schedule structured interview. Psychiatric and Personality Disorder(s) diagnosed by DSM-IV criteria.	None / NA	NA	Consecutive, non-selected admissions to an Adolescent Psychiatric Inpatient unit were administered a sleep-wake structured interview within 4-6 weeks of their hospitalization. Those teens who reported that they were unable to fall asleep before 0200 and had trouble awakening before 1100 were diagnosed with DSPS.	Enroll: 63 Compl: 63	17.4 +/- 2yrs (13-23 y.o.)	NA	Of the 63 patients enrolled, 10 patients (16%) were diagnosed with DSPS. All 10 patients diagnosed with DSPS belonged to a group of 26 patients (38%) with disorders characterized by affective lability (bipolar or schizoaffective disorder and borderline personality disorder).
{Dagan, 1998 #1030}	4	DSPS diagnosed by clinical assessment (by a "senior sleep physician") and actigraphy.	Melatonin, 5 mg / 6 weeks	2200 hrs	Looked to evaluate the effectiveness of Mel treatment for DSPS as well as side effects. Furthermore, wanted to see if improvement was linked to any aspect of the disorder. Treatment and follow-up study of patients given Mel 5 mg qhs for 6 weeks.	Enroll: 61 Compl: 61	30.17+ 11.26 (16-54)	None	96% reported that Mel improved their DSPS. This occurred in < 4 weeks in 93.5% of patients. Of those that reported improvement, 91.5% relapsed to pre-Mel sleeping patterns after Mel ingestion ceased. Immediate relapsers (< 1 week after stopping Mel = 29% of subjects) had more severe DSPS at baseline than delayed relapsers (> 8 weeks after stopping Mel = 27%).
{Dagan, 1999 #1028}	4	All CRSDs with diagnosis made by physician based on ICSD criteria. In addition, the authors imposed their own criteria of difficulty going to sleep before 2:00 and waking up before 10:00.	Detailed clinical sleep interview. / 1 week of actigraphy.	NA	Two studies were conducted to refine diagnostic criteria for CRSD and suggest more sensitive diagnostic measures. Study 1 was a case series of 322 CRSD patients who underwent a detailed sleep interview. Study 2 compared a random subset of 50 of these CRSD patients to 56 age, gender and socioeconomic matched controls.	Study 1 Enroll: 322 Compl: 322 Study 2 Enroll: 50 Compl: 50	Mean NS (3.5-68) Mean NS (18-56)	NA	DSPS was most common diagnosis (83.5%). 90% of patients reported onset during childhood or adolescence and 10% as adults, supporting the role of age as a risk factor. Other CRSD diagnoses were reported at rates of: ASPS at 1.2%, irregular at 1.9%, non-24hr at 12.1%.
{Dagan, 2005 #2009}	4	Clinical assessment	Actigraphy; salivary Mel, and oral temperature as phase markers/Actigraphy for 3 weeks. Mel and temperature for 24 hrs.	NA	Case report of a 14 y.o. boy who had been diagnosed with depression, schizotypal personality disorder, and learning disabilities. Re-evaluation, including PSG and wrist actigraphy, was done because of symptoms of recurrent sleepiness.	Enroll:1 Compl:1	14	Published norms	A previously missed diagnosis of non-24-hour CRSD was made and treatment was initiated.

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{Dahlitz, 1991, #1909}	2	DSPS by clinical criteria	Melatonin 5mg or placebo / 4 weeks treatment, 1 week washout, 4 weeks treatment	2200 (5hrs before mean sleep onset time)	This was a randomized double-blind, placebo-controlled cross-over study in which 8 subjects with DSPS were treated with both placebo and Mel for 4 weeks each, with a 1 week washout in between treatments. Baseline measurements were established with 4 weeks of sleep diaries prior to treatment along with PSG and phase markers (plasma Mel levels and aMT6).	Enroll: 8 Compl: 8	34.63 ± 18 (14-61)	Placebo phase vs. Mel phase	During Mel treatment, sleep onset time advanced by 82 mins (p=.002), and wake time advanced 117 mins (p=.001) compared to placebo. Mel helped advance bedtime and wake time, but didn't improve overall daytime alertness.
{Daurat, 2000 #1910}	2	Jet Lag	Zoplicone 7.5 mg / D1-D4	30 minutes before bedtime	Westward travel (5 time zones) Measured actigraphy, temp cycle and self-reported sleep quality	36 total subjects, but ony 24 analyzed	51.2+/-2	Placebo	Increased sleep duration by actigraphy and improved sleep quality rating on first post-flight night with treatment, faster resynchronization of rectal temperature rhythm on D2
{Dawson, 1991 #1911}	2	Healthy normals	BL exposure (6000lux) / 4 hours	2400-0400 on the first night	Randomized, controlled trial examining the extent to which appropriately timed exposure to BL would accelerate the phase delay of core body temperature	Enroll: 6 Compl: 6	(21.2+3.1)	Normal light exposure all 3 nights of 150-200 lux	Both groups showed a significant delay from baseline, however the mean phase position of the BL group was significantly later [1053 hrs vs. 0737 hrs, $t(11)=4.9$, $p<.01$). Mean SE in the treatment group NS different from normal night sleep.
{Donaldson et al,1991 # 2680}	2	Jet Lag	Temazepam 20 mg/5 nights	qhs night of travel and qhs x 4 nights after travel	11 hour eastward flight x 2 (first Sydney to London, second London to Sydney). 7 day break between trips. Group took either 20 mg temazepam or placebo on first flight and then crossed over on second (and took for 4 nights after trip). Outcomes: sleep diary, performance tasks (reaction time, pencil and paper tests, circadian rhythm measures (CBT, aMT6, Urinary cortisol).	Enroll: 10 Compl:10	28-53 y.o. (mean not stated)	Placebo	Subjective sleep: ss better sleep with temazepam with decreased SOL and decreased awakenings.
{Dowling, 2005 #1640}	2	Nursing home staff identified individuals with disturbed rest-activity rhythms	Morning bright light >2500 lux / 10 weeks	9:30-10:30 am	This study examined the effects of morning bright light, compared to usual room light, on nighttime sleep, daytime wakefulness, and rest-activity rhythms in nursing patients with Alzheimer's disease. Subjects were randomized to treatment condition.	Enroll: 46 Compl: 46	84 (10) (60-98)	usual room light (150-200 lux)	There were no significant effects of morning light treatment on nighttime sleep or daytime wakefulness. There were trends toward significance for amplitude and acrophase of rest-activity rhythms. There was some evidence that those with the most disturbance showed the most improvement.
{Eastman et al, 2005, # 2339}	2	Normal	Advancing Sleep Schedule/Advancing sleep schedules by 1 or 2 hours for 3 days	PM – earlier bedtime AM- intermittent bright light	15 subjects advanced sleep schedule by 2 hours per day and 11 by 1 hour per day. Advancing went for 3 days with use of PM lights out and AM intermittent bright light. Over the duration of the protocol, compared actigraphy, sleep diaries, questionnaire responses and DLMO.	15 in 2 hour group. 11 in 1 hour group.	26.6 +/- 4	2 hour vs. 1 hour advance comparison	DLMO advanced by 1.9 hours in the 2 hour group and 1.4 hours in the 1 hour group (not ss).

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{Eastman, 1994 #497}	2	Normal	Bright Light (5000lux) or Dim light (500lux)/6 hours for 2 nights Welder's Goggles (.35 transmission)/Home travel time	Around the time of the baseline temperature minimum During travel home window	2x2 Designed study comparing the relative contributions of bright light during the night shift and dark goggles during daylight for phase shifting circadian rhythms during shift work.	Enroll: 50 Compl: 50	(19-38) Median=24	2x2 Design with factors including bright light, dim light, goggles and no goggles.	The group that received bright light and goggles underwent the largest phase shift (Mean=7.9 hrs) whereas the group kept in dim light and without goggles underwent the smallest (3.2 hrs). Both the bright light (F=6.426, p=.015) and goggles (F=4.497, p=.039) were important for providing temperature rhythm phase shifts.
{Eastman, 1995 #1914}	2	Healthy Normals	BL (5000lux) / 0, 3, or 6 hours	Around the time of baseline Tmin	Field study comparing the impact of varying durations of BL exposure (0, 3, or 6 hours) on phase shifting.	Enroll: 33 Compl: 33	(18-44) Median=24	Duration of BL exposure of 0, 3, or 6 hours	The main effect for BL duration was significant [F(2,43)=22.274, p<.0001], however the phase shift in the 6-hour group NS from the 3-hour group.
{Edwards, 2000 #1916}	2	Jet Lag	Melatonin 5 mg / D1-D4	1800-1900 (D-1) 2200-2300 D1-D4	Eastward travel (10 time zones) Self-reported jet lag sxs/questionnaire, grip strength, intramural temperature	13	40 +/-13 40 +/- 12?	Placebo	There was no difference between groups for grip strength, intra aural temperature, jet lag VAS, or jet lag questionnaire
{Fetveit, 2003 #1918}	3	Disturbed sleep based on actigraphy	Bright light therapy (6000-8000 lux) / 2 weeks	8:00-11:00 am	This study examined the effects of light treatment on sleep in nursing home residents with dementia. Sleep was monitored with actigraphs for 2 weeks pretreatment and 2 weeks of treatment. Treatment was for 2 hours each morning and fell between 8:00 and	Enroll: 18 Compl: 11	86.1 (8.9) (72-101)		There were significant improvements in sleep efficiency, SOL, WASO and early morning awakenings. There was no effect on time of peak activity (acrophase).
{Folkard, 1990 #1216}	4	Clinical assessment	Melatonin 5 mg / 30 days placebo 31 days melatonin	21.5 h. 23.5 h	Case study of a 60 y.o.totally blind man given a single-blind trial of melatonin or placebo at bedtime.	Enroll: 1 Compl: 1	60	Single blind, placebo-controlled, crossover.	Stabilization of sleep onset times with elimination of daytime naps.
{Folkard, 1993 #522}	3	Healthy adults on a rotating shift schedule	Mel, 5 mg / 6 successive day sleeps and 4 successive night sleeps x2 separate blocks	0642hrs. ± 7.6mins. (SEM)-Day bedtime or 0039hrs. ± 12.7mins. (SEM)-Night bedtime	To study the efficacy of oral Mel in phase shifting/re-aligning the circadian system to a rotating shift schedule, a group of police officers were randomly assigned to a double-blind, placebo-controlled, crossover study to receive Mel or placebo across 6 successive day sleeps while on night shifts and 4 normally timed night sleeps while on day shifts.	Enroll: 17 Compl: 7-completed melatonin & placebo phases; 8-completed just Baseline	29 ± 7 y.o. (21-48 y.o.)	Placebo; Day sleep periods compared to normal night sleep periods	Results of this preliminary study suggest that oral Mel, 5 mg, taken prior to a day sleep episode has beneficial effects on subsequent reported sleep and alertness on the night shift. Day Sleep Quality was rated higher after Mel (p=.003) compared to either placebo or baseline and reported Day Sleep Duration increased (p=.026). What is unclear from this study is whether this was simply a hypnotic effect of the Mel vs a circadian effect. Data from the normal night sleeps were too limited for conclusions other than a similar improvement in reported Sleep Quality on Mel compared to placebo or baseline (p<.001) with no significant effects on reported sleep onset, offset, or duration.

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{Foret, 1998 #526}	2	Healthy normals	Bright light intensity (1000lux vs. 100lux) / 24 hours	18:00-08:00	8 healthy subjects were studied during 39-hour spans in which they remained awake. During 1 experiment, subjects were exposed to 100lux of light between 18:00 and 08:00. During the 2nd experiment they were exposed to 1000 lux during the same time span. The purposes of this study were to simulate a long night shift (12 hours) and evaluate the effects of all-night exposure to light on the main circadian physiological markers.	Enroll: 8 Compl: 8	(19-28)	Dim light (100lux) compared to bright light (1000lux).	The "1000 lux condition" resulted in marked suppression of melatonin secretion (p<.04). With regard to core body temperature minimums, differences between groups during the sleep deprivation night were significant for average minimum core temperature (p<.04) and average time of CBT (p<.01). In this study, nocturnal exposure to 1000 lux attenuated the decrease in core temperature. This study suggests that nocturnal exposure to lower light intensities is capable of modifying circadian variables more than previously estimated.
{Garbarino, 2004 #1920}	3	Shift working police drivers	Sleep behaviors including napping / NA	NA	This study involved both a retrospective and prospective component where shift-working police officers who had been involved in an accident were asked via telephone interviews to recall their sleep behaviors prior to the accident. The aim of this study was to evaluate the influence of sleep behavior on shift-work car accidents and the efficacy of napping behavior as a self-initiated counteractive strategy to sleepiness. Study evaluates the role naps play in preventing sleep-related accidents in Italian shift-working police drivers.	Enroll: Retro Arm: 1195 Pro Arm: 90 Compl: Retro Arm: 1195 Pro Arm: 84	Retro= 28+6 Pro= 29+4	NA	The study seems to confirm that napping before working a night shift is an effective countermeasure to alertness and performance deterioration associated with night work. Moreover, this self-initiated behavior could have a prophylactic efficacy in reducing the number of car accidents. Our data indicate that napping behavior before night work can be an effective countermeasure to alertness and performance deterioration in a large sample and in real-life conditions. Data concerning the usual sleep and nap timing reported by shiftworkers involved in this study allowed us to estimate the sleep pressure at the time of accident. Occasional deviations from normal habits could have increased sleepiness and fatigue and, consequently, the risk of accidents. In spite of this possible underestimation of sleepiness, our data show that, in the mean of a rather large sample, the risk of having an accident is related to the homeostatic sleep pressure and could be reduced by adopting a nap behavior.
{Guillem-inault, 1993 #1123}	4	Dyschronosis in children with moderate to severe MR diagnosed clinically in which previous treatment with hypnotics or behavior therapy had failed. Nocturnal sleep disruption was verified by sleep logs or sleep logs and actigraphy	Bright light (either outside sunlight in the spring and summer or artificial [minimum 4000lux] in the cloudy and rainy season) and behavioral program. / 45 minutes of bright light each morning for 8 months	Every morning at 7:00am	14 children with moderate to severe MR and who had failed treatment of their sleep disturbance with medication and/or behavior therapy were referred to a sleep disorders center and provided a treatment regime consisting of bright light therapy.	Enroll: 14 Compl: 14	Mean Age=2.9 yrs (9months-4 years)	Pre-Post	5 out of 14 patients responded to treatment. Analysis of responder's sleep logs indicated a consolidation of nocturnal sleep and a statistically significant difference in nocturnal and 24-h TST from baseline.
{Hack, 2003 #2012}	2	Non-24hr (blind)	Melatonin: 0.5 mg daily for one full circadian beat cycle / 21-81 days	2100	A placebo-controlled (crossover) trial of melatonin given to totally blind subjects with free-running, non-24-hr circadian rhythms with the aim of entrainment. Urinary cortisol and aMT6s (the urinary metabolite of melatonin) were assessed to determine ci	10	48.2 + 12.5 (32-65)	Placebo crossover design	Six subjects entrained (2 after an intial lag), 1 had shortened period, and 3 continued to free-run

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{Harma, 1990 #561}	4	No diagnosis	Age/Two consecutive days	Every two hours while awake	Health female nurses on rotating shifts measured oral temperature and rated sleepiness (100 mm analog scale) acrophases for first two days after shift change.	Enroll:145 Compl:145	20-49	Sample stratified by age: 22-29, 30-39,40-49	Temperature rhythms shifted in all groups. No effect of age.
{Harma, 1994 #564}	2	No diagnosis	Age/4 days	Serial sampling	Subjects spent five days and nights in a sleep laboratory setting mimicking their usual schedule and duties. After one day shift, they "worked" three night shifts. Outcome measures: Serial rectal temperature and salivary melatonin; sleep duration and structure (charge sensitive bed); and subjective measures of sleep and alertness.	Enroll:14 Compl:14	Young: 24 (19 – 29) Old: 57 (53-59)	Young vs. old	During the first and second nights, older workers cope better, but after three nights, aging associated with increased sleepiness due to insufficient circadian adjustment. as estimated by the oral temperature rhythm.
{Hart, 2005 #1923}	2	Healthy Adults screened by "comprehensive" medical & psych evals	Simulated Rotating Shift Schedule in Lab; Zolpidem, 10 mg/placebo – Methamphetamine, 10 mg/placebo - Zolpidem/methamphetamine / 21-days=Rotating Day & Night Shifts (shifts alternated 3x across 21-day study w/ 1-day rest inbetw); 15-days on drug/placebo	Day Shift=0830hrs to 1730hrs w/ bedtime at 2400hrs (8.25hr sleep per); Night Shift=0030hrs to 0930hrs w/ bedtime at 1600hrs (8.25hr sleep per); Methamphetamine/ placebo given 1hr after waking (0915hrs or 0115hrs) from sleep on either shift; Zolpidem/ placebo given 1hr prior to bedtime (2300hrs or 1500hrs) on either shift	A double-blind, placebo-controlled study assessed the acute effects of methamphetamine and the next-day effects of zolpidem alone and in combo w/ methamphetamine on performance, mood, and sleep, in healthy normal adults undergoing a simulated, rotating shift schedule across 21-days in a residential lab context.	Enroll: 8 Compl: 8	31.6 +/- 7.8 yrs	Placebo	Reported sleep durations were 2-hrs less prior to the 1st simulated, night work shift compared to that reported following the 1st day shift on placebo, w/ no other sign diffs in reported sleep parameters by either shift or drug condition. Methamphetamine alone, improved performance and mood on the night shift, while zolpidem alone, disrupted mood with limited improvement in next-day performance, and the methamphetamine-zolpidem combo had minimal effect on either mood or performance.
{Hashimoto, 1998 #1925}	4	Clinical assessment	Sleep log, Phase assessment with plasma mel, mel administration / Two year assessment, (data presented for 8 months), Five weeks of treatment	Daily mel, 1 – 3 mg at 21:00	Case report of totally blind subject who was documented to have free-running mel rhythm but normal sleep schedule. Two years later subject developed sleep disturbance and mel treatment was given with in an attempt to entrain the free-running rhythm	Enroll:1 Compl:1	24	None	Free-running mel rhythm shown to be a risk factor for eventual sleep disturbance (Non-24-hr CRSD).
{Hashimoto, 1998 #1925}	4	Clinical assessment	Sleep log, Phase assessment with plasma melatonin, melatonin administration / Two year assessment, (data presented for 8 months), Five weeks of treatment	Daily melatonin, 1 – 3 mg at 21:00	Case report of totally blind subject who was documented to have free-running melatonin rhythm but normal sleep schedule. Subsequently (two years later) developed sleep disturbance. Melatonin treatment was given with in an attempt to entrain the free-running rhythm.	Enroll:1 Compl:1	24	None	Free-running melatonin rhythm shown to be a risk factor for eventual sleep disturbance (Non-24-hour CRSD).
{Hatfield, 2004 #1661}	2	Dementia by DSM-IV & NINCDS-ADRDA criteria; MMSE=20-30 (13Ss) for Mild (CDR=1.0) & MMSE=19-30 (14Ss) for moderate (CDR=2.0) dementia	Mild vs Moderate dementia / 28-Daya	Continuous 24-hr sampling of activity counts; Saliva samples every 4hrs from 0800-2400hrs x 2-days during weeks 2 & 4	Cross-sectional (mild vs moderate) and longitudinal (28-days w/ 1yr f/u) actigraphy and serial sampling of salivary cortisol (for 2-days during weeks 2 & 4 and again 1yr later) were used to compare the impact of Dementia.	Enroll: 27 Compl: 27 (14 had f/u study 1-yr later for test/re-test reliability)	68.5yrs (60-82 yrs) =Dementia Ss; 71.8yrs (66-84 yrs) =Healthy Elderly	Normal Elderly Ss	Increasing severity of dementia was assoc w/ progressive disorganization and decreasing amplitude of the daily pattern of activity/rest in Ss w/ Alzheimer's disease living at home.

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{Hayakawa, 1998 #1927}	4	Non-24hr (sighted)	Bright light (>2500 lux) Melatonin (1 mg) / Light: 31 days. Melatonin duration of treatment not reported.	Light: Starting at 13:00, the gradually advanced to 09:00. Melatonin: 21:00	Case report of 20-year old man with non-24-h sleep/wake schedule since age 16, documented by diary. Dropped out of school at age 17 because of sleep disorder. Light therapy conducted in hospital. Melatonin treatment as outpatient	1	20	Pre-treatment (patient was own control)	Successful entrainment to both light therapy and melatonin. Improved sleep and daytime alertness.
{Hayakawa, 1998 #1927}	4	Non-24hr (sighted)	Bright light (>2500 lux) Melatonin (1 mg) / Light: 31 days. Melatonin duration of treatment not reported.	Light: Starting at 13:00, the gradually advanced to 09:00. Melatonin: 21:00	Case report of 20-year old man with non-24-h sleep/wake schedule since age 16, documented by diary. Dropped out of school at age 17 because of sleep disorder. Light therapy conducted in hospital. Melatonin treatment as outpatient	1	20	Pre-treatment (patient was own control)	Successful entrainment to both light therapy and melatonin. Improved sleep and daytime alertness.
{Hayakawa, 2005 #2010}	4	Clinical assessment	Semi-structured psychiatric interview to obtain DSM-III diagnoses. Sleep logs. Actigraphy / Four to Six weeks of observation.	N.A.	Case series of Non-24-hour CRSD (N = 57) diagnosed after completing sleep logs and actigraphy. Psychiatric evaluation done on each diagnosed subject. The population was characterized statistically and the relationship between sleep patterns and other v	Enroll: 57 Compl:57	20.2 + 7.0 (range not reported) 26.2 + 8.5	None	Psychiatric disorders preceded the onset of Non-24-hour CRSD in 28%. Of the remaining patients, 34% developed major depression after the onset of Non-24hr.
{Hilliker, 1992 #1928}	3	Normal Ss screened by physical exam, medical hx, lab tests, PSG & sleep hx	Median split of MEQ scores for Morningness (scores of 57-74) vs Non-Morningness (scores of 25-52); Simulated Night Shift in the lab / 5 simulated night work shifts in the lab & 4 daytime sleep episodes at home	2230hrs to 0700hrs- lab night shifts; 0900hrs to 1700hrs-home day sleep episodes	The Placebo condition data - in response to morningness (MT) vs. non-morningness (non-MT) tendency - are reported from a larger, counterbalanced, cross-over, double-blind study to examine the effect of triazolam/placebo on a simulated night shift schedule during 2 blocks of 5 nights in the lab (1 w/ triazolam and 1 w/placebo).	Enroll: 15 Compl: 15 (7-MT's and 8-non-MT's)	Mean=41 yrs (32-53 yrs)	Non-Morningness	The results of this study suggest poorer adaptability to night work reported by morning types (MT), w/ MTs being sleepier during a night shift compared to non-MTs. Both physiological sleep tendency (MSLT) and reported sleepiness (SSS) were greater across much (at 0025-0030hrs, 0225-0230hrs, and 0425-0430hrs) of a simulated night work shift in MT compared to non-MT, despite the data from actigraphy that showed no sign diff in Day sleep episode duration betw the MTs and the non-MTs. Subjective Day sleep length (by log), however, was estimated to be much less (255.7mins) in the MTs compared to 342.5mins estimated by the non-MTs (p=.01).
{Hirschfeld, 1996 #972}	2	Event itself – acute 8-hr advance of sleep-wake and light-dark cycles	Zolpidem, 10mg Bright Light (>2000lux) / 2 days for zolpidem or Bright Light	1445hrs (15 mins ahead of bedtime) for zolpidem or placebo; 2300hrs (Day 2) to 1500hrs (Day 3), then 2300hrs (Day 3) to 1500hrs (Day 4) for the Bright Light or dim light	Three separate, randomized lab studies in the same group of normal Ss tested whether bright light exposure and pharmacological sleep facilitation (zolpidem) at bedtime would rapidly advance the 24-hr profile of plasma TSH following an acute, 8-hr advance	Enroll: 8 Compl: 8	21-33yrs	Placebo Dim light (+/-200lux)	Both Bright Light (BL) exposure and zolpidem limited TSH secretion rebound upon awakening following the 1st shifted night. On placebo in dim-light, the shifted sleep during usual daytime hrs failed to inhibit TSH levels combined w/ a dramatic TSH secretio

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{Horowitz, 2001 #1929}	2	Healthy Normals	BL (2500lux) Fixed sleep schedule(FSS) / BL=2.5 hours FSS=n/a	BL= 0230-0500 FSS=0800-1600	Study tested the hypothesis that circadian adaptation to night work is best achieved by combining bright light during the night shift and scheduled sleep in darkness.	Enroll: 54 Compl: 52	26.99+6.22	This design yields four groups of subjects: BL &Fixed Sleep, Room Light & Fixed, BL & Free Sleep and Room Light & Free Sleep	Study data demonstrate that scheduling of sleep/ darkness should play a major role in prescriptions for overcoming shift work-related phase misalignment. Both bright light and a fixed sleep/dark schedule significantly phase delayed sDLMO
{Ito, 1993 #1043}	4	DSPS diagnosed by ICSD criteria	Chronotherapy with or without supplemental pharmacotherapy, pharmacotherapy alone, vitamin B12, or other. Pharmacotherapy was triazolam (n=6) and/or vitamin B12 (n=5). / NS	Variable	This is a case series of patients with DSPS who had undergone some form of treatment. Response to treatment and the condition after treatment were investigated with the use of hospital records and mailed questionnaires 3-11 years after treatment.	Enroll:14 Compl:14	27.0+5.2	Treatments compared to one another	Six patients treated with chronotherapy, though three were then given triazolam after chronotherapy and all showed full recovery after treatment. In three of them, the DSPS relapsed one year afterwards. Four of five patients treated with pharmacotherapy showed a partial recovery with one of these relapsing one year after treatment. Three patients were treated with "other" sleep schedule changes with variable responses.
{Iwase, 2002 #1930}	3	DSPS Non-24hr (sighted)	Assessment of polymorphisms, of the hClock gene with PCR amplification / One sample		Investigation of the frequency of polymorphisms of the human Clock (hClock) gene in DSPS and non-24-hr patients compared to unaffected controls.	DSPS = 59 Non-24hr = 37	DSPS: 28.0 ± 9.7 Non-24hr: 27.0 ± 8.3	Unaffected controls	The frequencies of the R533Q and H542R alleles in patients with DSPS or N-24 were very low and not significantly different from those in control subjects.
{James, 1998 #596}	2	Rotating Shift workers	Mel, 6 mg / 4-6 consecutive night shifts x 4 treatment cycles (2 Mel, 2 placebo)	30-mins. prior to each Day sleep episode while on the night shift	To determine whether oral Mel is effective in helping rotating, night shift workers minimize circadian rhythm disruption, Mel or placebo was taken prior to day sleep episodes in a double-blind, single-dose, randomized crossover study in a group of EMT/paramedic volunteers over 4 blocks of treatment cycles with 4-6 consecutive night shifts.	Enroll: 22 Compl: 22	29 ± 8 y.o. (20-41 y.o.)	Placebo	The only significant clinical finding of oral Mel prior to day sleep was fewer interim awakenings during the subsequent day sleep episode compared to placebo (p=.011). Although oral Mel improved sleep quality (~12%) compared to placebo, this improvement was not statistically significant and was without concomitant improvements in night shift performance.
{Jamieson AO et al. 2001, 2706}	1	Jet Lag	Zolpidem 10 mg vs. Placebo/3 or 4 consecutive nights (4th optional)	First nighttime sleep after travel	Multi-center, double-blind randomized, placebo-controlled, parallel-groups study of 138 adult experienced travelers while on regular eastward transatlantic assignments originating in the US. Subjects randomized to 10mg zolpidem or placebo for three (optionally 4) consecutive nights starting with the first nighttime sleep after travel. Sleep assessed with daily questionnaires.	Enroll: 138 Compl:133	Zolpidem 45.4 Placebo 44.3	Placebo	Zolpidem group had significantly better sleep than placebo on fist night (TST, $p<0.05$), with trend in same direction on second night of treatment (TST, $p<0.053$).

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{Jorgensen, 1998 #600}	2	Shift Work	Sublingual melatonin 10mg / 2-5 nights depending how night shift schedule	In the morning at the end of a night shift	Double-blind, placebo-controlled trial to determine whether exogenous melatonin improves daytime sleep and nighttime alertness in physicians working the nights shift. Subjects were given melatonin or placebo in the morning after each night shift. All subjects had trials of both placebo and melatonin with a minimum of 5 days in between. Subjects kept sleep logs each day. Alertness was measured using the Stanford Sleepiness Scale (SSS) completed at the beginning, middle and end of each nightshift and with VAS scales.	Enroll: 20 Compl: 18	32 range 25-40	Placebo	There were no significant differences between melatonin and placebo on measures of sleep or nighttime alertness. There was a trend towards an increase in alertness at the end of the nightshift.
{Kamei, 2000, #1932}	4	DSPS and non-24	Melatonin / 0.3-1mg for 3 months(?)	Melatonin taken 5, 3, and 1hr prior to bedtime	46 patients with either DSPS or non-24hr sleep-wake syndrome took melatonin 3 times prior to sleep. 17 patients (12 DSPS and 5 non-24) responded favorably to melatonin	46	23	DSPS vs. Non-24	40% effectiveness in having DSPS patients respond with less total sleep time, as well as 31.2% of the non-24 group. No significant difference between the non-24 and DSPS groups. 40% effectiveness in having CRSD patients respond with less total sleep time.
Katzenberg, 1998	2	Unaffected	Measurement of polymorphisms	Single sample	A single nucleotide polymorphism located in the 3' flanking region of the human CLOCKgene was investigated as a predictor of diurnal preference (MEQ scores) in a population-based random sample of 410 normal adults.	410	50.0±7.9	Correlated incidence of polymorphism MEQ scores.	Subjects carrying one of the two CLOCKalleles, 3111C, had a significantly lower mean MEQ scores.
{Kayumov, 2001 #1936}	1	DSPS diagnosed according to ICSD criteria by a psychiatrist-sleep specialist.	Melatonin 5 mg / 4 weeks melatonin, 1 week washout, 4 weeks placebo in random order	Between 19:00 and 21:00 chosen by each patient. Mean time 21:03	This double-blind, placebo-controlled, crossover study examined the effects of 5 mg Mel on sleep and daytime alertness in patients with DSPS. 2 nights of PSGs were done at baseline, after 4 weeks of Mel, and after 4 weeks of placebo. For PSGs, only the second night data was analyzed. aMT6 and sleep questionnaire data was also collected after each phase.	Enroll: 22 Compl: 20	35.6 (14.0) men 30.8 (12.4) women	Placebo	There was a significant decrease in PSG SOL in the Mel phase (20.2 min) compared to the placebo phase (58.9 min). There were no other significant effects on sleep. At the end of the Mel phase compared to the placebo phase, SSS and composite fatigue scores were no different. aMT6 levels reflected Mel ingestion.
{Kerkhof, 1996 #1937}	4		Sleep log / 2 weeks		This study examined the relationship between temperature rhythms and morningness-eveningness in both constant routine and entrained conditions. Subjects were chosen who scored extremely high or low on the MEQ. Subjects maintained a sleep log and measured oral temp and subjective alertness every 3 hours (while awake) for two weeks. A subset (5 M-types and 5 E-types) wore an actigraph for 11 days. Subjects then underwent a 24h constant routine during which CBT was measured.	Enroll: 14 (7 M-types, 7 E-types) Compl:14:	M-types: 23.9 (22-2), E-types: 23.6 (20 - 28)	Oral temperature	In entrained conditions: Maximum CBT (oral) was 4.6 hours earlier in M-types vs. E-types. The midpoint of the sleep period and maximum alertness were also significantly earlier in M-types. Sleep log findings were corroborated by a significant group difference in actigraphy (acrophase). During constant routine, CBT occurred 2.1h earlier in M-types vs. E-types types.

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{Klein, 1993,#1938}	4	Non-24 hr	Blind / Diary for 15 years In laboratory for 3 months.	NA	Case study of a 63 y.o. man, totally blind since age 15, that had kept a remarkable sleep diary for 15 years documenting periodic bouts of insomnia and daytime somnolence. He was studied in the laboratory for 3 months with nightly PSG, continuous core bo	1	63	None	Bouts of insomnia and daytime sleepiness were related to periodic desynchrony between his free-running circadian rhythms and the timing of sleep
{Kokkoris, 1978 #2022}	4	Clinical assessment	Continuous CBT monitoring, sleep logs / 76 days of temperature monitoring, 6 months of sleep logs	Daily monitoring	This is a case study of a 34 y.o. man with an eight year history of non-24-hr CRSD with an approximate sleep schedule period of 24.33 hr.	NS	34	Published norms	During the study period, the sleep and temperature rhythms oscillated with an observed period of 24.8 hr.
{Lapierre, 1995, #1261}	4	Non-24hr	Melatonin 0.5 mg / 20 months	17:30 (2.5 h. before desired bedtime) for 4 days, then 19:30 for duration	Case report of a 5 y.o. girl, blind since birth, with severe mental retardation related to partial trisomy 22. She exhibited a non-24-h sleep wake cycle (diary data) with an average period of 25.2 h. Prior treatment with behavioral methods and hypnotics	1	5		Improved sleep schedule
{Lavie, 1990 #2681}	2	Jet Lag	Midazolam 7.5 mg/5 nights	qhs x 4 nights after travel	6 hour eastward and westward trips separated by 14 days. 18 subjects took trips and divided as follows: Group 1 (6): midazolam on eastward and placebo on westward Group 2 (6): placebo on eastward and midazolam on westward Group 3 (6): midazolam on both trips Outcomes: actigraphy and sleep quality questionnaire	Enroll: 18 Compl: 18	30-55 y.o. (mean not stated)	Placebo	Actigraphic sleep: ss improved TST with midazolam on nights 1 and 3 on eastward travel only and in SE on eastward travel only.
{Leger, 1996, 1373}	2	Non-24hr ISWD	PSG /		Totally blind subjects with free-running circadian rhythms were studied with PSG for one night. Reduced TST and other sleep abnormalities were associated with the complaint of daytime sleepiness and poor sleep in blind subjects.	26 totally blind with free-running rhythms	44.3 + 12.1 (26 - 67)	Matched for age, sex, marital status	Blind subjects had reduced TST, longer SOL, reduced SE and reduced REM.
{Lewy, 1983 #2015}	4	Blind (n=9 without light perception)	Plasma mel / 24 hrs. during first part, then 24 hrs. q week X 4 weeks	Weekly assessment (N = 2), Single assessment (N = 8)	10 blind individuals (9 without light perception) underwent analyses of Mel circadian secretory rhythms. Activity-rest cycles of all subjects seemed to be entrained to day-night cycle.	10	36±NS (26-62)	Sighted subjects (n=2f, 20 and 21 y.o.)	6/10 blind subjects had unusual Mel secretory patterns. 3 subjects began secretion atypically early in the evening, and 3 began secretion unusually late at night, continuing into late morning or early afternoon. Of the 2 subjects studied longitudinally, 1 appeared to have 24-hr. period in secretory rhythm, and 1 appeared to free-run, with a period of ~ 24.7 hrs.

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{Lewy, 2001 #139}	4	Plasma melatonin used as a phase marker	Melatonin 0.5 mg / 60 to 120 days	1 –2 hours before preferred bedtime	Three totally blind subjects with free-running rhythms had been previously entrained to melatonin administration beginning with 10 mg, stepped down to 0.5 mg. In this study, the subjects were re-treated starting with a 0.5 mg dose.	Enroll:3 Compl:3	44.3 + 2.5 (42 – 47)	Pre-treatment determination of free-running rhythm.	All three subjects entrained to a 0.5 mg. dose within several weeks.
{Lewy, 2001, #312}	4	Non-24hr	Melatonin 10 mg daily / 4 to 8 weeks	1 hour before preferred bedtime	Analysis of treatment data for 10 totally blind subjects with free-running melatonin rhythms who were entrained with 10 mg melatonin given daily by mouth for 4 – 8 weeks	8 totally blind free-running rhythms	Not reported	Pre-treatment circadian period (subjects used as their own control)	All subjects converted from free-running to normally entrained rhythm
{Lewy, 2002 #140}	4	Melatonin used as phase marker	Daily melatonin 0.5 mg / 208 days	One hour before preferred bedtime	Case study of a 46 year old totally blind man with non-24-hour free-running rhythms who had failed to entrain with melatonin treatment of 10 mg per day for 83 days and 20 mg per day for 60 days. It was hypothesized that the higher doses failed because th	Enroll:1 Compl:1	46	Pre-treatment circadian period.	The subject clearly entrained after 47 days of treatment and maintained entrainment for 161 days.
{Lewy, 2004 #311}	4	Plasma melatonin used as circadian marker	Melatonin 0.5 mg (N = 6) and 0.05 mg (N = 1) / 54 to 367 days	One hour prior to preferred bedtime	Seven totally blind people with free-running melatonin rhythms were given daily melatonin treatment. In all seven subjects, treatment was initiated in the delay zone of the PRC. This study addressed the question of whether it was critical to initiate mel	Enroll:7 Compl:7	45.1 + 14.6 (21 – 67)	Pre-treatment condition	All subjects entrained to a daily low dose of melatonin initiated on the delay zone. It was concluded that treatment could be initiated at any time and entrainment would occur when the free-running rhythm coincided with the advance zone of the melatonin
{Lockley, 2000, #1598}	2	Non-24hr	Melatonin 5 mg / 35 – 71 days	2100 (military time)	Seven totally blind men with free-running rhythms treated with 5 mg melatonin at 2100 for 35 – 71 days. Five (out of 7) were crossed over to placebo. Several phase markers were used.	7	44.6 ± 8.4 33 - 60	Placebo cross-over in 5 subjects Pre-treatment period estimate in 5 subjects; post-treatment period estimate in the remaining 2 subjects	With active treatment, 3 subjects entrained, 1 shortened circadian period, and 3 continued to free-run
{Lowden, 1998 #650}	2	Jet Lag – by Flight itself across 9-time zones westward or eastward	Adopting a destination bedtime schedule or remaining on home-base bedtime schedule W/ sunglasses/blockers for daylight hrs / 50hrs	2400hrs -destination bedtime x2 nights or 1700hrs (0200hrs CET) upon arrival followed by 1500hrs (2400hrs CET) for the 2nd layover sleep period w/ light input restriction (90% w/ sunglasses) from 1000hrs to sunset	A balanced crossover design across 2 separate flights tested a potential countermeasure to jet lag of allowing flight attendants to remain on their home-base sleep/wake schedules during short (2-days) destination layovers after a westward (9-time zones) f	Enroll: 23 Compl: 19	31-59 yrs, mean=42yrs (SD-NS)	NA	Remaining on home-based time during a 2-day layover reduced sleepiness and global jet lag ratings most likely due to 1) the absence of exposure to a circadian alertness minimum; 2) a shorter time awake (19.8 hrs vs 22.5 hrs for local time shift cond) on t

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{Lowden, 2004 #1944}	3	Shift workers	Bright Light (2500lux) / The first break in the BL(bright light exposure) condition had a mean length of 20.0 ± 0.48 mins. and the second break lasted for 20.9 ± 0.78 mins.	Variable, however 44% of all breaks were initiated between 03:00 and 04:00 hrs.	The study assessed, in an industrial setting, the effects of BL on sleepiness, sleep and Mel, during night work and during the following readaptation to day work. In a crossover design,18 workers at a truck production plant were exposed to either BL (2500 lx) during breaks or normal light during 4 consecutive weeks. The present study tested if a short (20 mins.) exposure to BL during regular breaks would improve night shift alertness, suppress Mel and improve sleep across a series of night shifts, and also whether any effects would be seen on readaptation to day work.	Enroll: 24 Compl: 18	36.2 ± 3.0 y.o.	No true placebo since participants were aware of the two different conditions	The present study showed a clear effect of BL during breaks on nightshift alertness, sleep and Mel levels. The present study shows positive results of BL during night work on physiology, alertness and sleep and give further support for the use of photic stimulation to increase adaptation to night work.
{Marquie, 1999 #663}	4	Shiftwork	Age /		This study examined the relationship between age and sleep with a questionnaire. Subjects were 32-, 42-, 52-, and 62-year olds.	32-yr olds n=896 42-yr olds n=971 52-yr olds n=899 62-yr olds n=470	NS	Older vs. younger adults	Greater age was associated with more difficulty staying asleep and greater use of hypnotics, regardless of work schedule. Shiftworkers were more likely to report difficulty falling asleep and morning awakenings. However, when only shiftworkers were examined the effect of age was no longer significant.
{Marquie, 1999 #664}	2	Shift workers	Age (32, 42, and 52) /		This study examined the relationships between age, shiftwork and job stress on subjective sleep quality with questionnaires.	Enroll: 2767 Compl: 2103 (76% completed questionnaire)	32 (32.4%) 42 (35.1%) 52 (32.5%) mean(SD) NS	Older vs. younger adults	Shift workers vs. day workers reported more sleep disturbance at age 32 and 42 but not at age 52.
{Martin, 1998 #1945}	3	Healthy Normals	Intensity of light exposure / 3 hours	Light was administered during the first 3 hours of the first night shift, and moved 1 hour later each night to accomodate phase shift.	The main objective of this study was to determine the effect of light intensity on circadian rhythm phase shifts in a field setting by comparing high-, medium-, and low intensity light treatments during simulated night shifts.	Enroll: 35 Compl: 35	26.3+6.2 yrs	Low intensity light(<250lux) Medium intensity light (1070-1400 lux) High intensity light (5200-7500lux)	During days 10-12 of night work, there was NS difference between the high and medium groups in percentages of subjects with a mean Tmin that occurred during the daytime S/D period (100% vs 85%).
{McArthur, 1996, #1946}	4	Non-24hr	Melatonin (0.5 mg) / 4 weeks	2100 (military time)	Treatment of a 41 y.o. sighted man with a Non-24-hour CRSD is reported. A 7-week pre-treatment assessment demonstrated a free-running melatonin rhythm that was correlated with his free-running sleep pattern, documented with actigraphy. The amplitude of	1	41	None	Prior to treatment, the patient manifest free-running sleep/wake and melatonin rhythms with a period of 25.1 hr. Following treatment, his period was near 24 h (24.1) and his phase was entrained at a delayed phase

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{McCurry, 2005 #2699}	1	Diagnosed probable or possible AD, confirmed by physician and caregiver reports of a sleep disturbance	Mixed (Light, Exercise, Sleep Scheduling and Hygiene	Eight weeks/Unspecified	RCT of Alzheimer patients (and their caregivers) testing an eight week mixed intervention to improve sleep vs. a control condition of general dementia info and caregiver support. Active treatment improved sleep at post and follow-up	Enroll: 36 Compl: 36	63-93	general dementia info and caregiver support	Actigraphic sleep (one week) at each assessment point; pre, post and six months
{Mishima, 1994 #1140}	3	Sleep wake schedule disorder OR insomnia according to DSM-III-R criteria.	Morning bright light (3000-5000 lux) / 4 weeks, 2 hour per day	0900-1100	This study used morning bright light therapy to improve sleep and behavior in institutionalized patients with dementia. Nursing staff recorded whether subjects were awake or asleep once per hour for 2 months: 2 weeks pretreatment, 1 month of treatment.	Enroll: 14 Compl: 14	patients 75 (61-83) controls 75 (65-81)	Healthy Sleepers	Nighttime sleep significantly increased and daytime sleep decreased in dementia patients at the end of treatment compared to pretreatment. There was no effect of light therapy on serum melatonin levels.
{Mishima, 1999 #1280}	4	Disturbed sleep/wake patterns determined by sleep diaries completed by nursing staff q2 hr for 2 weeks.	Serum melatonin rhythms and actigraphy / 24h for melatonin and 8 days for actigraphy		This study compared melatonin rhythms in older adults with and without Alzheimer's disease. Throughout the study subjects wore actigraphs and nursing staff completed observations of sleep/wake every 2 hours.	Enroll: 10 Compl: 10	patients 75.7 controls 78.3 (only means given)	Healthy Sleepers	Dementia patients had higher nocturnal activity in both hours (3.4 vs. 1.3) and percentage (22.6% vs. 10.8%). There were no differences in daytime or total activity. Melatonin rhythms were fragmented in of dementia patients compared to controls.
{Mitchell, 1997 #688}	2	Healthy Normals	BL (facilitating or conflicting Direction of shifted sleep/dark (advanced or delayed) / 3 hours	Timed to advance or delay based on the PRC, shifted by 1 hour each day.	Study is a 2x2 designed study investigating the relative importance of the timing of BL and the timing of the S/D period for circadian adaptation.	Enroll: 32 Compl: 32	24.7+4.6 yrs	BL facilitating with S/D advanced BL facilitating with S/D delayed BL conflicting with S/D advanced BL confliction with S/D delayed	Logilinear analysis determined that significantly more subjects had large phase shifts (>6 hours) with facilitating BL than with conflicting BL (z= -2.59, p<.01) and significantly more subjects had large shifts with delayed S/D than with advanced S/D (z=
{Monchesky, 1989 #692}	1	Insomnia in shiftworkers	Zopiclone 7.5mg / 13 nights	30 min before bed	Randomized, double-blind trial comparing zopiclone to placebo for the treatment of insomnia in shiftworkers. All subjects alternated between 2 weeks of dayshift and 2 weeks of nightshift. Subjects took placebo for 1 night and then either zopiclone or placebo for 13 nights.	Enroll: 25 Compl: 25	34.9 (1.24) range 22-55	Placebo	Compared to placebo, zopiclone led to improvements in subjective sleep induction and sleep soundness questions. Improvements were maintained throughout the treatment period. There was no difference between treatments on subjective ratings of work performance.
{Monk, 2000 #985}	2	NS	Age / NS	NS	This study sought to determine whether the asymmetry in response to phase shifts favoring phase delays that is seen in younger adults is also true of older adults. Older adults underwent either a 6h phase delay (n=10) or a 6h phase advance (n=10) while CBT and sleep were monitored..	Enroll:20 Compl:20	77.5 (delay) 80.7 (advance) (range 67-87)	NS	There was greater disruption to CBT rhythm amplitude and sleep following phase advance compared to delay, as in younger adults. Phase adjustment was faster and more ordered in the delay group. These results failed to confirm the hypothesis that older adults have a different pattern of adjustment to phase shifts than younger adults, which could have made them more susceptible to particular CRSDs.

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{Moon, 1990 #702}	2	shiftwork	Zopiclone 7.5 mg / 4 days (1 shift cycle)	At bedtime	This study examined the effects of zoplicone on sleep and mood in shift workers using a randomized, double-blind, placebo-controlled design. All subjects worked a schedule of 2 12-hour day shifts, 24 hours off, 2 12-hour night shifts, and 4 days off. Subjects received zopiclone and placebo in random order with 4 days of washout in between. Mood and alertness were rated on VAS scales and sleep was assessed with the Leeds Sleep Evaluation Questionnaire. Performance was assessed with brief neurobehavioral tests.	Enroll: 12 Compl: 12	23 range 18-35	Placebo	Compared to placebo, zopiclone significantly improved nighttime sleep before day shifts and there was a trend towards an improvement in daytime sleep before night shifts. Improvements were in sleep latency and quality ratings but not in ratings of ease of awakening or post-sleep behavior. There were no effects on measures of performance, mood, or alertness.
{Muehlbach, 1995 #1949}	1	Healthy normal adult sleepers diagnosed by medical hx & physical; screening PSG & MSLT	Simulated Night Shift; Caffeine, 2 mg/kg x2 nightly doses; daily AM Bright Light (5K-7.5K lux) / 5 nights on night shift w/ AM bright light; 3 nights on caffeine or placebo	2300hrs-0830hrs-night shift; 2220hrs-2250hrs & 0120hrs-0150-hrs-caffeine or placebo; 0830hrs-0900hrs-Bright Light	In a double-blind placebo-controlled study, caffeine was tested as a countermeasure to sleepiness across a simulated night work shift schedule in young adult volunteers. Caffeinated (2 mg/kg) or decaf (placebo) coffee was administered right before and 3-hrs into the night shift for the 1st 3-nights followed by decaf only on nights 4 and 5. All Ss were exposed to AM (0830-0900) bright light daily to simulate sunlight exposure on the way home from a night shift.	Enroll: 15 (caffeine) Compl: 15	19-30 yrs=range for all 30 Ss 24.7yrs=mean (SD=NS)-caffeine group; 23.9=mean (SD=NS)-placebo group	Placebo (decaf coffee)	Caffeine decreased physiological sleepiness (as measured by the MSLT) across the night shift compared to placebo ($p<.03$), with no sign effects on subsequent daytime sleep as measured by PSG - i.e. no diffs in SO Lat, TST, intermittent wake time, # of awakenings (>15-secs) or in sleep stage architecture - betw the caffeine and placebo groups. The caffeine group rated themselves as more "Alert" (by 25%) on night 1 compared to the placebo group ($p<.05$), but both groups reported a general incr in alertness from nights 1 to 3 ($p<.001$).
{Mundey, 2005 #2046}	2	DSPS (ICSD criteria)	Melatonin 0.3 or 3.0 mg / 4 weeks	Taken 1.5 – 6.5 hrs prior to DLMO (Phase I), then taken 1 hr earlier than previous set time (Phase II)	The authors tested the effects of 2 doses of Mel (0.3 mg or 3.0 mg) or placebo on circadian phase advance in DSPS patients in a double-blind study. Circadian phase was determined via salivary DLMO and CBT (via rectal probe).	Enroll: 22 Compl: 13	28.15 + 5.74 (22 – 42)	Placebo	Both doses of Mel effectively advanced DLMO and CBTmin. Also, the earlier the Mel was administered relative to DLMO, the larger the phase shift. However, sleep onset, as assessed by wrist actigraphy, was not advanced significantly by Mel treatment.
{Oginska, 1993 #735}	3	Not Diagnosed	Gender/NA	NA	Investigation of possible gender differences in susceptibility to shift work-related health and social problems. Rotating shift workers were matched for age. Assessment consisted of a battery of questionnaires, demographics, self-reports of sleep quantity and quality as well as the declared need for sleep, subjective health complaints, and opinions about shift work.	Enroll:166 Compl:166	NR	Males compared to females	Women slept less than men, especially compared to their perceived requirement. Also sleep was more disrupted, and they were more likely to be drowsy at work. They had more physical symptoms.

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{Okawa, 1990, #1955}	4	Non-24 and DSPS	Vitamin B12 / Both patients: About 1 yr.	Both patients: 1.5mg/day	2 patients, one with non-24, the other with DSPS, received treatments of B12 to offset their delayed phases. For the non-24 patient, other interventions had failed. For the DSPS patient, he was in the hospital for kidney problems when his DSPS was treated	2	Non-24: 15 DSPS: 55	0	Both patients developed a 24hr phase about a week after beginning B12 therapy. In the 15yr old patient, sleep logs showed that on treatment 24-hr phase was achieved; however, when treatment was halted, patient resumed non-24hr.
{Okawa, 1997 #1957}	1	DSPS diagnosed clinically according to ICSD	Methylcobalamin (vitamin B-12) 3 mg / 4 weeks	2 tablets taken 3 times per day after each meal for a total of 3 mg / day	Multi-center, double blind investigation of the efficacy of methylcobalamin (vitamin B-12) for DSPS. Outcomes included sleep diaries and general questionnaires regarding sleep and sleep quality.	Enroll: 55 Compl: 50	26.8+1.3	Placebo	No significant differences in clinical symptoms were observed between the groups. Statistical analysis of sleep diary parameters also revealed no significant differences between groups. Study suggests that Vitamin B-12 was not effective for the treatment
{Okawa, 1998 #1958}	4	ICSD - DSPS or non24hr	Light exposure Chronotherapy Vitamin B12 (.5-1.5mg) Triazolam (.125) / 1 hour for 2-4 weeks 3 hours later for 5 days 1 month	6-7am After each meal 30 minutes before bedtime	Study which followed a particular protocol for treating adolescents who presented with DSPS or Non-24 hour. The protocol included light exposure, chronotherapy, vitamin B12, and triazolam.	Enroll: 20 Compl: 20	16.2+1.7 (12-19)	Other procedures	Bright light therapy with or without additional treatment was successful in all 10 patients under treatment. 13 of 20 patients who completed the study were successfully treated by chronotherapy.
{Okawa, 1998 #1959}	4	9 patients with DSPS & 2 patients with Non-24hr.	Melatonin, 1-3mg / NS	DSPS: Melatonin taken in 2 ways – Advancing (taking dose .5-1hr before habitual bedtime) or abrupt (1-2hrs before desired bedtime). Non-24: Patients took Melatonin 1hr before bedtime when sleep phase started delaying.	11 patients completed 2 weeks of baseline sleep log and actigraphy before beginning melatonin treatment for an unspecified period of time. CBT recorded in 5 patients was used to measure circadian phase.	11	Range = 16-46	DSPS (n=9) vs. Non-24 (n=2)	Melatonin was reported to be effective in phase advancing 6/11 patients (5DSPS, 1non-24).
Oren, 1992	4	DSPS; Non-24 hr	Inappropriately Timed Light		Case reports of 3 young men with DSPS who were treated with chronotherapy (systematically sleeper later around the clock) who subsequently developed FRD	3	24 (22-28)		FRD may be an adverse outcome of chronothrerapy
{Oren, 1997 #1149}	4	Non-24hr (sighted)	Bright light (2500 lux) in the morning, light avoidance in the evening (goggles). / 6 months	Bright light from 07:00 to 09:00 Light avoidance from 1800 to 2300	Case report of a 37-year-old male with a 9 year history of with a non-24-h sleep-wake disorder treated bright light in the morning, avoidance of light in the evening, and strict enforcement of dark at night. Sleep wake pattern was documented with actigraphy. PSG, melatonin profiles (and other hormones-TSH, Cortisol, Testosterone) and core temperature rhythms were evaluated before and after treatment.	1	37	Pre-Treatment	Successful entrainment to a 24 hr. sleep wake schedule. Normal phase of melatonin profile.

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{Ozaki, 1996 #1960}	3	According to ICSD criteria but not stated by whom	Sleep diaries Actigraphy CBT / 4 weeks (diaries) 6-10 days (actigraphy and CBT)	NA	This was a case-control study of 7 patients with DSPS who were studied to examine the relationship between sleep-wake patterns and CBT rhythms. Sleep diaries were kept for 4 weeks to determine habitual sleep-wake patterns. CBT was monitored for 6-10 days at home. Actigraphy was also used in 3 patients.	Enroll: 16 (7 with DSPS) Compl: 16	DSPS: 30.9 (20-53) Controls: 24.6 (21-38)	Healthy sleeper controls	Sleep onset and offset from sleep diaries were significantly delayed in patients vs. controls. Sleep length was significantly longer in DSPS patients. CBT nadir was significantly delayed in DSPS patients vs. controls. The phase angle between sleep onset and CBT nadir was not different between the groups, though the angle between CBT nadir and sleep offset was longer in DSPS patients vs. controls.
{Palmer, 2003 #1961}	3	ASPS	265 lux "Enhanced light" / 28 days	2-3 hour exposure, ending 1 hour prior to their "usual" bedtime	In-home delivery of phototherapy in older adults under 2 conditions: 265 lux "Enhanced evening light" or 2 lux "placebo dim light". 2-3hr phototherapy per evening for 28 days. Sleep diary, actigraphy, and urinary aMT6s were analyzed.	Enroll: 65 Compl: 47	70.04+- 6.44 (60-86)	Dim Light	No effect of either phototherapy condition on changing circadian phase (as estimated by urire metabolite of melatonin, pre- vs. post-treatment). 17 minute delay in sleep onset reported in "enhanced light" group.
{Paul et al, 2004, #2574}	1	Jet Lag	Placebo or Melatonin 2 mg or Zopiclone 5 mg /1 night	2200 destination time	5 hour eastward flight. Each subject went on this trip 3 times (serving as their own controls). Upon arrival (0200/0400), sleep from 0500/0700 to 1200/1400, then awaken and at 2200 took pill and try to go to sleep. Assessed outcomes of actigraphy and questionnaires..	30	Approximately 40	Placebo	Actigraph assessment on night pill taken revealed, compared to placebo, both Melatonin (M) and Zopiclone (Z) resulted in ss improvements in TST, SL, # of awakenings, and WASO. M and Z were not different from each other in these measures.
{Pereira, 2005 #22}	3	DSPS	Assessment of diurinal preference by MEQ / one time	NA	12 people with diagnosed DSPS had their genotypes compared with the genotypes of three groups of people who were M-types, I-types, or E-types, based on the MEQ. A random sample of control subjects from the general population (that did not complete the MEQ) was included as well. Correlations between hPer3 length polymorphisms and MEQ type, DSPS and control were made.	Enroll: 58 M-types; 40 E-types; 58 I-types; 12 DSPS 110 random controls Compl: Same	MEQ: 25.95 ± 7.1 DSPS: 28.88+/-11.5 Random controls: 48.91 ± 17.35	DSPS Genotype vs. MEQ M/I/E-types in unaffected normals and vs. random controls	Higher 5-repeat (5/5) and lower 4-repeat (4/4) alleles were found in the DSPS group than the general population or E-types. M-types had similar frequencies of alleles to the DSPS patients.
{Petrie, 1989 #1383}	2	Jet Lag – travel across 12-time zones eastward or westward	Eastward (advance) 12-time zone travel or Westward (delay) 12-time zone travel Melatonin, 5mg, or Placebo Melatonin 5mg / 26-hr flight travel 7-days on Melatonin or placebo 3 pre, 3 post	Melatonin or placebo betw 1000hrs and 1200hrs (local time) for 3 days prior to and during flights; betw 2200hrs and 2400hrs (destination time) for 3 days after flights 10- 1200 pre, 22-2400 on	In a randomly assigned placebo-controlled crossover study, adult volunteers were given oral melatonin or placebo prior to, during and following, eastward and westward transcontinental flights across 12-time zones to determine whether melatonin would allev	Enroll: 20 Compl: 20 10 each way	28-68 yrs	Placebo (gelatin lactose)	Results support the use of melatonin as a remedy for jet lag on long haul flights (12-time zones). Ss taking melatonin reported <jet lag, were <tired during the day, and required <time to re-establish a normal sleep pattern and energy level during waking

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{Petrie, 1993 #1965}	2	Jet Lag	Melatonin 5 mg- Early Placebo Early, Melatonin Late or Placebo / D-2 – D5 Mlt D1- D5 D-2 – D5	D-2 0800 D0 MN D1-D5 – 2200/MN	Westward (5 time zones) VAS for Jet Lag D1-D6, PMS and Stanford SS D1-D6, D6 retrospective global	30	34.9+/- 7.7	Placebo	No change in VAS dialy report, POMS or Stanford Sleepiness Scale between 3 groups, but improved retrospective measures of jet lag, sleep disturbance, recovery and alertness only for late MLT
{Pierard, 2001 #992}	2	None	Caffeine (300 mg), Melatonin (5 mg), placebo / See intervention timing for details	MT: before flight 1700 hrs, during flight 1600 hrs, after flight 2300 hrs (France time). Caffeine: 0800 hrs for the 5 days following the flight. Placebo: at all of these times listed above plus at 2300 hrs days 1-3 after flight	The purpose of this study was to assess the ability of caffeine to resynchronize circadian rhythms following a transmeridian east-bound flight. Caffeine's efficacy was compared to melatonin given according to phase response principles to resynchronize cir	Enroll: 27 Compl: 27	35.3 + 8.1 yrs (19 – 47)	Placebo test group	Caffeine ingestion resulted in a resynchronization in cortisol rhythm by day 5 after arrival in France whereas placebo ingestion resulted in a continued delay in cortisol resynchronization until day 9. The ingestion of melatonin resulted in a cortisol pr
{Pillar, 2000 #182}	4	Severe psychomotor retardation – congenital in 4 cases, 5th diagnosed w/ autism – all 5 had irregular sleep/wake patterns; could not communicate, read or write, 4 could not ambulate independently & were w/out urinary or fecal continence	Melatonin, 3 mg / 4-weeks	1830 hrs/daily	To determine whether oral melatonin could improve the irregular sleep/wake patterns in children w/ severe psychomotor retardation, 5 children underwent 1 week of 24-hr actigraphy w/ concurrent sleep logs by caregivers pre- and post 4-weeks of melatonin	Enroll: 5 Compl: 5	8.2 +/- 3.6 yrs (3-13 yrs)	NA	The results of this study support the consideration of melatonin administration in children w/ severe psychomotor retardation and an irregular circadian sleep-wake rhythm.
{Porcu, 1997 #1968}	2	Normal sleepers diagnosed by hx - no reported sleep probs, psych or med hx, drug-free w/ a monophasic sleep per from ~2300-0700hrs confirmed by 1 week sleep log at home	Acute sleep-wake cycle inversion; Temazepam, 20 mg, or placebo / 24-hrs for the sleep-wake inversion x2; 1 dose of TMZ or placebo	1430 hrs (+/- 30mins) to 2200hrs – sleep opportunity; 2300hrs to 0700-simulated night work shift; TMZ or placebo given at 1430hrs	In a double-blind, placebo-controlled crossover study, the efficacy of a single dose of temazepam or placebo was assessed on day sleep by PSG in the lab during an acute inversion of the sleep-wake cycle in normal young adult sleepers.	Enroll: 8 Compl: 8	33.7 +/- 10.2 yrs	Placebo (gelatin capsule)	Temazepam (TMZ) was an effective hypnotic for elongating diurnal sleep in an acute inversion of the sleep-wake cycle and may be useful in promoting diurnal sleep when an acute shift of the sleep-wake cycle is needed for short periods of a few days. Daytime TST by PSG following 20mg of temazepam (TMZ) was 60% higher (308.7 mins) compared to daytime TST on placebo (189.9 mins, p=.03) due to more NREM S2 sleep (176.6 mins) after TMZ compared to placebo (100.9 mins, p=.03).
{Porcu, 1997 #766}	2	Healthy Normals	Temazepam (TMZ) 20mg / NA	Just before daytime nap period at 1430 (+30minutes)	A double-blind, placebo controlled investigation of the efficacy of TMZ to induce and maintain sleep in the "forbidden zone for sleep" during the day. The study also assessed the relationship between subjective and objective measures of sleep and wakefulness.	Enroll: 10 Compl: 10	33.5+9.4yrs	Placebo	TMZ affected daytime sleep, lengthening total sleep time (about 106 minutes) with respect to PLC. Despite this difference, the higher diurnal TST did not lead to any objective or subjective decrease in sleepiness the following night.

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{Puca, 1996 #772}	3	Shiftworkers Insomnia based on a sleep questionnaire	Triazolam 0.25 mg / 21 days	30 minutes before bed	This study examined the effects of triazolam on their quality of life and sleep. All subjects completed questionnaires related to sleep, mood, and performance. Subjects complaining of disturbed sleep (n=15) and high ratings of disability were given triazolam for 21 days. Shiftworkers were compared with day workers on questionnaires but the results are not relevant to the PICO questions so are not reported.	Enroll: 93 Compl: 93 15 subjects met criteria for medication component of study	37.55 (8.17) shiftworkers 35.20 (11.71) day workders Range 20-58	None	Triazolam produced improvements in sleep as rated on a sleep questionnaire, as well as an improvement in quality of life.
{Purnell, 2002 #1970}	2	Shift workers	Napping during nightshift / 20 mins.	01:00-03:00	The purpose of this workplace evaluation was to assess the effects on performance, alertness and subsequent sleep of strategic napping on 12-hr. overnight shifts. In a counterbalanced crossover design, 24 male aircraft maintenance engineers working in a forward rotating 12-hr. shift pattern volunteered to take part in the study for 2 work weeks. The main purpose of the present study was to identify the benefits (if any) of the opportunity to take a single nap on the night shift in the workplace for subsequent performance and alertness of a group of aircraft maintenance engineers. The present study also sought to determine the effect of the nap on subsequent sleep and the extent of persistent sleep inertia following a single 20-min. nap.	Enroll: 24 Compl: 24	34.75±10.13 y.o. (21-59)	Placebo	The present study showed a significant decline in speed of performance on a vigilance task by aircraft maintenance engineers on the first night shift. However, a single 20-min. nap taken at 03:00 hrs. in the workplace during the first night shift significantly improved performance and restored it back to baseline levels measured at the beginning of the shift. Moreover, the nap had no effect on the main sleep period taken after the shift.
{Quera-Salva, 1997 #1971}	2	Shift worker on rapid rotating shift	Shift Time / 7 days (day shift) or 5 days (night shift)	NA	The authors investigated the relationship between performance, sleep (timing and amount), sleepiness, and Mel acrophase in 2 groups of nurses. The day shift nurses worked 5 days on/2 days off while the night shift nurses worked a 3/2 schedule with 3 days on/2 days off or 2 days on/3 days off on a rotating basis.	Enroll: 40 Compl: 40	D: 35 ± 7 N: 36 ± 7	Night shift nurses compared to day shift nurses	Day shift nurses had a regular Mel acrophase (~0500 hrs.) while night shift nurses had a regular acrophase on days off ~ 0718 hrs.) but not on work nights. However, a subgroup of night nurses (n = 6) showed a rapid delay in their Mel acrophase to 1208 hrs. These nurses performed better than the other night nurses on performance tasks and nearly as well as day shift.
{Reilly, 2001 #1973}	2	Jet Lag	Temazepam 10 mg / D1-D3	Before Bedtime	Westward (5 time zones) Subjective measures of sleep, reaction time and strength measures	9	30.2(10.8) 28.5(9.2)	Placebo	Minor improvement of subjective jet lag measure and sleep quality; other measures unchanged

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{Reynolds, 2002 #994}	4	Jet Lag diagnosed by self report	Argonne Diet / 4 days	Beginning on the 4th day before departing	Pseudocontrolled study investigating the frequency of jet lag among troops deployed across multiple time zones, to show the effect of the Argonne diet in preventing jet lag, and to encourage further study of dietary interventions to prevent jet lag. Stud	Enroll: 95 (deployment) 39 (return) Compl: 95 (deployment) 34 (return) (For the return group 25 subjects were eliminated from the analysis due to missing information on their questionnaires)	Mean=33yrs (19-58	Self selected diet users versus nonusers	Of the 186 deployed personnel, 49 (26%) experience jet lag after arriving in Korea and 132 (71%) experienced jet lag after returning home. The duration of jet lag deploying (1-6 days, median=3 days) was less than that upon returning (1-14 days; median=4
{Roden, 1993 #2677}	3	No diagnosis	Plasma melatonin and cortisol/h	Hourly sampling	Out of 50 potential subjects, 9 night workers were selected for further study because they scored highest on measures of satisfaction with nightwork. Plasma samples for melatonin and cortisol were obtained under controlled conditions in lab starting after 5 – 6 nights of work. There were 7 approx. matched controls who worked normal diurnal hours..	Enroll:9 Compl:9	S: 31 + 8.3 C: 27 + 2.6	Case control	Only one of the 9 subjects shifted rhythms. All the others remained in a diurnal orientation, no different from control.
{Rosenthal, 1990 #1975}	2	DSPS diagnosed clinically (Weitzman 1981 criteria) and verified by sleep logs, actigraphy, and other sleep disorders ruled out by PSG	Bright Light (2500 lux) and evening dark goggles vs. Dim Light (300 lux) and evening clear goggles / Light exposure was for 2 hours between 0600-0900 Goggles were worn from 1600 to dusk 2 weeks per each condition	Light - between 0600 and 0900 Goggles - between 1600 to dusk	Crossover designed study testing the hypothesis that patients with DSPS can have their circadian rhythms successfully phase advanced by a combination of environmental BL in the morning and light restriction in the late afternoon and evening. Measured CBT and MSLTs to look at effects on circadian rhythms.	Enroll: 20 Compl: 20	NS	Crossover Design	Both the pattern of CBT and the morning SL values indicated that a significant phase advance in circadian rhythms had occurred in the “active” condition as compared with the “control” condition. Temperature profiles revealed a significant phase advance during the “active” condition but not the “control.”
{Sack, 1992 #2008}	2	Non-24 hr	Assessment of serum Mel rhythms / 30-60 Days	NA	Plasma Mel was measured approximately biweekly on at least 3 occasions for phase determination. These data were compared to Mel profiles of sighted subjects obtained during the four seasons of the year.	20	37.86 ± 6.0 (29-57)	Normally entrained sighted subjects	Most of the blind subjects had CRSD. Eleven of the 20 blind subjects had free-running Mel rhythms.

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{Sack, 2000 #2006}	2	Non-24hr (blind)	Melatonin N= 7: 10 mg N=3: 10 mg step down to 0.5 mg. / 3 to 9 Weeks	One hour before their preferred bedtime	Treatment with 10 mg of melatonin (or placebo) daily in totally blind subjects who had free-running, non-24 hr. circadian rhythms. They were then crossed over to the other treatment. The timing of the endogenous melatonin onset was measured as a marker o	7	48 ± 5 (42 - 57)	Plecebo cross-over design	Base line circadian period averaged 24.5 hours (range, 24.2 to 24.9). In six of the seven subjects the rhythm was entrained to a 24.0-hour cycle during melatonin treatment (P<0.001). With the step-down schedule, entrainment was maintained with 0.5 mg.
{Sallinen, 1998 #1977}	2	Shift work by history of shift work	Naps / 30 mins. or 50 mins.	Ending at either 0150 or 0440	Study investigated whether the length of a nap during a night shift is important and whether this interacts with the timing of the nap by employing naps of either 30 or 50 mins. in duration and placed in either the first or second half of a night shift. The focus was on their effects on early morning alertness. Sleep inertia and impairment of daytime sleep following the nap also were examined.	Enroll: 14 Compl: 14	(31-52)	2x2 within subjects design plus control	Results suggest that a short nap is a feasible countermeasure for sleepiness in night shift work, although it is unable to keep alertness at the level observed at the beginning of the night shift. It is, however noticeable that during the first 10-15 mins. after awakening from a short nap some sleep inertia may exist.
{Santhi, 2005 #1978}	3	Healthy normals	Timing of Sleep episode / 4 day shifts followed by 3 night shifts	Sleep schedule 1: 14:00-22:00 Sleep schedule 2: 8:00-16:00	The study examined the effect of two fixed sleep schedules in facilitating the transition to night shift work by promoting appropriate shifts of the circadian system. The study explored scheduled daytime sleep (in darkness) as an alternative countermeasure to alleviating shiftwork-induced circadian misalignment: timed sleep/dark and natural light exposure.	Enroll: 18 Compl: 18	26.1+4.8 yrs	Compared 2 different sleep schedules	The circadian phase of the Pre-Night Shift Sleep group (sleep episode: 14:00–22:00) was advanced by nearly an hour while that of the Post-Night Shift Sleep group (sleep episode: 08:00–14:00) was delayed by more than 2 h. sDLMO and CBT phase, were similarly affected, suggesting that the different sleep schedules had shifted the timing of the master circadian pacemaker.
{Satlin, 1992 #1154}	4	Severe Sundowning in institutionalized Alzheimer's patients by DSM-III-R & NINCDS/ADRDA criteria; MMSE=0.6 +/- 1.1; identified as Sundowners by nursing staff w/recurrent or exacerbation of behav disturbs.	Evening Bright Light (1.5K-2K lux) / 2-hrs x 1 week	1900hrs to 2100hrs	Would evening bright light improve sleep-wake patterns and reduce agitation in institutionalized Alzheimer's patients with severe sundowning, clinical symptom ratings by nursing staff were compared to 48-hrs of actigraphy.	Enroll: 10 Compl: 10	70.1 +/- 5.1 yrs	NA	The relative amplitude of the circadian rest-activity rhythm increased w/ the bright light tx (p=.02) and was assoc w/ improved clinical ratings of sleep-wake patterns (baseline to bright light tx change, p=.04), baseline to post-light tx change, p=.02).
{Satoh, 2003 #1979}	2	ASPS	hPer2 mutation /	NA	2 Japanese families with members affected by ASP were evaluated for a mutation in hPer2 similar to that found in Caucasian families with ASPS. Subjects, living at home, were diagnosed by ICSD criteria and by sleep times, MEQ or by salivary DLMO timing	9	Not reported	Affected vs. Unaffected.	No significant linkage with the previously reported hPer2 missense mutation.

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{Schweitzer, 2006 #2105}	1	Not diagnosed	napping, caffeine, and napping plus caffeine/2 – 4 consecutive nights	2.5 h. nap opportunity; and/or caffeine (4 mg/kg) 30 min. prior to night shift.	Two studies (lab and field) to evaluate napping [N] , caffeine [C], and Nplus C on performance and alertness: Lab study; parallel design (4 groups). Field study: crossover design. Outcome measures: MWT, psychomotor performance, actigraphy., subjective measures.	Lab: Enroll/ Comp.:51 Field: Enroll: 53 Comp: 39	Lab: 31.2 (19-65) Field:33.5 (20-55)	Lab: Placebo Field: Crossover	Napping, caffeine, and combination (strongest effect) increase alertness and improves performance in night workers.
{Sharkey, 2001 #212}	1	Normal – Simulated shift work	Mel – 1.8g sustained release. / 2 Days	30mins before daytime sleep on 2 consecutive days	Simulated shift work with 2 baseline nights, 2 consecutive nights shiftwork nights, and 1 recovery night. Subjects were exposed to 30mins of light prior to sleep (~10,000lux) prior to daytime sleep. Mel or placebo treatment given 0.5h before daytime sleep.	21	27±5.0	Placebo (within subject crossover	Mel improved TST only during the 1st daytime sleep episode compared to placebo. Sleep on the 2nd day was NS different in the 2 sessions.
{Sharkey, 2002 #1980}	1	Normals in simulated shift work paradigm	Melatonin: 0.5 mg or 3.0 mg / 8 nights	7.5 hr before normal bedtime	Subjects were normal, healthy individuals who underwent 8 consecutive nights of simulated shift work and sleep at non-normal times. They were administered placebo, 0.5 mg melatonin, or 3.0 mg melatonin before the first 4 non-normal sleep periods. The authors were interested in whether a timed melatonin administration would phase shift these subjects.	Enroll: 32 Compl: 32	24.2 + 4.8 yrs (19 – 35)	Placebo	Melatonin produced a larger shift in circadian body temperature minimum and the DLMO. The phase advance of 3.0 mg (3.9 hrs) was larger than the 0.5 mg (3.0 hrs) condition.
{Shibui, 1998 #1981}	4	Non-24hr	Continuous CBT / 35 Days to 6 months	NA	3 cases of non-24hr CRSD are described in which continuous CBT was used to document circadian rhythms. The onset of the low temperature zone (time period when temperature was below the mean) was used as the phase marker.	3	(31-43)	NA	Confirmed non-24-h circadian rhythms. Temperature marker well-correlated with DLMO in 1 subject.
{Shibui, 1998 #1982}	4	Non-24hr	Low Body Temperature Mean Zone /	NA	Researchers used a “low temperature zone” (LT) to establish phase, where temperature is in the bottom mean. 3 non-24hr patients were studied using this marker to determined whether it was an effective and accurate tool for establishing phase and diagnosis.	3	31, 30, and 43	NA	In case #1, the patient had an LT-zone appearance consistent with her 25hr phase, and when compared with serum melatonin levels, had a roughly parallel delay in phase. In case #2, the patient’s LT readings were consistent with his irregular sleep patterns. In case #3, previously unsuccessful attempts at entraining his circadian phase to 24hr became successful when the light therapy was coordinated with his LT-zone patterns. The LT-zone appears to be well-coordinated with DLMO, and is a more cost-effective procedure.
{Siebler, 1998 #1320}	4	Non-24	Long term melatonin 5 mg. Acute dose escalation (1 to 3 mg). / 6 yrs of treatment interrupted for a double-blind, placebo-controlled, dose escalation trial. (about 6 wks	Between 9 and 10 pm	A case report of a woman with an approximately 25-hr sleep wake cycle since early childhood that was treated successfully with a nightly dose of oral melatonin. The etiology was probably related to a large suprasellar tumor. The treatment was interrupte	1	23	Placebe	Melatonin (but not placebo) successfully entrained the patient’s sleep to a normal schedule.

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{Singer, 2003 #1321}	1	Alzheimer's patients with sleep disturbance based on actigraphy and caregiver questionnaire	2.5mg sustained release 10mg immediate release / 8 weeks	1 hour before habitual bedtime	This study examined the effects of melatonin on insomnia in patients with Alzheimer's disease using a multicenter, randomized, placebo-controlled design. Total nighttime sleep measured with actigraphy was the primary outcome.	Enroll: 157 Compl: 151 52 placebo 54 2.5mg 51 10mg	77.4 (8.9)	Placebo	There were no significant effects of either melatonin dose on actigraphic sleep compared to placebo.
{Smith, 2001 #842}	4	Shift workers with mean shiftwork experience of 12.91 years	Age / NA	NA	Cross sectional survey examining age-related effects of shiftwork. Outcomes assessed included non-specific measures of sleep disturbance, fatigue, mental and physical well-being, social disruption, anxiety, coping, age, shiftwork experience, marital status, sleep needs, morningness and vigourousness.	Enroll: 306 Compl: 286 included in analyses	36.03+8.20	Participants were grouped by age: 1. Youngest=20-32.9 yrs 2. Mid=33-39.9 yrs 3. Oldest=40+ years	The broad picture offered by the findings suggest that aging may be linked to degraded tolerance of shiftwork. On shift drowsiness and sleep quality results tended to support the view that older shiftworkers experience greater drowsiness and poorer sleep quality around night shifts. The older groups also reported higher levels of fatigue on nights.
{Spitzer, 1999 #1983}	1	Jet Lag	Melatonin 5 or 0.5 mg / 6 Days	Bedtime or shifting schedule (one of the 0.5 mg groups)	Eastward (6 time zones crossed) Columbia Jet Lag Scale (subjective report)	197	44 +/- 7	Placebo	No effect on global jet lag scale
{Stewart, 1995 #858}	3	Shift workers	Light treatment (8800-10670 lux) Light avoidance (staying indoors or wearing dark goggles) / 3-4 nights before the first night-shift and continuing for 4 days after landing. BL during the first half of the subjective night	Timing of bright light was variable and occurred during the most sensitive phase of the PRC	This non-randomized, controlled trial of the efficacy of a light treatment program with bright light exposure and light avoidance components to promote adjustment to shift work schedules in workers in the Payload Operations Control Center at the Marshall Space Flight Center.	Enroll: 8 Compl: 8	Tx= 36.6+10.50yrs C= 32.9+7.7yrs	No treatment	Control subjects reported poorer quality sleep, more arousals from sleep, and greater difficulty falling asleep, compared to normal nighttime sleep. The treatment group reported that on 3 of 4 variables, their daytime sleep during mission shiftwork was better than normal nighttime sleep. Similar effects were seen on 4 measures of self-reported, retrospective job performance. Treatment subjects fared better than controls on 14 daily variables measured and were no worse than controls on 2 other variables. Scores on the SSS indicated that control subjects were sleepier than treatment subjects.
{Suhner, 1998 #1987}	1	Jet Lag	Melatonin 0.5m g IR, 5 mg IR, or 2 mg CR / 4 days post travel	Bedtime	Eastward travel across 6 – 8 time zones Sleep logs, POMS, self rated symptoms	234	36	Placebo	D2 better sleep quality, shorter sleep latency and more rested with melatonin (5 mg IR best)
{Suhner, 2001 #1986}	1		Melatonin (M) 5 mg, Zolpidem (Z) 10 mg , M + Z at 5 + 10 mg / 5 nights	1700-2100 D0-D4	Eastward over 6-9 time zones. Measure objective outcome using actigraphy and subjective jet lag ratings and symptom scores.	35 (M) 34 (Z) 20 (M+Z)	NS	Placebo	(M) 5 mg - Improved self-estimated sleep time in flight, morning confusion (Z) 10 mg - Improved self-estimated sleep time in flight and decreased latency in flight, improved sleep quality post-flight, decreased confusion but > side effects vs. (M) (M+Z) 5

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{Suhner, 2002 #1988}	2	Sleep maintenance insomnia >1 year duration. Diagnosed with a clinical interview and 2 weeks of sleep logs. Diagnosis was confirmed by PSG and CBT min earlier than 4 AM at baseline.	Evening BL (4,000 lux) during the acute phase (phase 1). During the maintenance phase (phase 2), the evening light group also wore dark sunglasses if outside before 11 AM. / 11-13 nights (phase 1) 12 weeks (phase 2)	Every night for 2 hours in the range of 8-11 PM (phase 1) 2 nights per week (phase 2)	This study examined the efficacy of long-term evening bright light exposure in improving sleep maintenance insomnia in older adults. In phase 1 of the study, BL was administered 2100-2300 for 11-13 consecutive nights. In phase 2 of the study, subjects continued BL 2 times per week but were randomly assigned to treatment at either 2100-2300 or 1500 to 1700. PSG, CBT min and subjective sleep quality were measured at baseline, after phase 1 and monthly during phase 2.	Enroll: 15 Compl: 14 Incomplete CBT data for 4 subjects and incomplete sleep data for 3 subjects.	71.5 SD NS (63-84)	Controls in phase 2 received afternoon light treatment (1500 to 1700)	Acute treatment led to significant phase delays in average CBT minima (02:59 vs. 04:33) and average sleep onset (11:09 vs. 11:53). There were no effects on TST or SE. There was a significant effect on the phase angle between the sleep midpoint and CBT min. During phase 2, CBT min reverted to baseline in both groups, and though sleep onset remained delayed in the active treatment group, it was not significant.
{Thorpy, 1988 #1085}	4	DSPS dx by a psychologist and neurologist	PSG / 2 nights	1 PSG during the week and 1 on the weekend.	Descriptive study of 22 patients with DSPS. 11 subjects had 1 PSG, 9 of whom had an additional PSG to simulate a weekday night and a weekend night.	Enroll: 22 Compl: 9	15.1 range 10-19	DSPS only, weekend versus weekday comparison	On the weekend subjects slept longer (554 vs. 362 minutes), got up later (11:07 vs. 07:28), and had a greater % of REM sleep (22.9% vs. 14.6%).
{Tresguerres, 2001 #1011}	2	Jet Lag by intervention	7 time-zones to the west and 8 time-zones to the east by Age: <50 yrs and >50 yrs / 6 days – pre-during, post- design (2 days before flight, flight itself, 2 days layover, return flight and day after)	Continuous 24-hr recordings stored at 5-min intervals for actigraphy; every 6-hrs for urinary cortisol & aMT6s	To study the desynchronization betw body rhythms and the environment involved in jet lag, 24-hr activity, urinary 6-sulphatoxymelatonin (aMT6s) and free cortisol excretion, were monitored continuously over a 6 day protocol in male, transmeridian airline p	Enroll: 33 Compl: 33 (12 going 7-time zones west & 21 going 8 time-zones east); 16 Ss<50 yrs & 17 Ss>50yrs)	38.6 +/- 5.7yrs (31-47yrs); 58 +/- 1yrs (57-59yr) – Westward route 38.7 +/-2.1yrs(35-42-yrs); 55.1 +/- 2.2yrs (53-58yrs)-Eastward route	10 Non-flying airline personnel in Madrid	While the acrophase of the activity rhythm showed a corresponding delay or advance to the 7 or 8-time zone transition (resynchronized) w/in the 48-hr layover period at the new destination, the acrophases for both urinary cortisol and melatonin (aMT6s) exc
{Tzischinsky, 1992 #1340}	4	Clinical assessment	Melatonin 5–10 mg / 9 weeks	Trial 1: 5 mg for 4 weeks at bedtime. Trial 2: 10 mg for 2 weeks at bedtime.. Trial 3: 5 mg for 3 weeks 2 –3 hour prior to bedtime..	This is a case report of an 18 y.o. totally blind boy who had DSPS demonstrated by actigraphy. He was treated with three different trials of Mel: 5 mg at bedtime, 10 mg at bedtime, and 5 mg 2 – 3 hours prior to habitual bedtime.	Enroll: 1 Compl: 1	18	Second trial involved a placebo crossover design.	Mel at bedtime failed to produce a response at either dose, but when given 2 – 3 hours prior to habitual bedtime (about 20:00), his sleep problems resolved. The authors concluded that the earlier administration was coincident with the phase advance portion of the phase response curve.
{Walsh, 1988 #905}	1	Healthy normals	Triazolam / 4 days	07:30 (30 minutes prior to daytime sleep period)	Double-blind, placebo controlled crossover designed study investigating physiological sleep tendency utilizing the MSLT on 6 consecutive nights. Aims of study: 1) the patterns of objective sleepiness during simulated shiftwork 2) Evaluate whether alertness at night would be significantly increased though improved daytime sleep produced by triazolam 3) to compare young and middle aged adults	Enroll: 18 Compl: 18	Young adults= Mean=23.3 (20-27) Middle aged adults= Mean=45.2 (34-55)	Placebo and group comparisons	1. NS treatment effect was found. 2. Despite the increased TST and improved consolidation of sleep produced by triazolam, there was little indication of improved nocturnal alertness. 3. Subjects in the young adult group were, on the average, significantly less sleepy than subjects in the middle aged group [F=5.22, df=1,16, p<.04) with mean latencies of 12.8 and 9.9 respectively.

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{Walsh, 1990 #1747}	2	Healthy normals	Caffeine administration (4.0mg/kg body weight) / 1 night	Between 2220 & 2250 hours	Double-blind placebo controlled, crossover studies investigating the effect of caffeine upon measures of sleepiness/alertness during typical night shift hours in 2 separate studies: one employing mild caffeine users and a similar study of moderate caffeine users.	Enroll: Study A: 10 Study B: 6 Compl: Study A: 10 Study B: 6	A: Mean=30.3 (21-37) B: Mean=31.5 (23-47)	Placebo	Study A: Caffeine increased MSLT latency by an average of 6.3 minutes across the night as compared to placebo. Caffeine significantly increased RTSW latencies. Study B: MSLT latencies were significantly longer in the caffeine condition, (p<.03). RTSW data also showed a significant drug effect (p<.008). SSS results showed NS differences in either study.
{Walsh, 2004 #1995}	1	Healthy normal adult sleepers verified by med & psych hx, physical, & screening by PSG & MSLT	Simulated night shift; Modafinil or placebo; daily AM sunlight exposure (500-1.5K lux); Day sleep / 4 - 24-hr periods	2300-0700hrs-night shift; 2200hrs-modafinil or placebo; betw 0730hrs and 0815hrs-30-mins of sunlight; 0815-0830hrs to whenever they awoke (at least 6hrs, but no more than 8hrs in bed) for Day sleep	In a double-blind placebo-controlled (in-lab) study of modafinil for sleepiness across a simulated night shift, Ss were randomly assigned to receive either modafinil or placebo for 4 nights, an hour ahead of a work shift (2300-0700), followed by 30-mins of AM sunlight exposure to simulate a drive home, and then a PSG Day-sleep episode.	Enroll: 16 (Modafinil) Compl: 16	18-65 yrs for entire group; 29.7 +/- 13.2 yrs=modafinil; 33.2 +/- 11.4yrs-placebo	Placebo	The results of this study suggest that modafinil is a weak countermeasure to sleepiness across a simulated night work shift in normal Ss. The ability to stay awake (MWT) was stronger in the modafinil group compared to placebo across the 1st night shift at 3 of 4 time pts (p<.01), but inconsistent on subsequent nights because the placebo group showed an increasing ability to stay awake (p<.012), while the modafinil group basically stayed at the same level of alertness across all nights (p>.2). The placebo group reported more sleepiness (SSS) on the 1st night shift (p=.058) compared to the modafinil group, but sleepiness declined across successive nights in both groups (p<.002), despite the fact that both groups also showed a sign incr in sleepiness across the night in parallel with the circadian trough of the alertness rhythm (p<.001).
{Watanabe, 2000 #1997	4	Non-24 hr	Bright light phototherapy for 3 hr. per day / 20 Days	1.5 hr. after CBT miniimum	A case of non-24 hr CRSD (documented for the prior 2 months) treated with in a hospital setting with phototherapy, is reported	1	17	None	Immediate entrainment of the free running temperature rhythm and normalization of the sleep schedule.
{Waterhouse, 2002 #2000}	4	Jet Lag by Transmeridian flight itself	Eastward travel across 10-time zones 2 flight arrival times at the destination / 6-days post-flight	Every 4-hrs from 0800hrs to 2400hrs; tympanic temp taken 3-5 times/daily betw 0800 and 2400hrs	In a field study looking at the value of many variables as predictors of jet lag severity, a mixed group of athletes, trainers, and academics, flying from the UK to attend a conference in Australia completed sleep logs, visual analogue scales on jet lag s	Enroll: 85 Compl: 85	32.1 +/- 13 yrs (SEM)	NA	Age, experience, and arrival time were predictors of Jet lag severity and symptoms. By contrast, personality variables – e.g. chronotype, flexibility in sleep habits and fatigue coping style – had no predictive power despite a literature to the contrary.
{Weber, 1980 #2013}	4	Clinical assessment	Sleep log / 4 years	daily	This is a case report of a 28 year old sighted student who kept a sleep diary for four years.	Enroll: Compl:	(24-28)	None	The diary documented a non-24hr CRSD with an average period of 25.6 hrs. but with a wide range of 22.9 to 40.0 hrs. However, 42% of observed sleep-wake cycle periods were equal to 24.0 hrs. and 39% were equal to 25.3 hrs. Thus the average is not representative.

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{Wyatt, 2004 #2001}	1	Normal, healthy subjects by clinical history and examination. Regular sleep-wake patterns verified by 24-hr actigraphy for 1-week prior to in-lab protocol.	Forced Desynchrony; caffeine; or placebo / 25-days; 25-days; 29-days	28.57 hrs. wake episodes;14.28 hrs. sleep episodes; hourly caffeine or placebo starting 1-minute after imposed wake-up time & ending 1.57 hrs. prior to imposed bedtime	The effectiveness of hourly caffeine (0.3mg/kg) capsules was tested for counteracting the deterioration in alertness and performance over extended wakefulness (28.57 hrs) in a double-blind, placebo-controlled, parallel-group design using a Forced Desynchrony protocol (in healthy men with normal sleep-wake patterns). Sleep was recorded by PSG, wakefulness during Wake periods was verified by continuous EEG/electrooculogram recordings, and circadian period/phase was verified by plasma Mel levels and rectal CBT.	Enroll: 8 (caffeine) Compl: 8	(18-30 y.o.)	Placebo	Hourly caffeine (0.3mg/kg) tablet dosing across extended periods of wakefulness enhanced the ability of subjects to remain awake by counteracting the increasing homeostatic sleep drive (presumably by antagonizing the build-up of adenosine). The result was a reduction of EEG-verified, accidental sleep onsets compared to the placebo group. Subjects on placebo were asleep 1.57% of the time during scheduled wake periods compared to only 0.32% for those on hourly caffeine (p=.005). Although the 1st extended wake period following caffeine was associated with a decrease in reported sleepiness, this effect reversed after the 1st long sleep episode, with the caffeine subjects reporting more sleepiness - independent of circadian phase or duration of prior scheduled wakefulness - compared to the placebo group (p<.05). Thus, the cost to hourly caffeine dosing was a paradoxical increase in subjective sleepiness. Increased sleepiness was reported by subjects in both groups late in extended wake periods and at the circadian phase normally encountered near wake-up times.
{Yamadera, 1998 #2002}	3	DSPS (n=72), Non-24 (11), Irregular (3)	Oral Vitamin B12 (1500micrograms), bright light (2500lux), and unspecified hypnotics / 4 Weeks?	BL-therapy: 2hrs after waking	Out of 562 patients, 86 patients diagnosed with primary CRSDs were compared to 40 “control” patients with secondary CRSDs to compare the efficacy of several treatments	126	Primary CRSD: 28±9.5	Primary vs Secondary CRSD	The primary CRSD group responded better to B12 and BL-therapy treatments than the secondary CRSD group. 65% of Primary patients responded to treatment vs. 25% of Secondary patients.
{Yoon, 2002 #2004}	2	Shift workers	Bright light (4000-6000lux) Sunglass wearing / 4 hours During ride home	01:00-05:00 n/s	With practical applicability in mind, the aims of this study were: first, to observe whether nocturnal alertness and daytime sleep are improved by light exposure of tolerable intensity and duration in a real workplace; and second, to evaluate whether attenuating morning light is important in adaptation of real night shift workers.	Enroll: 12 Compl: 12	(21-24)	3 different groups: 1. Room light (RL) 2. Bright Light (BL) 3. Bright Light with sunglasses (BL/S)	Results suggest that sleep qualities and quantities were most prominently improved in BL/S, followed by BL, alertness on VAS increased most remarkably in BL/S, followed by BL. Although differences were statistically non-significant, performances in BL and BL/S tended to improve compared to RL Overall, the results were that in BL/S, where bright light exposure was provided at night and morning light was attenuated by wearing sunglasses, more alertness during the night shift and better daytime sleep were observed than in BL. However, subjects in BL, where both bright light exposure at night and sunlight exposure at morning were done, also felt more alert at night and slept better in the daytime than those in RL.

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{Yoon, 2002 #2005}	2	Night Shift Workers	Melatonin Morning Sunlight Exposure / N/A 30 minutes	09:00 hrs 08:00-09:00	Twelve nightshift nurses received three treatments: Placebo (Pla), Melatonin (Mel), and Melatonin with Sunglasses (Mel-S). Each treatment procedure was administered for 2 d of different 4d nightshifts in a repeated measures crossover design. The aims of this study were: first, to assess whether melatonin administration facilitates nightshift adaptation; and second, to determine whether the beneficial effect of melatonin, if observed, is enhanced by attenuating morning sunlight exposure.	Enroll: 12 Compl: 12	(23-27yrs)	The three treatments were placebo (Pla), melatonin (Mel), and melatonin with sunglasses (Mel-S).	The Sleep Period Times ($p<.01$) and Total Sleep Times ($p<.01$) were significantly improved by melatonin administration. Though no significant difference was observed among the three treatments ($p=.158$), the tendency was for nocturnal alertness to be increased by melatonin administration in Mel and Mel-S ($p=.051$); ($p=.259$) respectively). Attenuation of morning sunlight exposure had no effect on the findings.
Alessi CA, 1995	3	Nursing home residents judged to be incontinent	Psychotropic medication (Y/N)	N/A	The sleep quality of 176 incontinent nursing home patients was assessed over two non-consecutive 24-hour periods by 2 nights of actigraphy and two days of behavioral observation and then compared as a function of psychotropic medication status (yes/no). Use of psychotropic medications was not associated with better sleep quality but was associated with a modest reduction in patient movement while in bed.	Enroll: 186 Compl: 176	86.4 + 8.1	Psychotropic medication (Y/N)	Sleep quality assessed by 2 nights of actigraphy and two days of behavioral observation
Campbell 1993	2	ASPS (ICSD-1)	4000 lux white light/12 consecutive nights (2 hrs. duration each night)	20:00-23:00(timing based on baseline CBT)	Subjects treated with active or sham treatment, comparisons made between baseline and post-treatment CBT, PSG, Repeated Test of Sustained Wakefulness (RTSW).	Enroll:16 Compl:16	70.4±4.85(NR)	50 lux red light	S.E. improved in active tx group, with NREM stage 2, decreased WASO and NREM stage 1. Bedtime also delayed 29 mins ($p<0.01$) in active tx group, but no significant changes in wakeup time or time in bed. CBT delayed 2.21hrs. ($p<0.01$) in active tx group. RTSW not affected.
Costa G, 1993	3	SWD	bright light: 2350 lux ; four 20-minute exposures	during night duty work shift	Resuscitation unit nurses working on a fast rotating shift schedule (two consecutive night shifts) were exposed to short periods of bright light during their night duty to test a possible positive effect on their tolerance to night work. Two nights with normal lighting (20-380 lux) and two nights with bright light (2350 lux) were compared. Self-ratings, activity logs, performance testing, and hormonal secretion (cortisol, aMT6s, adrenalin, noradrenaline) were assessed.	15	23.4 (21- 29)	Within subject crossover design	Self-rated Better self-rated physical fitness; less tiredness and sleepiness; a more balanced sleep pattern; and higher performance efficiency (letter cancellation test).

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Drake CL, 2004	3	SWSD	Standard questionnaire; One administration	N/A	A questionnaire was administered by telephone to a large random sample of adults to assess excessive sleepiness and/or insomnia. Subjects who worked nights and who complained of sleepiness and/or insomnia were diagnosed as SWSD. Subjects with a diagnosis of SWSD were compared to unaffected night workers and to day workers.	360 rotating shiftworkers; 174 permanent nightworkers	40.3 + 11.9	Unaffected night workers and dayworkers	SWSD had higher rates of ulcers, sleepiness-related accidents, absenteeism, depression, and missed family and social activities more frequently compared to those shift workers who did not meet criteria ($P < .05$).
Dumont M, 2001	3	Night workers (not SWSD)	Recording of light exposure, assessment of phase shift; 56 hr. of ambulatory recording plus 24 hr. in lab	Admitted to lab after a run of night shifts.	Light exposure was measured for three days along with actigraphy. Subsequently, phase was assessed using he timing of urinary aMT6s	30 permanent night nurses	36.0 ± 8.5 (26 - 55)	The timing of light exposure was correlated with the degree of phase shift.	5 S's delayed, 3 advanced, 22 showed no change from daytime phase. Delayed S's slept in darker bedrooms.
Ebisawa T, 2001	4	DSPS/Unaffected	Determination of polymorphisms/ Once	N/A	Analyzed the human perod3 (hPer3) gene as a possible risk factor for DSPS	78	NS	Unaffected controls	One of the haplotypes was associated with DSPS
Englert, 1998	2	ISWD	Sleep medication yes/no	N/A	Stratified random sample of 516 older adults from the Berlin Aging Study were examined for relationships between taking sleep medications and complaints of poor sleep quality. 19.1% of the older adults were taking sleep medications. Univariate and discriminant analyses showed neither self-reported duration of sleep nor difficulties sleeping through the night differentiated medication users from non-users. However, difficulties falling asleep and global complaints about disturbed sleep did so.	Enroll: 516 Compl: 516	>70 years	No sleep medication	Subjective sleep quality measures
Hoban, 1989	4	FRD	Bright morning light (2500 lux for 2 hours upon awakening)/102 days	Upon awakening	Case report of a 40-year-old sighted woman with FRD. During the pre-treatment period, both the sleep-wake and melatonin rhythms had a period of 25.1 h. Clock time of light exposure was held constant for 6 days and then slowly advanced until the subject was arising at her desired time of day.	1	40	Subject was own control	Light treatment caused the stabilization of the free-running rhythms, advancement to a normal phase and entrainment to the 24-hr day.
Hohjoh H, 2003	3	DSPS/Unaffected	Determination of polymorhpisms/ Once	N/A	This study examined the association between Arylalkylamine N-acetyltransferase (AA-NAT), therate-limiting enzyme in melatonin hormone synthesis, and delayed sleep phase syndrome (DSPS).	50	NS	Unaffected controls	The frequency of the 129 threonine allele is significantly higher in the patients than in the controls ($P=0.0029$), suggesting that that AA-NAT could be a susceptibility gene forDSPS

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Jan JE, 2000	4	ISWD	Melatonin 2 – 12 mg; 22 days for comparison trial; months to years for open label.	Bedtime	Complex dose-finding and comparison study of controlled-release (CR) vs. fast release (FR) melatonin given to children with severe neurodevelopmental difficulties of various kinds (including some blind children). Outcome measure was clinically judged global improvement.	42 N = 16 for comparison of controlled-release (CR) vs. fast release (FR)	For comparison trial: 10.1 + 4.9	Subjects were their own controls	The most effective dose of CR melatonin was 5.7 mg, slightly lower than the most effective FR dose of 7 mg.
Jan JE, 1994	4	ISWD	Melatonin: 2 – 10 mg	Bedtime	15 children (most of whom were neurologically multiply disabled--nine patients had ocular or cortical visual impairment) with severe, chronic sleep disorders were treated with 2 to 10mg of oral melatonin, given at bedtime. Nine had fragmented sleep patterns, three had delayed sleep onset and three others had non-specific sleep disturbance.	15			Benefits of treatment were significant, and there were no adverse side-effects.
Jones, 1999 #1979	2	ASPS	MEQ PSG MSLT CBT DLMO Actigraphy Sleep logs/ Maximum of 4 weeks for actigraphy.	"No consistent seasonal bias for date of inpatient study in FASPS compared with control subjects."	3 kindreds with FASPS identified. 12 subjects (n=6 FASPS, n=6 controls) admitted for inpatient studies, including 2 nights of PSG assessments, followed by MSLT assessments. Circadian phase determined with DLMO and CBT. Sleep logs, actigraphy recorded pre-(sleep logs), during (actigraphy) and post-inpatient assessments. MEQ scores also compared. 1 subject evaluated in temporal isolation facility.	Enroll:12 Compl:12	37±18 (20-69);control subjects age-matched ±6 yrs.	Unaffected individuals (i.e. no CRSD)	Results define a hereditary circadian rhythm variant in humans associated with a short tau, autosomal dominant in nature. CBT and DLMO also advanced. PSG measures of sleep phase including the time of sleep onset, sleep offset, first SWS and first REM sleep were advanced by almost 4 hrs. in FASPS subjects compared with those of control subjects. PSG measures of sleep quality and quantity were within normal limits for both FASPS(n=5) and control (n=6) subjects:total sleep time(minutes),%stage1 sleep,%REM,and %SWS. Mel and temperature rhythms were both phase-advanced by 3-4 hrs. in FASPS subjects compared to controls. Phase-advance of self-reported sleep times in FASPS and control subjects was consistent with actigraphy and sleep log data.
Kendall 2001 #2053	4	FRD	Reassessment of circadian period/ Circadian period assessed at approx. 10 year intervals	At least three serial DLMO's	To determine whether the aging process produced quantifiable differences in the circadian period (tau) of totally blind men who had free-running circadian rhythms.	6	38 + 6 at initial assessment	Subject used as their own control.	All subjects exhibited a longer tau in the 2nd assessment (mean increase 0.13 + 0.08 h ($p < 0.01$). Did not support the commonly held view that tau shortens during human aging.
Koller M, 1993	3	Nightworkers (not SWSD)	Light exposure; 6 days, 24 h per day	48 on work days and 48 h on days off	Light exposure was measured using a photocell mounted on spectacles, comparing days on night shift and days off, as well as comparing day night workers and day workers	6	Nightworkers 32.8 + 6.2 Dayworkers 37.3 + 8.6	Nightworkers vs. Dayworkers For nightworkers: work days vs. days off.	Night workers receive very low levels of light exposure compared to day workers.

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Koller, 1994 #620	3	Shift Work	Light dosimetry, sleep logs, actigraphy/48 hrs	Actigraphy & Dosimetry: 30sec epochs for 48hrs Sleep logs: 48hrs	Several night shift workers wore a light dosimeter on (non)corrective eyeglasses and completed sleep logs during a 2 day period of night shift work to evaluate the effect of light exposure on phase rhythm and sleep behavior. Worker's activity was measured subjectively by activity/sleep logs, and objectively measured by back actigraphy and marker buttons. Saliva samples were collected every 2hrs and measured for cortisol & MLT levels.	14: 5 shifters, 9 non-shifters	Range: 25-50yrs	Shifters (phase delay ≥ 6hrs) vs. Non-Shifters (phase delay ≤ 6hrs)	Near-significant correlation (.51, p=.057) of cortisol acrophase with melatonin. MLT phase position >180deg and cortisol phase position ~ 135deg. Significantly smaller phase angle between cortisol and melatonin in shifters compared to non-shifters. Shifters demonstrated a delayed melatonin phase profile compared to non-shifters. With less intensity of morning bright light, the more the melatonin acrophase delayed (r=-.8, p<.001); also, the less the duration of morning bright light, the more expressed the melatonin phase delay (r=-.69, p<.05)
Lack 1993	4	ASPS (sleep questionnaire, logs)	2500 lux white light intensity/2 nights (4 hrs. duration each night)	20:00-24:00	After 1-week baseline collection of sleep log and actigraphy data, CR protocol performed, with CBT and aMT6 assessments.. "Approximately a week later," subjects exposed to 2 evenings light treatment, followed by repeat CR protocol, with assessments as above. Following recovery sleep, actigraphy and sleep logs maintained during 5-day follow up period.	Enroll:15 Compl:9	53.4±NR (NR)	Red light 150 lux (2 subjects underwent identical pre-and post-treatment protocol/assessments as for active group. 2 weeks after completion, continued with active treatment protocol. Because of negative results and inherent costs, no further subjects tested	Significant delays in all temperature rhythm parameters. DLMO delayed by over 2 hours. No significant difference in sleep onset time. Final wakeup time significantly delayed by mean of 72 minutes and TST significantly lengthened by 73 minutes.
Lack 2005	2	ASPS(sleep logs, sleep questionnaire)	2500 lux white light intensity/2 nights (4 hrs. duration each night)	20:00-01:00	After 1-week baseline collection of sleep log and actigraphy data, CR protocol performed, with CBT and aMT6 assessments.. Between 5-10 days subsequently, subjects exposed to 2 evenings light treatment (active or sham), followed by repeat CR protocol. Actigraphy and sleep logs maintained during 4-week follow up period. At end of first and fourth weeks, aMT6 and questionnaire data collected.	Enroll: 25 Compl: 24	51.2 ± NR (36-68)	Red light <100 lux	CBT delayed by over 2 hrs. in active group, vs. no change from sham treatment. DLMO pre/post light exposure demonstrated significant interaction effect, which appeared to result mainly from delay in active tx group. Interaction effects maintained at follow-up at weeks 1 and 4. Average weekly actigraphy- and sleep log-derived data (baseline, first and fourth follow-up periods)
McArthur 1998	2	ISWD	Melatonin (2.5 to 7.5 mg, based upon individual body weight) vs. placebo, cross over trial/Baseline: 2 wks. Each treatment: 4 week	Bedtime	Girls with Rett syndrome were monitored 24 hours a day over a period of 10 weeks using wrist actigraphy. Baseline sleep-wake patterns were assessed for 1 week. Subsequently, patients underwent a 4-week melatonin treatment period in a double-blind, placebo-controlled, crossover protocol that employed a 1-week washout between treatment trials.	9	10.1	Crossover design; each subject was her own control	At baseline, sleep efficiency was low (mean 68.0 + 3.9% SE), sleep-onset latency was long (42.1+ 12.0 minutes) TST was short (7.5 + 0.3 hours) and fragmented (15 + 2 awakenings per night). Melatonin significantly decreased sleep-onset latency [19.1+ 5.3 minutes (P<0.05)] during the first 3 weeks of treatment.

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Midwinter MJ, 1991	4	Night workers (not SWSD)	Assessment of circadian phase using the timing of urinary aMT6s excretion; Urine collected for 48 hr. at weekly intervals	Winter vs. Summer	The circadian phase of nightworkers in the Antartic was assessed before and after a run of night work. Full spectrum white light exposure (greater than 2500 lux) for 1 hour twice a day was used to treat 5 S's, and 6 S's were left untreated as controls.	11	24.4 (21-33)	Winter vs. summer Bright articficial light vs. ambient light	The acrophase of the melatonin rhythm was significantly delayed from 5.22 h. min to 14.54 h. min (summer) and 8.73 h.min to 13.23 h.min (winter) during a week of night-shift work. Readaptation of the rhythm following night-shift work was markedly slower during the Antarctic winter taking 3 weeks compared to summer where the baseline phase position was re-established after 1 week.
Moldofsky 1986	4	ASPS by Clinical History	Sequential phase advance of bedtime by 3 hrs. every 2 days/2 weeks	NA	62 yo man with symptoms of ASPS underwent phase advance chronotherapy until bedtime set at 23:00. Pre- and post-PSG comparisons performed.	Enroll:1 Compl:`1	62 y.o. (n=1)	NA	TST increased by 1.9 hrs, %WASO increased by 6.9%, %REM decreased by 14.4%, %SWS decreased by 12.1%. Felt subjectively more alert and energetic at altered (delayed) sleep schedule.
Moline ML, 1992	4	Unaffected (simulated jet lag)	Six hour phase advance in time isolated laboratory environment; Time isolation for 15 days, phase-shifted for 8 – 9 days	N/A	All subjects were maintained in temporal isolation 15 days. For the first 6-7 days, sleep and meals were scheduled to approximate their habitual patterns. Daily routines were then shifted 6 hours earlier. The new schedules were followed for the next 8 or 9 days.	Middle-aged = 8	Middle-aged = 37 – 52, Young = 18 - 25	Middle-aged vs. young	For the first 4-day interval after the shift, middle-aged S's had larger increases of WASO and earlier termination of sleep than young subjects; also they had larger decreases in self-rated alertness and well-being and larger increases in sleepiness, weariness.

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Monane M, 1996	2	Nursing home residents	Sedative use: yes/no; Sedative use for at least 5 days/month	N/A	An observational, cross-sectional, and longitudinal study of 145 institutionalized elderly subjects (83.0 years; range, 65 to 105) from 12 Massachusetts nursing homes. Demographics and all medication use during a one-month baseline period was recorded. A blinded research assistant performed detailed neuropsychologic testing and administered a series of standardized questions concerning difficulty sleeping, early morning awakening, and time spent awake in bed. Medication use and patient assessments were repeated after a 6-month interval. One or more sleep-related complaints were present at baseline in 94 (65%) of the residents studied. Logistic regression found no relationship at baseline between use of sedative agents and the presence or absence of sleep complaints. After 6 months of follow-up, 27 (19%) of the residents had decreased their use of sedative-hypnotic agents and 23 (16%) had increased their use. However, there was no relationship between decreased use of sedative-hypnotic agents and worsened sleep or between their increased use and improved sleep. Sleep complaints occur in the majority of institutionalized elderly persons. Neither cross-sectional nor longitudinal analyses showed a relationship between patterns of sedative-hypnotic use and the presence, absence, or change in sleep complaints.	Enroll: 145 Compl: 145	83.0 (65 - 105)	Sedative use: yes/no at either baseline or at follow-up	Subjective sleep quality assessment
Ohta 1991	4	FRD	Vitamin B12, 3 mg per day/Approx. 6 mo	Not reported	Case study of sighted 17 y.o. boy with circadian period of 24.6. No evidence of B12 deficiency.	1	17	Open label	Prompt enrainment to a normal 24-h schedule.
Okawa M, 1987	4	FRD	Strictly enforced sleep-wake and feeding schedule; variable	Daytime	Four congenitally blind children aged 4-12 years, with severe or moderate mental retardation, were studied.	4	4,7,11,12	Compared to pretreatment baseline	Compared to pretreatment baseline
Pallesen 2005	2	ASPS (interview, sleep logs)	10,000 lux white light intensity/21 days (30 minutes duration each night)	Approximately 1 hour before bedtime	After 2-week baseline period (sleep logs x14 days, actigraphy x7 days), subjects randomised to 21 evenings light treatment (active or sham). Possttreatment registrations for actigraphy and sleep logs last 7 and 14 days, respectively, of 21-day treatment.	Enroll:31 Compl:31	63.1±6.9 (55-79)	Red light of approximately 200 lux	Actigraphy- and sleep log- derived bedtime, SOL, TST, S.E., early morning awakening, and final wakeup time. Lights out time assessed for sleep logs only. With respect to log data, significant interaction of time x group noted only for early morning awakening. None of actigraphic variables exhibited significant changes that could be attributed to light therapy.

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Quera-Salva MA, 1996	2	Night workers (Not SWSD)	Assessment of phase adaptation; Nightworkers: 5 days Dayworkers: 7 days	Daily actigraphy and sleep logs. Two 24-hr urine collections.	Sleep-wake was determined by sleep logs and actigraphy. To measure aMT6s levels, urine was collected at 2-hour intervals on the last work day and on the last day off.	Nightworkers: N = 20 (3 days on, 2 days off)	Nightworkers: 36 + 7 Dayworkers: 35 + 7	Nightworkers compared to dayworkers.	Night-shift workers slept significantly more on days off. Napping on the job occurred in 9/20 night-shift workers (mean 114 minutes) between 3 and 6 a.m. The acrophase of 6-sulfatoxymelatonin in day-shift nurses occurred at similar times on workdays and off days. In night-shift nurses, the acrophase was about 7 a.m. on days off, but had a random distribution on workdays.
Reid K, 2001	2	SWD	Age; six consectutive days	Simulated 12 hour shift rotation consisting of two 12 hour day shifts (0700-1900), followed by two 12 hour night shifts (1900-0700).	Thirty two subjects were allocated to groups according to age.. During the work period subjects completed a computer administered neurobehavioural performance task every hour	16 “young”	“Young” 21.2 ± 2.7 “Older” 43.9 ± 6.8	“Young” vs “Older”	Performance for the older subjects was consistently lower than for the younger subjects.
Ross, JK, 1995	4	Night workers (not CRSD)	Bright light (2500 – 3000 lux) vs, dim red (>500 Ix); 2 hr	1100 - 1300	Changes in sleep parameters during and after night-shift and the effects of bright vs. dim light treatment on re-adaptation after night-shift during winter in the Antartic (75 ° south). Subjects kept daily sleep diaries and mood ratings from one week before to three weeks after night-shift and received either treatment during the first week after night-shift. Plasma melatonin (for 24 h at the end of weeks 1, 2 and 4), and urinary aMT6s (for 48 h weekly) were measured.	14	(21 - 35)	Bright light (2500 – 3000 lux) N= 9: vs. dim red (>500 lux) N= 7	Plasma melatonin and aMT6s rhythms delayed by 7-8 h. The white light group readapted slowly, apparently by phase delay, as assessed by aMT6s measurement. The red light group readapted slightly, but significantly (ANOVA, $p < 0.01$) faster than the white light group.
Sack RL, 1997	1	SWD	Melatonin vs. placebo; Four weeks	Daily administration mg at usual bedtime	A placebo controlled trial of melatonin intended to shift circadian (melatonin) rhythms to be congruent with sleep schedule.	24	21 - 55	Crossover design. Subjects were their own controls.	Seven subjects responded specifically to melatonin; 8 responded to both melatonin and placebo, and 4 responded to neither.
Serfaty, 2002	1	SWD	Melatonin 6 mg ; 7 weeks	Usual bedtime	A randomized double blind placebo controlled cross over trial was undertaken to test the hypothesis that slow release exogenous melatonin 6mg improves sleep for people with dementia.	44 entered 25 completed	84.2 + 7.6		Melatonin had no effect on median total time asleep, number of awakenings, or sleep efficiency. Conclusion: Contrary to previous findings, we found no evidence that two weeks of exogenous melatonin is effective in improving sleep in people with dementia.
Takano A, 2004	4	DSPS/Unaffected	Determination of polymorphisms/ NA	N/A	Analyzed all of the coding exons of the human CKIe gene in DSPS and controls	98	Patients: 27 ± 9.1 Controls: 32 ± 8.6	Unaffected	N408 allele in CKIe plays a protective role in the development of DSPS (and FRD) through alteration of the enzyme activity.
Toh KL, 2001	1	ASPS; Structured interview(capable of falling asleep before 20:30 and waking before 05:30 local time daily and throughout the year, with numerous other qualifying characteristics./MEQ	Genetic linkage analysis, SSCP analysis, functional characterization of mutation; N/A	N/A	ASPS kindred 2174 (from Jones 1999 manuscript) underwent linkage and other genetic analyses to determine genetic basis of FASPS.	Enroll:NA Compl:NA	N/A	Unaffected	FASPS individuals from this kindred have a serine to glycine mutation with the CKIε binding region of hPER2,which causes hypophosphorylation by CKIε in vitro.

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Uchiyama, 2002 #1993	2	Non-24hr	Inappropriately timed Light exposure, promoting phase delays/ Presumed to be chronic, possibly related to genetic factors.	Hypothesis: excessive light exposure in the evening promoted inappropriate phase delays leading to non-24-hr CRSD.	Six normally sighted patients with non-24-hr CSRD were matched with six healthy controls. After a baseline actigraphic assessment at home, all subjects participated in a laboratory based ultrashort sleep-wake protocol with simultaneous measurements of circadian phase utilizing the dim light melatonin onset (DLMO).	12 subjects (6 patients, 6 controls)	26.6 + 9.0 (16 – 39)	Age and sex matched normal controls.	The interval from sleep propensity onset to melatonin midpoint was 1.9 hrs shorter, and that from melatonin midpoint to sleep propensity offset was 1.4 hrs longer in the non-24 patients compared to controls.
Walsh, 1991	1	Unaffected volunteers	A double-blind, counterbalanced, crossover administration of triazolam (0.25 - 0.5 mg) or placebo; Seven days	Prior to daytime sleep	Sleep tendency (MSLT and repeated test of sustained wakefulness) during a simulated night shift schedule was measured following daytime sleep after bedtime administration of triazolam or placebo involving two tours of five laboratory nights and four daytime home sleep periods was used. Duration of daytime sleep measured by actigraphy.	15	41.1 (32 – 53)	Crossover, repeated measures design.	Triazolam lengthened daytime sleep as measured by wrist actigraph and improved nighttime alertness but subjects did not perceive improved alertness at night after triazolam-aided daytime sleep
Weibel L, 1997	2	SWD	Plasma melatonin and CBT rhythms; Once with night sleep and once after an acute shift of their sleep period to daytime.	24-h cycle	To determine whether the melatonin (MT) rhythm is adapted to a permanent nocturnal schedule. Eleven night workers were studied during their usual 24-h cycle, and 8 day-active subjects during two 24-h cycles, once with night sleep and once after an acute shift of their sleep period to daytime.	11	Nightworkers: 28.7 + 5.0 (25 – 41) Controls: not stated	Health day workers	Night workers showed a great variability in their Mel profiles, with the onset of the MT release varying between 2145 and 0505.
Wyatt 2006, #2590	3	DSPS compared to unaffected controls	DLMO x 3/Assessments separated by at least 5 days--2 scheduled at the end of the week	Salivary samples collected every 30 minutes for 6 hours.	To assess stability and predictors of circadian phase in participants with delayed sleep phase syndrome (DSPS) relative to normal-sleeping matched controls.	8	DSPS: 22.9 + 2.7 Control: 23.0 + 2.6	Age-matched normal controls	DLMO stable and occurred significantly later in patients with DSPS than in controls ($p = 0.006$), even on an ad lib schedule.
Xu Y, 2005	4	ASPS; Self-reported habitual sleep/wake schedule, clinical interviews	Screening of candidate genes for circadian mutations.	N/A	Pedigree with familial ASPS underwent screening of candidate genes for circadian mutations.	Enroll:5 Compl:5	41±NS (20-65)	Unaffected family members.	A missense mutation in the CKIepsilon gene was identified in affected family members.

Abbreviations Table

aMT6s	Uninary 6-sulphatoxy melatonin
ASPS	Advanced sleep phase syndrome
B12	Vitamin B12
BL	Bright light
CBT	Core body temperature
Compl	Completed
CRSD	Circadian rhythm sleep disorders
D-1	Day one
DLMO	Dim light melatonin onset
DSM-IV	Diagnostic and Statistical Manual IV, American Psychiatric Association
DSPS	Delayed sleep phase syndrome
EDS	Excessive daytime sleepiness
EEG	Electroencephalography
Enroll	Enrolled
E-type	Evening type (MEQ)
hr.	Hour
hrs.	Hours
ICSD	International Classification of Sleep Disorders
ISWD	Irregular Sleep Wake Disorder
I-type	Intermediate type (MEQ)
KSS	Karolinska Sleepiness Scale
Mel	Melatonin
MEQ	Morningness-Eveningness Questionnaire
M/E	Morningness-Eveningness
MMSE	Mini-mental status exam
mins.	Minutes
MSLT	Multiple sleep latency test
M-type	Morning type (MEQ)
MWT	Maintenance of wakefulness test
N	Number of subjects
NA	Not available
NREM	Non-Rapid eye movement
NS	Not stated
NS	Not statistically significant
POMS	Profile of Mood States
PSG	Polysomnography, Polysomnogram
pts.	Patients
REM	Rapid eye movement
RTSW	?
sDLMO	Salivary dim light melatonin onset
SE	Sleep efficiency
SO	Sleep onset
SOL	Sleep onset latency
SRM	Social Rhythm Metric
SSS	Stanford Sleepiness Scale
SWSD	Shift work sleep disorder
Tmin	Core body temperature minimum
TSH	Thyroid stimulating hormone
TST	Total sleep time
WASO	Wake after sleep onset
y.o.	Year-old