Practice Management Tips For
SHIFT WORK DISORDER

INCREASE RECOGNITION OF SHIFT WORK DISORDER

For you:

- Keep the screening questions below in mind; use checklist if initially needed
- Incorporate a few sleep/wake questions into systems review at yearly visits
- Keep copies of the Epworth Sleepiness Scale or a sleep/wake log in patient exam rooms, and use them when appropriate

For your patients:

- Hang a poster in reception area and/or exam rooms to remind patients about the importance of sleep, especially associated with shift work

SCREENING QUESTIONS FOR SHIFT WORK DISORDER

- Do you often feel tired or sleepy at work?
- Do you have difficulty sleeping?
- What are your sleep times?
- What are your work hours?
- What are your sleep times on days off?
- Do you often struggle to stay awake, or have you ever fallen asleep while driving to or from work?
- Do you often have difficulty with your concentration, memory, or ability to pay attention?

ROLES AND RESPONSIBILITIES OF YOUR MEDICAL TEAM FOR SHIFT WORK DISORDER

For healthcare providers:

- Yearly review – ask patients about occupation and get sleep/wake history
- Explain diagnosis and importance of management of shift work disorder

For medical assistants and nurses:

- Insist that they check patient occupation when updating social history
- Help in patient education, counseling, handouts

For billing, diagnostic codes:

- Organic Circadian Sleep Disorder, shift work type: 327.36
- Sleep/wake schedule disorder, frequently changing: 307.45
- Mismatch of sleep/wake schedule with lifestyle needs: 780.55

WHEN TO REFER FOR SLEEP CONSULTATION

- If you are uncomfortable with or do not have time for managing shift work sleep/wake issues
- If you need to rule out other possibly comorbid sleep/wake disorders
  - Obstructive sleep apnea
  - Narcolepsy
  - Restless legs syndrome/periodic leg movement disorder
- If your treatments do not resolve sleep-related issues

MOTIVATE YOUR PATIENTS

Explain to patients that effectively managing their shift work disorder should help improve their **quality of life**, including their health, functioning, and safety – at work, at home, and on the road.

ICD-9 Diagnostic Codes/Reimbursement Issues Related to Shift Work Disorder

- ❑ 327.36: Circadian rhythm shift work disorder
- ❑ 307.45: Sleep/wake schedule disorder, frequently changing
- ❑ 780.55: Mismatch of sleep/wake schedule with lifestyle needs
- ❑ 780.79: Fatigue
- ❑ 780.52: Insomnia
- ❑ 307.42: Persistent insomnia
- ❑ 292.85 / 291.82: Other circadian rhythm sleep disorder due to drug or substance abuse

ICD9Data.com. http://www.icd9data.com/2007/Volume1/320-389/320-327/327/327.36.htm.

Patient Questionnaire

Do you often feel tired or sleepy during your awake hours?

Epworth Sleepiness Scale[1]

Rate Your Chance of Dozing Off: 0 = None, 1 = Slight, 2 = Moderate, 3 = High

Situation	Chance of Dozing Off
Sitting and reading	
Watching TV	
Sitting inactive in a public place (eg, in a theater or at a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car while stopped for a few minutes in traffic	
Total ESS* score	

*ESS score ≥10 indicates significant sleepiness.[2]
ESS = Epworth Sleepiness Scale.
1. Johns MW. *Sleep.* 1991;14:540-545.
2. Panossian LA, Avidan AY. *Med Clin North Am.* 2009;93:407-425.

Spanish version on the reverse side

Cuestionario Para Paciente

¿Usted se siente a menudo cansado o soñoliento durante sus horas despiertas?

Escala de somnolencia de Epworth[1]

Califique su probabilidad de quedarse dormido: 0 = Ninguna, 1 = Leve, 2 = Moderada, 3 = Alta

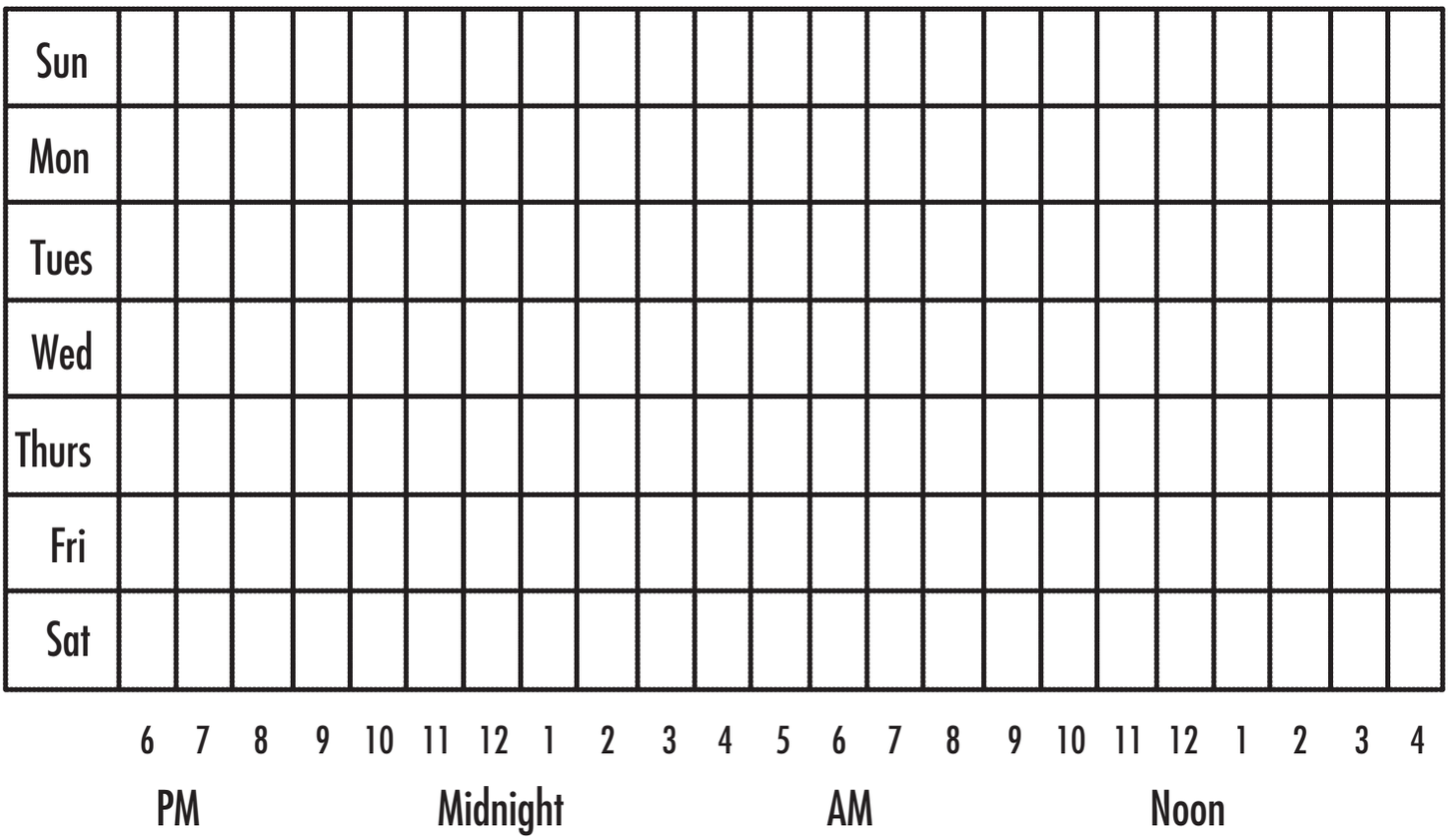
Situación	Probabilidad de Quedarse Dormido
Sentado leyendo	
Viendo televisión	
Sentado inactivo en un lugar público (p. ej. en un cine o en una reunión)	
Viajando como pasajero en un automóvil durante una hora sin interrupción	
Recostado para descansar por la tarde, cuando las circunstancias se lo permiten	
Sentado y conversando con alguien	
Sentado tranquilo después de un almuerzo sin alcohol	
Sentado en un automóvil detenido unos minutos por el tráfico	
Puntaje total de la ESS*	

*Puntaje de la ESS ≥10 indica somnolencia excesiva.[2]
ESS = Escala de somnolencia de Epworth.

1. Johns MW. *Sleep.* 1991;14:540-545.
2. Panossian LA, Avidan AY. *Med Clin North Am.* 2009;93:407-425.

Sleep/Wake Log

↓ In bed ↑ Out of bed ✗ Lights out; trying to sleep ↔ Asleep



Total: _____

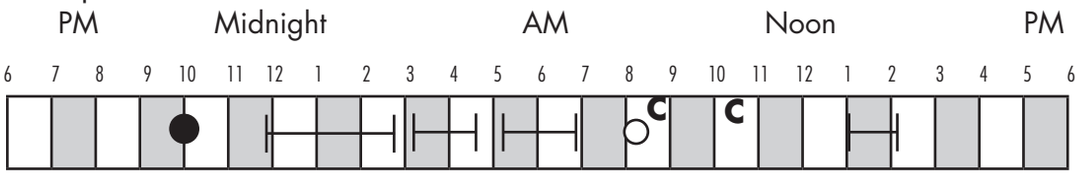
Morgenthaler T, et al. *Sleep*. 2007;30(11):1445-1459.

SLEEP/WAKE LOG

Name: _____

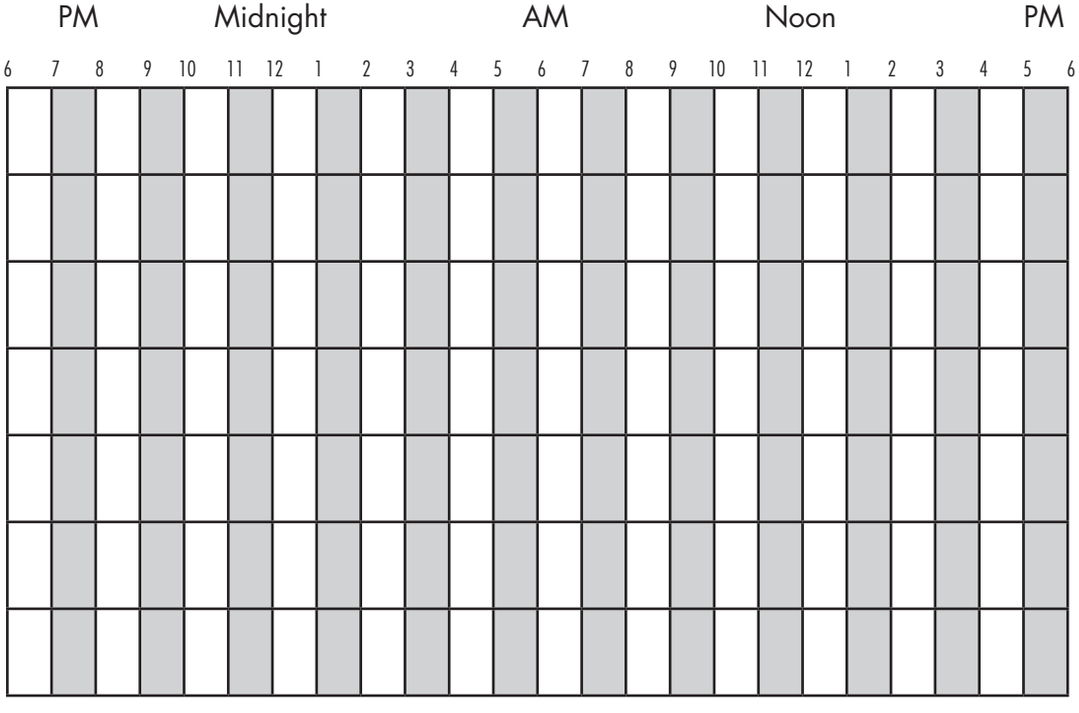
Use these symbols ● Lights out or in bed trying to sleep ⊢⊣ Asleep ○ Lights on or out of bed for the night C Caffeinated coffee or soda

Example:



Day Date	How much sleep?	Sleeping aid, alcohol, medications? Time, type, amount	Sleep quality?	Awake-time fatigue?
Fri 06/11	6 hours + 1 hour nap	6:30 PM 1 beer 10 PM Ambien 10 mg	Hi (Mod) Lo	(Hi) Mod Lo

Fill out in the morning | Fill out in the evening



Day Date	How much sleep?	Sleeping aid, alcohol, medications? Time, type, amount	Sleep quality?	Awake-time fatigue?
_____	_____	_____	Hi Mod Lo	Hi Mod Lo
_____	_____	_____	Hi Mod Lo	Hi Mod Lo
_____	_____	_____	Hi Mod Lo	Hi Mod Lo
_____	_____	_____	Hi Mod Lo	Hi Mod Lo
_____	_____	_____	Hi Mod Lo	Hi Mod Lo
_____	_____	_____	Hi Mod Lo	Hi Mod Lo
_____	_____	_____	Hi Mod Lo	Hi Mod Lo

Adapted from Spielman & Glovinsky, NY, 1991.

Fold back this page before administering this questionnaire

INSTRUCTIONS FOR USE

for doctor or healthcare professional use only

PHQ-9 QUICK DEPRESSION ASSESSMENT

For initial diagnosis:

1. Patient completes PHQ-9 Quick Depression Assessment on accompanying tear-off pad.

2. If there are at least 4 ✓s in the blue highlighted section (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.

3. ***Consider Major Depressive Disorder***

— if there are at least 5 ✓s in the blue highlighted section (one of which corresponds to Question #1 or #2)

Consider Other Depressive Disorder

— if there are 2 to 4 ✓s in the blue highlighted section (one of which corresponds to Question #1 or #2)

Note: Since the questionnaire relies on patient self-report, all responses should be verified by the clinician and a definitive diagnosis made on clinical grounds, taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient. Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning (Question #10) and ruling out normal bereavement, a history of a Manic Episode (Bipolar Disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

To monitor severity over time for newly diagnosed patients or patients in current treatment for depression:

1. Patients may complete questionnaires at baseline and at regular intervals (eg, every 2 weeks) at home and bring them in at their next appointment for scoring or they may complete the questionnaire during each scheduled appointment.

2. Add up ✓s by column. For every ✓: Several days = 1 More than half the days = 2 Nearly every day = 3

3. Add together column scores to get a TOTAL score.

4. Refer to the accompanying PHQ-9 Scoring Card to interpret the TOTAL score.

5. Results may be included in patients' files to assist you in setting up a treatment goal, determining degree of response, as well as guiding treatment intervention.

PHQ-9 SCORING CARD FOR SEVERITY DETERMINATION

for healthcare professional use only

Scoring—add up all checked boxes on PHQ-9

For every ✓: Not at all = 0; Several days = 1;
More than half the days = 2; Nearly every day = 3

Interpretation of Total Score

Total Score	Depression Severity
0-4	None
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression

Spitzer RL, et al. *JAMA*. 1999;282:1737-1744.

Patient Health Questionnaire (PHQ-9) for Depression

Over the last 2 weeks, how often have you been bothered by any of the following problems? (use "✓" to indicate your answer)	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself - or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3
Add colums		+	+	
(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card.)	TOTAL:			

10. If you checked off *any* problems, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?	
	Not difficult at all _____
	Somewhat difficult _____
	Very difficult _____
	Extremely difficult _____

Spitzer RL, et al. *JAMA*. 1999;282:1737-1744.

Insomnia Severity Index

Please answer each of the questions below by circling the number that best describes your sleep patterns *in the past week.* Please answer all questions.

Please rate the current (past week's) SEVERITY of your insomnia problem(s):	None	Mild	Moderate	Severe	Very Severe
Difficulty falling asleep	0	1	2	3	4
Difficulty staying asleep	0	1	2	3	4
Problem waking up too early	0	1	2	3	4

How SATISFIED/DISSATISFIED are you with your current sleep pattern?	Very Satisfied 0	Satisfied 1	Neutral 2	Dissatisfied 3	Very Dissatisfied 4

To what extent do you consider your sleep problem to INTERFERE with your daily functioning (eg, daytime fatigue, ability to function at work/daily chores, concentration, memory, mood, etc)?	Not at All Interfering 0	A Little 1	Somewhat 2	Much 3	Very Much Interfering 4

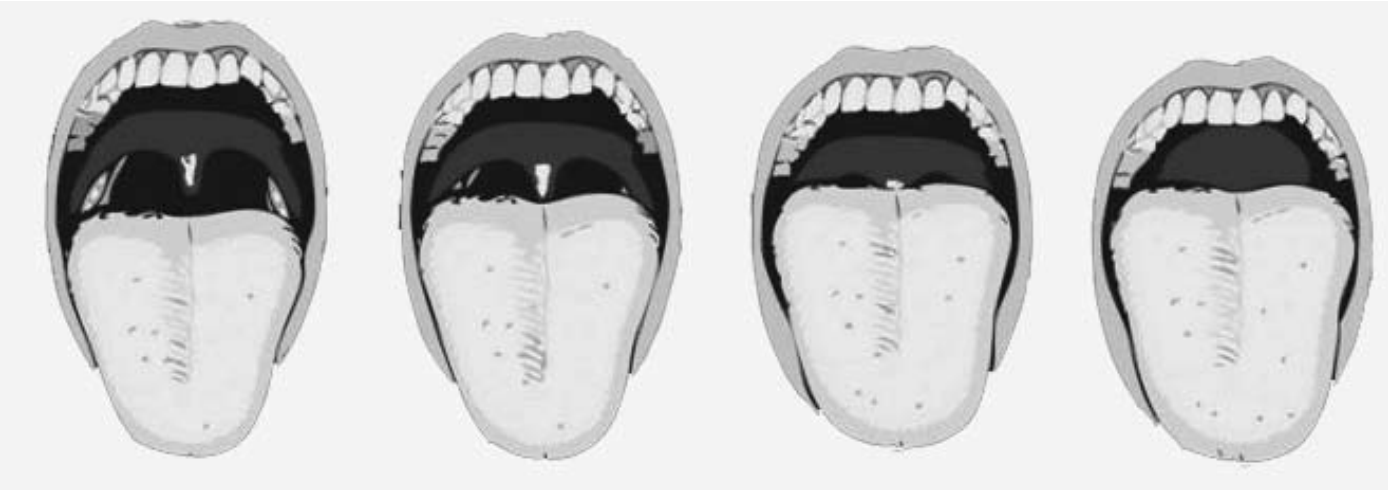
How NOTICEABLE to others do you think your sleeping problem is in terms of impairing the quality of your life?	Not at All Noticeable 0	A Little 1	Somewhat 2	Much 3	Very Much Noticeable 4

How WORRIED/DISTRESSED are you about your current sleep problem?	Not at All Worried 0	A Little 1	Somewhat 2	Much 3	Very Much Worried 4

Total: _____

Doghramji K. *Am J Manag Care.* 2006;12:S214-S220.
Used with permission from Morin CM. *Insomnia: Psychological Assessment and Management.* New York, NY: Guilford Press; 1993.

Mallampati Scale to Evaluate Obstructive Sleep Apnea



Class 1
Entire tonsil clearly visible

Class 2
Upper half of tonsil fossa visible

Class 3
Soft and hard palates clearly visible

Class 4
Only hard palate visible

Higher score is associated with greater risk for obstructive sleep apnea.

SHIFT WORK DISORDER

Take-Away Points

- ❏ Circadian rhythm misalignment is key to shift work disorder
- ❏ Excessive sleepiness and insomnia are symptoms of shift work disorder
- ❏ Shift work disorder is associated with circadian rhythm sleep disorders, mood disorders, and cardiovascular and metabolic disease
- ❏ Shift work disorder can be diagnosed based on sleep/wake history and sleep diary/log
- ❏ Management reduces risk for associated morbidities such as accidents, depression, sleepiness, and insomnia
- ❏ Ongoing management should be based on sleepiness severity, adverse events, comorbid conditions, treatment efficacy, and patient adherence
- ❏ Shift work disorder *can be* and *should be* managed effectively in primary care

SHIFT WORK DISORDER

Do You Have Shift Work Disorder?

- ✓ Do you often feel tired or sleepy at work?
- ✓ Do you have difficulty sleeping?
- ✓ What are your sleep times?
- ✓ What are your work hours?
- ✓ What are your sleep times on off-days?
- ✓ Do you often struggle to stay awake, or have you ever fallen asleep while driving to or from work?
- ✓ Do you often have difficulty with your concentration, memory, or ability to pay attention?

If you work a shift that involves a nonconventional sleep-wake schedule (before 7 AM or after 7 PM) and have excessive sleepiness and/or insomnia for ≥1 month, you may have Shift Work Disorder.

Epworth Sleepiness Scale[1]

Rate Your Chance of Dozing Off: 0 = None; 1 = Slight; 2 = Moderate; 3 = High	
Situation	**Chance of Dozing Off**
Sitting and reading	
Watching TV	
Sitting inactive in a public place (eg, in a theater or at a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car while stopped for a few minutes in traffic	

*ESS score ≥10 indicates excessive sleepiness[2]; ESS = Epworth Sleepiness Scale.
1. Johns MW. *Sleep.* 1991;14:540-545.
2. Panossian LA, Avidan AY. *Med Clin North Am.* 2009;93:407-425.

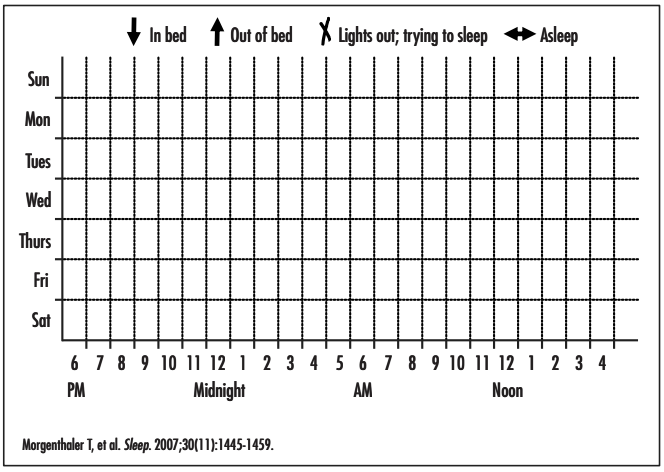
How Managing Shift Work Disorder Can Enhance Your Quality of Life

- ✓ If you do shift work or have Shift Work Disorder, you are at increased risk for:
  - Mood disorders*[1]
  - Depression†[2]
  - Ulcers†[2] GI disturbances*[3]
  - Cardiovascular and metabolic dysfunction*[4,5]
  - Stroke*[6]
  - Cancer*[7-9]

- ✓ You are also at a higher risk for accidents,[2] injuries,[10] and poor work performance[1] related to excessive sleepiness and mental fatigue. Shift work disorder can also have a negative effect on your personal relationships and may increase your risk of a motor vehicle accident.[11]

Effectively managing your shift work disorder and getting proper sleep can improve your quality of life, including your health, functioning, and safety—at work, at home, and on the road.

Sleep/Wake Log



Morgenthaler T, et al. *Sleep.* 2007;30(11):1445-1459.

*Shift work; †SWD.

1. Smith MR, et al. *Sleep.* 2009;32:1481-1489.
2. Drake CL, et al. *Sleep.* 2004;27:1453-1462.
3. Zhen Lu W, et al. *Eur J Gastroenterol Hepatol.* 2006;18:623-627.
4. Bøggild H, et al. *Scand J Work Environ Health.* 1999;25(2):85-99.
5. Martino TA, Sole MJ. *Circ Res.* 2009;105:1047-1061.
6. Brown DL, et al. *Am J Epidemiol.* 2009;169:1370-1377.
7. Hansen J. *Epidemiology.* 2001;12:74-77.
8. Davis S, et al. *J Natl Cancer Inst.* 2001;93:1557-1562.
9. Kubo T, et al. *Am J Epidemiol.* 2006;164:549-555.
10. Folkard S, Tucker P. *Occup Med.* 2003;53:95-101.
11. Akerstedt T, Peters B, Anund A, et al. *J Sleep Res.* 2005;14:14-20.

SHIFT WORK DISORDER

Bright Light Therapy for Shift Work Disorder

- ✓ Use bright lights (artificial lights) at work and during awake hours to help combat drowsiness and improve alertness
- ✓ Use bright lights from early in night shift through 2 hours before shift ends
- ✓ Avoid light during sleep hours
- ✓ Use dark sunglasses 1-2 hours before daylight bedtime
- ✓ Use light-blocking curtains or window shades while home
- ✓ Darken bedroom and passage to bathroom at home

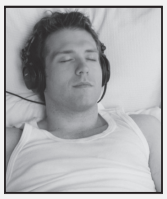
1. Morgenthaler TI, et al. *Sleep.* 2007;30:1445-1459.
2. Smith MR, et al. *Sleep.* 2009;32:1481-1489.

Sleep/Wake Hygiene Behaviors for Shift Work Disorder

Allocate adequate sleep time

Use light during wake times and dark during sleep times

Avoid nicotine, especially before bedtime*



Minimize noise, light, and extreme temperatures*

Avoid alcohol and heavy meals before bedtime*

* National Heart, Lung, and Blood Institute Working Group on Insomnia, 2000.

Treatment Options for Shift Work Disorder

Ask your clinician about which treatments are best for you

For Insomnia[1] — to increase sleep duration
- Sleep/wake hygiene behaviors
- Hypnotic medication
- Melatonin

For Daytime Sleepiness — to increase alertness
- Naps[2]
- Caffeine[3]
- Modafinil/Armodafinil[4,5]

For Circadian Rhythm Misalignment[1,6] — to increase sleep duration and alertness
- Bright light during work
- Melatonin (bedtime during the day)
- Avoid morning bright light

1. Morgenthaler TI, et al. *Sleep.* 2007;30:1445-1459.
2. Smith-Coggins R, et al. *Ann Emerg Med.* 2006,48:596-604.
3. Wyatt JK, et al. *Sleep.* 2004;2(3):374-381.
4. Czeisler CA, et al. *N Engl J Med.* 2005;353:476-486.
5. Czeisler CA, et al. *Mayo Clin Proc.* 2009;84(11):958-972.
6. Smith MR, et al. *Sleep.* 2009;32:1481-1489.

Drowsy Driving Tips

- Get a good night's sleep (7 to 9 hours) before you hit the road
- Don't be too rushed to arrive at your destination
- Use the buddy system when driving long distances
- Take a break every 100 miles or 2 hours: get a snack, switch drivers, or go for a run
- Take a nap — find a safe place to take a 15- to 20-minute nap, if you think you might fall asleep
- Avoid alcohol and medications that cause drowsiness as a side effect
- Avoid driving at times when you would normally be asleep
- Consume caffeine — the equivalent of 2 cups of coffee can increase alertness for several hours

Adapted from National Sleep Foundation's Countermeasures to Prevent Fall-Asleep Crashes.

SHIFT WORK DISORDER

Resources for Patients

BOOKS

Desperately Seeking Snoozin' by John Wiedman; 1999.

The Enchanted World of Sleep by Peretz Lavie; 1996.

If You Think You Have a Sleep Disorder (a Dell Mental Health Guide) by Anne Remmes, MD, and Roxanne Nelson; 1998.

Learn to Sleep Well by Christopher Idzikowski; 2000.

100 Q and A's About Shift Work Sleep Disorder by Mary A. Carskadon (coming in March 2011).

The Promise of Sleep: A Pioneer in Sleep Medicine Explores the Vital Connection Between Health, Happiness, and a Good Night's Sleep by William C. Dement; 1999.

Sleep Demons: An Insomniac's Memoir by Bill Hayes; 2001.

Sleep Secrets for Shiftworkers & People with Off-beat Schedules by David R. Morgan; 1996.

WEB SITES

American Academy of Sleep Medicine www.aasmnet.org

American Board of Sleep Medicine www.absm.org

Drowsy Driving http://drowsydriving.org

Sleep Research Society www.sleepresearchsociety.org

National Heart, Lung, and Blood Institute www.nhlbi.nih.gov/health/dci/Diseases/inso/inso_whatis.html (See "What Is Insomnia?")

National Institutes of Health, National Center on Sleep Disorders Research www.nhlbi.nih.gov/about/scsdr/index.htm (materials for professional and patient)

Talk About Sleep www.talkaboutsleep.com

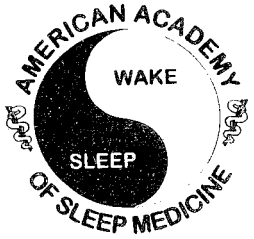
SleepEducation.com www.sleepeducation.com/Disorder.aspx/?id=63 (See "Circadian Rhythm Sleep Disorder, Other")

National Sleep Foundation www.sleepfoundation.org

The *International* Classification of SLEEP DISORDERS

Second Edition

Diagnostic & Coding Manual



American Academy of Sleep Medicine - Westchester, IL

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IV. Circadian Rhythm Sleep Disorders

For optimal sleep, the desired sleep time should match the timing of the circadian rhythm of sleep and wake propensity. Therefore, a recurrent or chronic pattern of sleep disturbance may result from alterations of the circadian timing system or a misalignment between the timing of the individual's circadian rhythm of sleep propensity and the 24-hour social and physical environments. These disorders may arise when the physical environment is altered relative to internal circadian timing or the circadian timing system is altered relative to the external environment. In addition to physiological and environmental factors, maladaptive behaviors influence the presentation and severity of the circadian rhythm sleep disorders.

As used herein, a circadian rhythm sleep disorder is defined by the following criteria:

General Criteria for Circadian Rhythm Sleep Disorder

A. There is a persistent or recurrent pattern of sleep disturbance due primarily to one of the following:
   i. Alterations of the circadian timekeeping system
   ii. Misalignment between the endogenous circadian rhythm and exogenous factors that affect the timing or duration of sleep
B. The circadian related sleep disruption leads to insomnia, excessive daytime sleepiness, or both.
C. The sleep disturbance is associated with impairment of social, occupational, or other areas of functioning.

All disorders described in the ensuing sections imply a sleep difficulty that meets each of the above criteria. The specific features that characterize each type of circadian rhythm sleep disorder are included within the individual diagnostic criteria.

> ***Note:*** *The formal names of these disorders are dictated by previous versions of the International Classification of Diseases system and, for the sake of consistency with this system, must be maintained. Given the unwieldiness and length of these terms, the preferred common names are listed in parentheses and are frequently used in the text.*

Circadian Rhythm Sleep Disorder, Delayed Sleep Phase Type
(Delayed Sleep Phase Disorder)

Alternate Names

Delayed sleep phase syndrome, delayed sleep phase pattern.

Essential Features

Circadian rhythm sleep disorder, delayed sleep phase type (DSP) is characterized by habitual sleep-wake times that are delayed, usually more than two hours, relative to conventional or socially acceptable times. Affected individuals complain of difficulty falling asleep at a socially acceptable time, but once sleep ensues, sleep is reported to be normal. A typical patient has difficulty initiating sleep and prefers late wake-up times. When allowed to follow his or her preferred schedule, the patient's circadian phase of sleep is delayed but is relatively stable. Attempts to fall asleep earlier are usually unsuccessful.

Associated Features

Individuals with delayed sleep phase disorder may demonstrate "sleep drunkenness" (extreme difficulty awakening and confusion) in the morning. The disorder has been associated with mental disturbances, particularly in adolescents. Schizoid and avoidant personality features, as well as depressive symptoms and depressive disorders, are associated with this disorder. In some individuals with DSP there may be an overlap with circadian rhythm sleep disorder, nonentrained type. Attempts to fall asleep earlier may result in prolonged sleep latency and promote the development of secondary conditioned insomnia. Individuals may use alcohol, or sedative, hypnotic, and stimulant substances to alleviate symptoms of insomnia and excessive sleepiness, thereby exacerbating their underlying sleep disorder.

Demographics

The exact prevalence of circadian rhythm sleep disorder, delayed sleep phase type, in the general population is unknown. It is more common among adolescents and young adults, with a reported prevalence of 7% to 16%. It is estimated that DSP is seen in approximately 10% of patients with chronic insomnia in sleep clinics.

Predisposing and Precipitating Factors

Almost all individuals with circadian rhythm sleep disorder, delayed sleep phase type, are evening types. Genetic factors such as polymorphism in the circadian clock gene *hPer3* are associated with delayed sleep phase syndrome. Environmental factors, including decreased exposure to light in the morning or exposure to bright light late in the evening, may exacerbate the delayed circadian phase. Maladjustment to changes in work and social schedules, travel across time zones, and shift work can precipitate this disorder. Individuals may use excessive caffeine and other stimulants, which may further delay sleep onset and thus exacerbate the delayed sleep time.

Familial Patterns

A positive family history may be present in approximately 40% of individuals with circadian rhythm sleep disorder, delayed sleep phase type. In one pedigree, delayed sleep phase disorder was suggested to segregate as an autosomal-dominant trait. Polymorphisms in *hPer3*, arylalkylamine N-acetyltransferase, human leukocyte antigen (HLA), and *Clock* have been suggested to be associated with delayed sleep phase.

Onset, Course, and Complications

Mean age of onset is 20 years, although the delayed sleep pattern often begins during adolescence. Onset in early childhood is also described; the onset may follow psychological, medical, or environmental stressors. Without treatment, circadian rhythm sleep disorder, delayed sleep phase type, is a chronic condition that lasts into late life. However, with increasing age, the timing of the sleep-wake cycle may advance, thereby decreasing the phase delay. Treatment using behavioral approaches can advance the timing of sleep hours, but there is usually a continual tendency and preference for delayed sleep hours and associated symptoms. Use of alcohol, sedative-hypnotics, or stimulants to treat symptoms of insomnia and sleepiness during normal waking hours may lead to substance abuse.

Pathology and Pathophysiology

The exact mechanisms responsible for delayed sleep phase disorder are unknown. An abnormal interaction between the endogenous circadian rhythm and the sleep homeostatic process that regulates sleep and wakefulness plays an essential role in the pathophysiology of circadian rhythm sleep disorder, delayed sleep phase type. Several studies demonstrate altered phase relationships relative to the light-dark cycle in patients with delayed sleep phase disorder. In these patients, sleep onset, sleep offset, and phase of circadian markers such as temperature and melatonin are delayed when compared to controls. Although this condition may be predominantly due to a misalignment between circadian timing and the external environment, alterations in the length of the circadian period or sleep recovery after sleep loss may also be contributing factors.

In children and adults, voluntary behaviors such as staying awake late at night and waking up late in the morning or afternoon may result in an abnormal relationship between the endogenous circadian rhythm and the sleep homeostatic process that regulates sleep and wakefulness. Delayed bed times and wake times may increase exposure to bright light in the late evening (a delay signal for the circadian clock) and decrease exposure to light in the early morning (an advance signal for the circadian clock), which promotes and perpetuates the delay in the circadian sleep phase.

Polysomnographic and Other Objective Findings

Recordings of sleep logs and actigraphy over a period of at least seven days demonstrate delayed sleep onset and sleep offset. Sleep onset is typically delayed until 1 a.m. to 6 a.m., and wake time occurs in the late morning or afternoon. Daily demands and schedules may result in an earlier than desired wake-up time during weekdays, but a delay in bedtime and wake-up time is almost always seen during weekends and vacation.

Polysomnography, when performed at preferred (delayed) sleep times, is essentially normal for age. If a conventional bedtime and wake-up time is enforced, however, polysomnographic recording will show prolonged sleep latency and decreased total sleep time.

Laboratory measures of circadian timing generally show the expected phase delay in the timing of the nadir of the temperature rhythm and dim-light melatonin onset (DLMO). However, wake-up time may be even more delayed relative to these circadian markers.

The Horne-Östberg questionnaire is a useful tool to assess the chronotype of "eveningness" and "morningness." Individuals with circadian rhythm sleep disorder, delayed sleep phase type, score as definite evening types.

Diagnostic Criteria

Circadian Rhythm Sleep Disorder, Delayed Sleep Phase Type

(Delayed Sleep Phase Disorder)

A. There is a delay in the phase of the major sleep period in relation to the desired sleep time and wake-up time, as evidenced by a chronic or recurrent complaint of inability to fall asleep at a desired conventional clock time together with the inability to awaken at a desired and socially acceptable time.

B. When allowed to choose their preferred schedule, patients will exhibit normal sleep quality and duration for age and maintain a delayed, but stable, phase of entrainment to the 24-hour sleep-wake pattern.

C. Sleep log or actigraphy monitoring (including sleep diary) for at least seven days demonstrates a stable delay in the timing of the habitual sleep period.

> ***Note:*** *In addition, a delay in the timing of other circadian rhythms, such as the nadir of the core body temperature rhythm or DLMO, is useful for confirmation of the delayed phase.*

D. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Clinical and Pathophysiological Subtypes

Not applicable or known.

Unresolved Issues and Further Directions

There is limited knowledge of the underlying pathophysiology of delayed sleep phase disorder. Recent evidence suggests that alteration in the homeostatic regulation of sleep may also play an important role. Recent advances in the understanding of the molecular basis for the generation and entrainment of circadian rhythms, together with the identification of a familial form of circadian rhythm sleep disorder, delayed sleep phase type, will lead to improved understanding of the mechanisms responsible for this condition, as well as targeted rational therapies.

Differential Diagnosis

Circadian rhythm sleep disorder, delayed sleep phase type, must be distinguished from "*normal*" sleep patterns, particularly in adolescents and young adults who maintain delayed schedules without distress or impaired functioning. Social and behavioral factors play an important role in the development and maintenance of the delayed sleep patterns. Personal, social, and occupational activities that continue into the late evening may perpetuate and exacerbate the sleep phase delay. In adolescents, the role of school avoidance, social maladjustment, and family dysfunction should be considered as contributing factors.

Delayed sleep phase disorder must be distinguished from other causes of difficulty maintaining sleep, including *primary* and *secondary insomnias*. In DSP, sleep initiation and maintenance are normal when the patient is allowed to sleep on the preferred schedule.

When individuals with delayed sleep phase disorder must arise before the desired wake time, morning sleepiness may be evident. Other forms of excessive sleepiness, from which this must be distinguished, do not generally exhibit the pronounced circadian pattern and do not abate with alterations in the sleep-wake schedule.

The development of delayed sleep phase disorder is influenced by alterations in circadian physiology as well as behavioral factors. Although social, psychological, and environmental factors may play a significant role in the development of delayed sleep phase, *ICSD-2* has chosen to list only a single delayed sleep phase diagnosis, with the recognition that most cases reflect variable chronobiologic and behavioral contributions.

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Circadian Rhythm Sleep Disorder, Advanced Sleep Phase Type
(Advanced Sleep Phase Disorder)

Alternate Names

Advanced sleep phase syndrome, phase advance, advanced sleep phase pattern.

Essential Features

Circadian rhythm sleep disorder, advanced sleep phase type (ASP), is a stable advance of the major sleep period characterized by habitual sleep onset and wake-up times that are several hours earlier relative to conventional and desired times. Affected individuals complain of sleepiness in the late afternoon or early evening, early sleep onset, and spontaneous early morning awakening. Individuals typically complain of early morning insomnia and excessive evening sleepiness. When patients are allowed to maintain an advanced schedule, their sleep is usually normal for age.

Associated Features

Individuals with circadian rhythm sleep disorder, advanced sleep phase type, experience chronic partial sleep loss and excessive sleepiness due to the invariable morning awakening. Attempts to stay asleep during the early morning hours may result in the development of secondary conditioned insomnia. Individuals may use alcohol, or sedative, hypnotic, and stimulant substances to alleviate symptoms of insomnia and excessive sleepiness, thereby exacerbating their underlying sleep disorder.

Demographics

The prevalence of ASP in the general population is unknown; it has about 1% prevalence in middle-aged and older adults and increases with age. Both sexes are affected equally.

Predisposing and Precipitating Factors

Almost all individuals with ASP are morning types. In addition, genetic factors may also influence the development of the condition. Early-onset cases displaying autosomal dominant transmission have been reported (see familial patterns). Environmental factors may precipitate, maintain, or exacerbate the advanced circadian phase.

Familial Patterns

Several familial cases of circadian rhythm sleep disorder, advanced sleep phase type, have been identified. Genetic factors should be suspected in younger patients. In all of the families, the trait segregated with an autosomal dominant mode of inheritance. A mutation in the circadian clock gene *hPer2* was localized in a large family with ASP. Other pedigrees do not carry this mutation, suggesting genetic heterogeneity.

Onset, Course, and Complications

Circadian rhythm sleep disorder, advanced sleep phase type, has been reported in childhood, but it typically begins during middle age and may remain a life-long condition. Without treatment, the disorder is a chronic condition. Although treatment such as behavioral approaches and bright light can delay the timing of sleep, there is usually a continual tendency and preference for earlier sleep hours. Use of alcohol, sedative-hypnotics, or stimulants to treat symptoms of insomnia and sleepiness during normal waking hours may lead to regular substance abuse.

Pathology and Pathophysiology

The precise mechanisms underlying the pathophysiology of circadian rhythm sleep disorder, advanced sleep phase type, are unknown. The endogenous circadian rhythm and the sleep homeostatic processes that regulate sleep and wakefulness are believed to interact abnormally. Alterations in the ability of the circadian clock to phase delay, a dominant phase advance region of the phase response curve to light or other entraining agents, or an endogenous circadian rhythm that is shorter than normal could result in an advanced sleep phase. A shortened endogenous period of circadian rhythms has been reported in a few individuals with familial circadian rhythm sleep disorder, advanced sleep phase type.

Polysomnographic and Other Objective Findings

Recording of sleep diary and actigraphy over a period of at least seven days demonstrates sleep onset and sleep offset that are advanced relative to conventional times. Sleep onset is typically advanced to between 6 p.m. and 9 p.m., and wake times to between 2 a.m. and 5 a.m. Daily demands may result in later than desired bedtimes. Polysomnography, when performed at the preferred sleep times (advanced), is essentially normal for age. However, if conventional bedtime and wake times are enforced, the polysomnographic recording may show decreased sleep latency, decreased total sleep time, and moderately short rapid eye movement sleep latency.

Laboratory measures to determine the phase of circadian rhythms generally show the expected phase advance in the timing of the nadir of the temperature rhythm and DLMO. However, wake-up time may be more advanced relative to these circadian markers. The Horne-Östberg questionnaire is a useful tool to assess the chronotype of "eveningness" and "morningness." Individuals with circadian rhythm sleep disorder, advanced sleep phase type, score as definite morning types.

Diagnostic Criteria

Circadian Rhythm Sleep Disorder, Advanced Sleep Phase Type

(Advanced Sleep Phase Disorder)

A. There is an advance in the phase of the major sleep period in relation to the desired sleep time and wake-up time, as evidenced by a chronic or recurrent complaint of inability to stay awake until the desired conventional clock time, together with an inability to remain asleep until the desired and socially acceptable time for awakening.

B. When patients are allowed to choose their preferred schedule, sleep quality and duration are normal for age with an advanced, but stable, phase of entrainment to the 24-hour sleep-wake pattern.

C. Sleep logs or actigraphy monitoring (including sleep diaries) for at least seven days demonstrate a stable advance in the timing of the habitual sleep period.

> *Note: In addition, an advance in the timing of other circadian rhythms such as the nadir of the core body temperature rhythm or DLMO, is useful for confirmation of the advanced circadian phase.*

D. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use or substance use disorder.

Clinical and Pathophysiological Subtypes

Not applicable or known.

Unresolved Issues and Further Directions

There is limited knowledge of the pathophysiology. An altered phase relationship between habitual sleep time and wake times and that of the phase of endogenous circadian rhythms may play an important role in the pathogenesis of the disorder. Recent advances in the understanding of the molecular basis for the generation and entrainment of circadian rhythms, gene mutation research, and identification of a familial form of advanced sleep phase disorder will lead to improved understanding of the mechanisms responsible for this condition, as well as the development of improved treatment approaches.

Differential Diagnosis

Circadian rhythm sleep disorder, advanced sleep phase type, must be distinguished from "*normal*" sleep patterns, particularly in the elderly who maintain advanced schedules without distress or impaired functioning (morning types or larks).

Advanced sleep phase disorder must be distinguished from other causes of early awakening, including *primary* and *secondary insomnia* problems. *Major depressive disorder* is a common cause of early awakening that must be considered. These patients do not typically manifest the early evening sleepiness that is characteristic of advanced sleep phase.

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Circadian Rhythm Sleep Disorder, Irregular Sleep-Wake Type
(Irregular Sleep-Wake Rhythm)

Alternate Names

No circadian rhythm, grossly disturbed sleep-wake rhythm, low-amplitude circadian rhythm, chaotic sleep-wake rhythm.

Essential Features

Circadian rhythm sleep disorder, irregular sleep-wake type, is characterized by lack of a clearly defined circadian rhythm of sleep and wake. The sleep-wake pattern is temporally disorganized so that sleep and wake periods are variable throughout the 24-hour period. Individuals have symptoms of insomnia and excessive sleepiness, depending on the time of day.

Associated Features

Napping is usually prevalent throughout the 24-hour period in individuals with circadian rhythm sleep disorder, irregular sleep-wake type. Total sleep time may be normal for age.

Demographics

Not known.

Predisposing and Precipitating Factors

Poor sleep hygiene and lack of exposure to external synchronizing agents such as light, activity, and social schedules, particularly in the institutionalized elderly, may be predisposing as well as precipitating factors involved in the development of circadian rhythm sleep disorder, irregular sleep-wake type.

Familial Patterns

Not applicable or known.

Onset, Course, and Complications

Onset of the condition may occur at any age. Little is known regarding the course and complications of circadian rhythm sleep disorder, irregular sleep-wake type.

Pathology and Pathophysiology

Anatomic or functional abnormalities of the circadian clock can result in an arrhythmic pattern of rest and activity. Weakened environmental-entraining agents may also contribute to the development of an irregular sleep-wake cycle. A low-amplitude or irregular circadian rhythm of sleep-wake pattern may be seen in association with neurological disorders such as dementia and in children with mental retardation.

Polysomnographic and Other Objective Findings

Sleep logs and actigraphy monitoring show the expected lack of a clear circadian rhythm of the sleep-wake cycle which, instead, is characterized by multiple irregular sleep and wake bouts throughout the 24-hour period. Polysomnography for at least 24 hours shows a loss of the normal sleep-wake pattern. Monitoring of other circadian rhythms, such as core body temperature, may also show a loss of clear circadian rhythmicity.

Diagnostic Criteria

Circadian Rhythm Sleep Disorder, Irregular Sleep-Wake Type

A. There is a chronic complaint of insomnia, excessive sleepiness, or both.
B. Sleep logs or actigraphy monitoring (including sleep diaries) for at least seven days demonstrate multiple irregular sleep bouts (at least three) during a 24-hour period.
C. Total sleep time per 24-hour period is essentially normal for age.
D. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Clinical and Pathophysiological Subtypes

Not applicable or known.

Unresolved Issues and Further Directions

There is limited knowledge of the pathophysiology. Further research into the relative contribution of alterations in environmental synchronizing agents such as light and activity versus a dysfunction of the endogenous circadian clock in the development of irregular sleep and wake patterns will lead to improved understanding of this condition.

Differential Diagnosis

Poor sleep hygiene and voluntary maintenance of irregular sleep schedules should be distinguished from irregular sleep-wake pattern. Irregular sleep and wake patterns associated with known neurological and medical conditions should be coded under *circadian rhythm sleep disorders due to medical condition.*

Individuals with irregular sleep-wake rhythms may present with complaints of insomnia, which suggest primary sleep initiation or maintenance problems, or *insomnia due to mental disorder* or *medical or neurological disorder.* Careful analysis of sleep logs or actigraphy will demonstrate multiple irregular periods of sleep throughout the 24-hour cycle.

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Circadian Rhythm Sleep Disorder, Free-Running Type (Nonentrained Type)

Alternate Names

Non–24-hour sleep-wake syndrome, hypernychthemeral syndrome.

Essential Features

Circadian rhythm sleep disorder, free-running type, (nonentrained type) is characterized by sleep symptoms that occur because the intrinsic circadian pacemaker is not entrained to a 24-hour period or is free running with a non–24-hour period (usually slightly longer). The sleep pattern can be quite variable. Some individuals adopt a sleep pattern that is congruent with their free-running pacemaker and shift their sleep times each day in concert with their circadian rhythms.

Associated Features

Most individuals with nonentrained circadian rhythms are totally blind, and the failure to entrain circadian rhythms is related to the lack of photic input to the circadian pacemaker. On the other hand, some totally blind people have a functional retinohypothalamic pathway or may be able to entrain to nonphotic cues, producing partial entrainment in some cases.

In sighted people, social and behavioral factors may also play an important role in the development and maintenance of the disorder, as there is an increased incidence of psychiatric and personality disorders. Occasionally, the disorder is associated with mental retardation or dementia. It has also been suggested that there may be an overlap between circadian rhythm sleep disorder, delayed sleep phase type, and circadian rhythm sleep disorder, free-running type (nonentrained type).

Demographics

Rare cases of this disorder have been described in sighted people, but the actual incidence of this disorder is unknown. It is thought that over half of totally blind individuals have circadian rhythm sleep disorder, free-running type (nonentrained type); about 70% of blind individuals complain of sleep disturbances, and 40% have chronic cyclic sleep disturbances. There are no known sex differences.

Predisposing and Precipitating Factors

Total blindness is the most common predisposing condition. In sighted people, the disorder can be induced by certain environmental conditions. It has developed after chronotherapy for circadian rhythm sleep disorder, delayed sleep phase type. Circadian rhythm sleep disorder, free-running type (nonentrained type) can be induced by isolation from normal time cues.

Familial Patterns

Not applicable or known.

Onset, Course, and Complications

Onset may occur at any age in blind individuals, and, in congenitally blind children, onset can occur at birth. If untreated, the course is chronic. Attempts to regulate sleep and wake times may promote the use of alcohol, sedative-hypnotics, and stimulants, which in turn may exacerbate the underlying sleep disorder. Depressive symptoms and mood disorders are often comorbid conditions.

Pathology and Pathophysiology

The intrinsic period of the human circadian pacemaker is usually longer than 24 hours and requires regular input from the environment to maintain synchrony to the 24-hour day. The light-dark cycle is the most important environmental time cue (Zeitgeber) in humans (as in other species), although nonphotic time cues also play a role in normal entrainment. A lack of photic input to the circadian pacemaker is clearly the cause of free-running rhythms in totally blind people. It has been suggested that, in sighted individuals, an extremely prolonged endogenous circadian period that is outside of the range for entrainment to the 24-hour cycle could result in lack of alignment of the circadian rhythm or an alteration in the response of the circadian clock to the entraining effects of light.

Polysomnographic and Other Objective Findings

Sleep studies yield different results depending on the degree of synchrony between sleep times and the circadian pacemaker at the time when the steep study is performed. Recording of sleep logs and actigraphy over prolonged periods demonstrate the lack of a stable relationship between the sleep-wake cycle and the 24-hour day. When sleep schedules follow the endogenous circadian propensity for sleep and wake, actigraphy and polysomnography are usually normal for age, but sleep-onset and wake times are typically delayed each day.

Serial measurements of circadian rhythms, such as the DLMO or the core body temperature rhythm, usually show a progressive daily delay of the phase of the rhythm consistent with a period that is longer than 24 hours.

Diagnostic Criteria

Circadian Rhythm Sleep Disorder, Free-Running Type

(Nonentrained Type)

A. There is a complaint of insomnia or excessive sleepiness related to abnormal synchronization between the 24-hour light-dark cycle and the endogenous circadian rhythm of sleep and wake propensity.

B. Sleep log or actigraphy monitoring (with sleep diaries) for at least seven days demonstrates a pattern of sleep and wake times that typically delays each day with a period longer than 24 hours.

> ***Note:*** *Monitoring sleep logs or actigraphy for more than seven days is preferred in order to clearly establish the daily drift.*

C. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Clinical and Pathophysiologic Subtypes

Not applicable or known.

Unresolved Issues and Further Directions

There is only limited knowledge of the underlying pathophysiology of circadian rhythm sleep disorder, free-running type (nonentrained type) in sighted individuals. The relationship between circadian rhythm sleep disorder, delayed sleep phase type, and circadian rhythm sleep disorder, free-running type, (nonentrained type) requires further study.

Differential Diagnosis

Some individuals with *circadian rhythm sleep disorder, delayed sleep phase type*, may demonstrate progressive delay of their sleep period for several days, and their symptoms may be confused with those of circadian rhythm sleep disorder, free-running type (nonentrained type).

Behavioral factors and psychiatric disorders, as well as medical and neurological disorders (including, in particular, blindness, but also dementia or mental retardation), may play a role in the development of circadian rhythm disorder, free-running type. However, in many of these cases, multiple physiologic, behavioral and environmental factors contribute to the condition. In the majority of these cases, the disorder should be coded as circadian rhythm sleep disorder, free-running type. This includes free-running rhythms that are associated with blindness. However, if the sleep disorder is believed to be predominantly or exclusively socially or environmentally induced, then it should be coded as *other circadian rhythm sleep disorder (circadian rhythm sleep disorder, NOS).* If there is evidence that the sleep disorder is predominantly or exclusively a function of medical or neurological disorders, then state and code as *circadian rhythm sleep disorder due to medical condition.*

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Circadian Rhythm Sleep Disorder, Jet Lag Type (Jet Lag Disorder)

Alternate Names

Time zone change syndrome, jet lag syndrome.

Essential Features

Circadian rhythm sleep disorder, jet lag type, is a circadian rhythm sleep disorder in which there is a temporary mismatch between the timing of the sleep and wake cycle generated by the endogenous circadian clock and that of the sleep and wake pattern required by a change in time zone. Individuals complain of disturbed sleep, decreased subjective alertness, and impaired daytime function. The severity of symptoms is dependent on the number of time zones traveled and the direction of the travel. Eastward travel (requiring advancing circadian rhythms and sleep-wake hours) is usually more difficult to adjust to than westward travel.

Associated Features

In addition to sleep disturbance and decreased daytime alertness, associated features may include general malaise and gastrointestinal symptoms.

Demographics

Jet lag affects all age groups. However, in the elderly, symptoms may be more pronounced, and the rate of recovery may be more prolonged than in younger adults.

Predisposing and Precipitating Factors

Sleep deprivation, prolonged uncomfortable sitting positions, air quality and pressure, stress, and excessive caffeine and alcohol use may increase the severity of insomnia and impaired alertness and function associated with transmeridian travel.

Familial Patterns

Not applicable or known.

Onset, Course, and Complications

Jet lag is a temporary condition. Symptoms begin approximately one to two days after air travel across at least two time zones and are self-limited. The severity and duration of symptoms are usually in proportion to the number of time zones traveled and the direction of travel. It is estimated that it takes one day per time zone for circadian rhythms to adjust to the local time. However, if traveling more than six time zones, circadian rhythms may shift in the opposite direction of the direction of travel, resulting in prolonged duration and severity of jet-lag symptoms. Exposure to light at inappropriate times may prolong the time of adjustment by shifting the circadian rhythms in the opposite direction. Menstrual symptoms have been associated with frequent travel in female airline personnel. Hypnotic use in association with alcohol to treat symptoms of jet lag has been associated with amnesia.

Pathology and Pathophysiology

The symptoms of circadian rhythm sleep disorder, jet lag type, are due to both desynchronization of endogenous circadian rhythms with local time and sleep loss.

Polysomnographic and Other Objective Findings

Objective laboratory testing is usually not indicated. When performed, polysomnography or actigraphy shows a loss of a normal sleep-wake pattern or a mismatch between the timing of sleep and wakefulness with the desired sleep-wake pattern of the local time.

Diagnostic Criteria

Circadian Rhythm Sleep Disorder, Jet Lag Type
(Jet Lag Disorder)

A. There is a complaint of insomnia or excessive daytime sleepiness associated with transmeridian jet travel across at least two time zones.
B. There is associated impairment of daytime function, general malaise, or somatic symptoms such as gastrointestinal disturbance within one to two days after travel.
C. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Clinical and Pathophysiological Subtypes

There are individual differences in the ability to adjust to rapid shifts in time zones; however, specific clinical subtypes have not been identified.

Unresolved Issues and Further Directions

Effective and practical strategies to combat jet-lag symptoms and improve performance and safety are needed.

Differential Diagnosis

A thorough history and physical examination should be performed to exclude other mental, physical, or sleep disorders. Somatic complaints of gastrointestinal or urinary symptoms (*nocturia*) may indicate an underlying medical condition.

When jet-lag symptoms persist, increasing frustration, negative expectations, and poor sleep hygiene may predispose the individual to the development of *psychophysiological insomnia.*

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Circadian Rhythm Sleep Disorder, Shift Work Type (Shift Work Disorder)

Alternate Names

Shift work sleep disorder.

Essential Features

Circadian rhythm sleep disorder, shift work type, is characterized by complaints of insomnia or excessive sleepiness that occur in relation to work hours that are scheduled during the usual sleep period. There are several types of shift-work schedules, including night shifts, early morning shifts, and rotating shifts. The sleep disturbance is most commonly reported in association with the night and early morning shifts. Total sleep time is typically curtailed by one to four hours in night and early morning shift workers, and sleep quality is perceived as unsatisfactory. In addition to impairment of performance at work, reduced alertness may also be associated with consequences for safety. The sleep disorder occurs despite attempts to optimize environmental conditions for sleep. The condition usually persists for the duration of the work-shift period. However, in some individuals, the sleep disturbance may persist beyond the duration of shift work.

Associated Features

Early morning work shifts starting between 4 a.m. and 7 a.m. may also be associated with complaints of difficulty in sleep initiation as well as difficulty awakening. Permanent evening shifts may also be associated with difficulties initiating the major sleep episode. Excessive sleepiness usually occurs during work shifts (mainly night), often accompanied by the need to nap and impaired mental ability because of the reduced alertness. Reduced alertness, not only during the work shift, may be associated with reduced performance capacity, and with consequences for safety. Also, major portions of free time may have to be used for recovery of sleep, which has negative social consequences. There is also increased irritability, presumably related to the lack of sleep or to the conflict between demands for sleep and demands for social activities.

Demographics

The prevalence of shift work disorder depends on the prevalence of shift work in the population. It has been estimated that 20% of the workforce in industrialized countries is employed in a job that requires shift work. Although the actual prevalence of clinically significant sleep disturbance and excessive daytime sleepiness due to work schedules is unknown, the total number of night-shift workers suggests that an estimated prevalence of 2% to 5% is reasonable. These figures do not, however, include individuals with early morning work, which may be another at-risk group. There is no known sex difference in vulnerability.

Predisposing and Precipitating Factors

Depending on the type of shift, diurnal or circadian preference may influence the ability to adjust to shift work. For example, individuals described as morning types appear to obtain shorter daytime sleep after a night shift. Persons with comorbid medical, psychiatric and other sleep disorders such as sleep apnea and individuals with a strong need for stable hours of sleep may be at particular risk.

Familial Pattern

Not applicable or known.

Onset, Course, and Complications

The condition is closely linked to work schedules and typically remits when the major sleep period is scheduled at a conventional time. Because there are so many different work schedules, ranging from an occasional overnight shift to regular night work, the course is quite variable. Since shift work is often combined with extended hours of duty, fatigue can be a complicating factor. Circadian adaptation is often counteracted by exposure to light at the wrong time of the day and the tendency of most workers to resume full daytime activities and nighttime sleep during weekends and vacations. It has been hypothesized that in some individuals, the condition may lead to chronic sleep disturbances.

Complications may include exacerbation of gastrointestinal and cardiovascular disorders. Disruptions of social and family life are frequent. Drug and alcohol dependency may result from attempts to improve the sleep

and wakefulness disturbances produced by shift work. Fatigue and excessive sleepiness due to the combination of sleep loss and circadian misalignment pose important safety concerns. The level of alertness required of the worker, in addition to the intensity of symptoms, needs to be taken into account when evaluating the disorder. For example, the threshold for intervention may be lower for workers whose performance is critical for personal or public safety (for example, a nuclear power plant operator).

Pathology and Pathophysiology

The condition is directly related to the sleep-generated interface by a circadian alerting process that corresponds with the time that the worker needs to sleep. The excessive sleepiness during the night appears to be partly related to cumulative sleep loss and partly due to decreased circadian alerting signal that corresponds with the work time. Tolerance to night work varies considerably and may involve differences in the degree of circadian adaptation ("clock resetting") to a night-work, day-sleep schedule. Alternatively, tolerance may be related to individual differences in the relative balance of circadian and homeostatic influences on sleep and wake regulation.

Polysomnographic and Objective Findings

The condition can usually be diagnosed by history. Polysomnographic recordings may be useful if the sleep disorder is severe or the etiology of the sleep disturbance is in question. Ideally, the sleep recording is performed during the habitual "shifted" sleep period. Monitoring of an episode of usual daytime wakefulness and night sleep during a daytime shift is ideal for comparative purposes. Polysomnography may demonstrate impaired quality of the habitual sleep period, with either a prolonged sleep latency or shortened total sleep time, depending on the timing of the sleep period in relation to the underlying phase of the circadian timing system. The sleep period may be fragmented, with frequent arousals and awakenings. The Multiple Sleep Latency Test (MSLT) may demonstrate excessive sleepiness during the time of the work shift.

Sleep diaries and actigraphy are very useful in demonstrating a disrupted sleep-wake pattern consistent with shift work sleep disorder. If available, measures of the unmasked melatonin or 24-hour temperature rhythm are useful to indicate the degree of circadian desynchrony.

Diagnostic Criteria

Circadian Rhythm Sleep Disorder, Shift Work Type
(Shift Work Disorder)

A. There is a complaint of insomnia or excessive sleepiness that is temporally associated with a recurring work schedule that overlaps the usual time for sleep.
B. The symptoms are associated with the shift-work schedule over the course of at least one month.
C. Sleep log or actigraphy monitoring (with sleep diaries) for at least seven days demonstrates disturbed circadian and sleep-time misalignment.
D. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Clinical and Pathophysiological Subtypes

There are substantial individual differences in the ability to adjust to shift work. However, definite clinical and pathologic subtypes have not been identified.

Unresolved Issues

Although there is sufficient information regarding the prevalence of shift workers in industrialized populations, less information is available regarding the actual prevalence of shift work disorder and its impact on health. Further research to improve the definition of what constitutes shift work disorder and a better understanding of the basis for individual differences observed in the ability to cope with shift work is needed.

Differential Diagnosis

The excessive sleepiness should be differentiated from that due to other primary sleep disorders such as *obstructive sleep apnea* or *narcolepsy. Insufficient sleep* related to conflicting daytime activities (for example, child care) or from environmental interference with sleep (for example, daytime noise) often contributes to sleepiness. Sometimes patients with *delayed sleep phase disorder* may adopt a night-work schedule that is more congruent with their sleep preferences.

Insomnia and *excessive sleepiness* may suggest other persistent circadian rhythm sleep disorders. However, historical information on the relation between the occurrence of disturbed sleep and work-hour distribution should provide sufficient information to indicate the correct diagnosis.

Increasing frustration, negative expectations, and poor sleep hygiene may predispose the person to the development of coexisting *psychophysiological insomnia. Drug and alcohol abuse or dependency* may result from efforts to treat the sleep disturbance.

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Circadian Rhythm Sleep Disorder Due to Medical Condition

Alternate Names

Not applicable or known.

Essential Features

The etiology of the circadian rhythm sleep disorder is an underlying primary medical or neurological condition. Depending on the underlying neurological or medical disorder, patients may present with a variety of symptoms, including insomnia and excessive sleepiness. The sleep-wake pattern may range from alterations in phase to irregular sleep-wake patterns.

Associated Features

The particular features of this disorder vary with the type of underlying medical or neurological condition.

Demographics

Demographics are specific for the different underlying disorders.

Predisposing and Precipitating Factors

The underlying neurological or medical condition is the precipitating factor. Decreased exposure to light and structured physical and social activities may also influence the severity of the condition.

Familial Patterns

Not applicable or known.

Onset, Course, and Complications

Disruption of the sleep-wake cycle leads to poor sleep quality and impaired neurocognitive as well as physical performance. Circadian rhythm disturbances are often observed in neurological disorders and may exacerbate the symptoms of the underlying condition.

Pathology and Pathophysiology

The presumed pathophysiology is an alteration of circadian timing due to the effects of the underlying neurological or medical condition.

Polysomnographic and Other Objective Findings

Sleep studies yield different results depending on when they are performed and the alterations in sleep architecture that may accompany the underlying medical or neurological disorder. Recordings of sleep diaries and actigraphy over a period of at least seven days demonstrate sleep onsets and sleep offsets that may be delayed or advanced relative to conventional times, irregular or free running. Laboratory measures to determine the phase and amplitude of circadian rhythms generally show the expected phase advance or delay of circadian rhythms or a decrease in the amplitude.

Diagnostic Criteria

Circadian Rhythm Sleep Disorder Due to Medical Condition

A. There is a complaint of insomnia or excessive sleepiness related to alterations of the circadian timekeeping system or a misalignment between the endogenous circadian rhythm and exogenous factors that affect the timing or duration of sleep.
B. An underlying medical or neurological disorder predominantly accounts for the circadian rhythm sleep disorder.
C. Sleep log or actigraphy monitoring (with sleep diaries) for at least seven days demonstrates disturbed or low amplitude circadian rhythmicity.
D. The sleep disturbance is not better explained by another current sleep disorder, mental disorder, medication use, or substance use disorder.

Clinical and Pathophysiological Subtypes

Several medical and neurological conditions have been associated with circadian rhythm disturbances.

Dementia: Sleep-wake cycle abnormalities and evidence of circadian rhythm dysregulation are common in patients with dementia and Alzheimer's disease, and the type of circadian abnormalities range from alterations in sleep phase to decreased amplitude or lack of discernible circadian rhythms. The disruption of the sleep-wake cycle has been implicated in the etiology of "sundowning" and nocturnal wandering in this patient population.

Movement disorders: Patients with Parkinson's disease may exhibit various types of circadian-rhythm alterations. In addition, motor fluctuations can exhibit marked diurnal fluctuation in patients with Parkinson's disease.

Blindness: Approximately 70% of blind individuals complain of sleep disturbances, and 40% have chronic recurrent cyclical sleep disturbances. Blind people with a free-running rhythm should be coded as circadian rhythm sleep disorder, free-running type; other rhythm disorders may be coded here.

Hepatic encephalopathy: Disturbances of the sleep-wake cycle are common among patients with hepatic disease. Patients with liver cirrhosis complain of insomnia and excessive sleepiness. A pattern of circadian rhythm sleep disorder, delayed sleep phase type, may be seen in these patients.

Unresolved Issues and Further Directions

Disruption of circadian rhythms is common in many neurological and medical conditions. However, the specific mechanisms by which the underlying neurological or medical conditions result in alterations in circadian rhythms are unknown.

Differential Diagnosis

The main difficulty in establishing the diagnosis is to determine whether the primary cause is a medical or neurological disorder or an alteration in exposure to circadian synchronizing agents such as light and activity.

Depending upon the particular type of circadian disturbance, clinical presentations may suggest difficulty initiating or maintaining sleep or excessive sleepiness. See Differential Diagnosis sections for other specific circadian rhythm sleep disorders for additional discussion.

Diagnostic Criteria

Circadian Rhythm Sleep Disorder Due to Medical Condition

A. There is a complaint of insomnia or excessive sleepiness related to alterations of the circadian timekeeping system or a misalignment between the endogenous circadian rhythm and exogenous factors that affect the timing or duration of sleep.
B. An underlying medical or neurological disorder predominantly accounts for the circadian rhythm sleep disorder.
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Other Circadian Rhythm Sleep Disorder (Circadian Rhythm Disorder, NOS)

Disorders that: 1) satisfy the criteria of a circadian rhythm sleep disorder, as defined above; 2) are not due to drug or substance; and 3) do not meet criteria for other circadian rhythm sleep disorders are classified here.

Other Circadian Rhythm Sleep Disorder Due to Drug or Substance

Disorders that: 1) satisfy the general criteria of a circadian rhythm sleep disorder, as defined above; 2) are due to a drug or substance; and 3) do not meet criteria for other circadian rhythm sleep disorders are classified here.

Screening for depression in primary care with two verbally asked questions: cross sectional study

Bruce Arroll, Natalie Khin, Ngaire Kerse

Editorial by Del Mar and Glasziou

Department of General Practice and Primary Health Care, Faculty of Medical and Health Sciences, University of Auckland, PB 92019, Auckland, New Zealand
Bruce Arroll *associate professor*
Ngaire Kerse *senior lecturer*
Department of Psychiatry, University of Auckland
Natalie Khin *PhD student*
Correspondence to: B Arroll b.arroll@auckland.ac.nz

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Abstract

Objective To determine the diagnostic accuracy of two verbally asked questions for screening for depression.
Design Cross sectional criterion standard validation study.
Setting 15 general practices in New Zealand.
Participants 421 consecutive patients not taking psychotropic drugs.
Main outcome measures Sensitivity, specificity, and likelihood ratios of the two questions compared with the computerised composite international diagnostic interview.
Results The two screening questions showed a sensitivity and specificity of 97% (95% confidence interval, 83% to 99%) and 67% (62% to 72%), respectively. The likelihood ratio for a positive test was 2.9 (2.5 to 3.4) and the likelihood ratio for a negative test was 0.05 (0.01 to 0.35). Overall, 37% (157/421) of the patients screened positive for depression.
Conclusion Two verbally asked questions for screening for depression would detect most cases of depression in general practice. The questions have the advantage of brevity. As treatment is more likely when doctors make the diagnosis, these questions may have even greater utility.

Introduction

Depression is a common and costly mental health problem seen often in general practice and general medicine.[1] In 2002 the US Preventive Services Task Force endorsed screening for depression but did not recommend a specific screening tool.[2] A systematic review found that screening for depression was not effective in improving psychosocial outcomes.[3] The US Preventive Services Task Force claims that its review is more extensive.

Many practitioners find the numerous case finding and screening questionnaires for depression too cumbersome and time consuming for routine use.[4] A feasible screening tool for use in general practice would comprise one or two questions, which, if positive, could be followed by further questions from the depression criteria. The primary care evaluation of mental disorders, designed to facilitate the diagnosis of common mental disorders in general practice, involved a screening questionnaire with 27 items and a follow up interview with a clinician.[5] The questionnaire included two questions about depressed mood: during the past month have you often been bothered by feeling down, depressed, or hopeless? and, during the past month have you often been bothered by little interest or pleasure in doing things? One study of these questions reported a sensitivity of 96% and a specificity of 57% compared with the quick diagnostic interview schedule.[6] We aimed to evaluate the questions when asked verbally, instead of in the written form, by general practitioners in the community.[5 6]

Participants and methods

From a database of Auckland general practices we randomly selected 15 general practices. Each general practitioner asked the two questions at any time during a consultation, and if either was positive, screening was considered positive. The general practitioners had access to the usual patient notes. They completed a form of the patient's responses and whether or not safety issues, such as suicidal thoughts, had been addressed. The study interviewer looked at the form after the patient had completed the mood module of the computer assisted composite international diagnostic interview.[7–9] Patients had no opportunity to start treatment before completing the composite interview. This interview takes the participant's answers, provided without any interpretation, probe, or explanation by the interviewer, as valid data for arriving at a diagnosis. It has been evaluated for test-retest reliability and compared with the schedules for clinical assessment in neuropsychiatry.[8 9]

The calculator on the University of Toronto website was used to determine the sensitivity, specificity, and likelihood ratios.[10–12] Our study was designed and analysed as recommended by the Standards for Reporting Diagnostic Accuracy Steering Group.[13]

Results

Overall, 670 consecutive patients were invited by their general practitioners to participate in our study. Of these, 476 took part (response rate 71.0%): 142 men, 330 women, and four had missing data (figure). The median age was 46 (range 16 to 90). We excluded 47 patients who were taking psychotropic drugs, 194

Table 1 Validity and positive predictive value for screening questions and physician diagnosis compared with composite international diagnostic interview as ideal screening tool for major depression

Screening question	Patients screened positive		Patients screened negative		Positive predictive value (%)
	True positive	False positive	True negative	False negative	
Both questions*	28	129	263	1	18
Depression question	25	111	281	4	18
Pleasure question	24	84	308	5	22

*Positive is yes to either question.

Table 2 Sensitivity, specificity, and likelihood ratios with composite international diagnostic interview as ideal screening tool for major depression

Screening question	Sensitivity % (95% CI)	Specificity % (95% CI)	Likelihood ratio	
			Positive test (95% CI)	Negative test (95% CI)
Both questions	97 (83 to 99)	67 (62 to 72)	2.9 (2.5 to 3.4)	0.05 (0.01 to 0.35)
Depression only question	86 (69 to 95)	72 (67 to 76)	3.0 (2.5 to 3.8)	0.19 (0.08 to 0.48)
Pleasure only question	83 (66 to 92)	79 (74 to 82)	3.9 (3.0 to 5.0)	0.22 (0.1 to 0.49)

declined, and eight were not asked the screening question. In total, 421 patients were asked the two screening questions. According to the composite interview, 28 of the 157 (18%) who screened positive were depressed, whereas only one of the 264 who screened negative was depressed.

Table 1 shows the raw data for both questions and each question and the positive predictive value when using the composite interview as the ideal screening tool. Table 2 shows the sensitivity, specificity, and likelihood ratios for both questions and the questions separately. A yes to either question was considered a positive response. The questions showed a sensitivity of 97% (95% confidence interval 83% to 99%) and a specificity of 67% (62% to 72%). The high sensitivity was accompanied by a high number of false positive results. This is reflected in the modest likelihood ratio for a positive test and the positive predictive value of 18%. On the other hand, the likelihood ratio for a negative test was low, and at the prevalence of 6% for major depression a negative test would almost always be a true negative (negative predictive value 99%).

What is already known on this topic

Screening for depression in general practice is effective at diagnosing depression and optimising treatment

Screening tests are usually in written form

What this study adds

Two questions verbally asked are potentially useful for screening for depression owing to reasonable validity and brevity

A reasonable trade-off exists between true and false positives

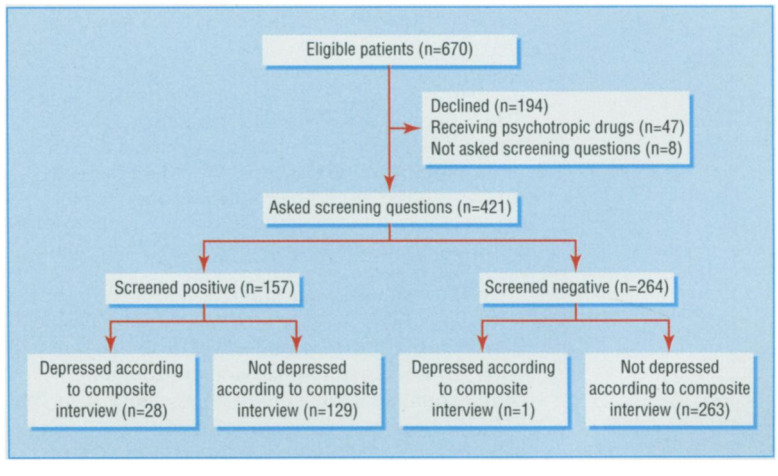
The questions detect most cases of depression

Discussion

Two verbally asked questions from the original primary care evaluation of mental disorders have good sensitivity and reasonable specificity for screening for depression. The 97% sensitivity we found is an improvement over the 29% to 35% often reported.[14] The post-test probabilities suggest about five false positives for every true positive when asking the questions alone. This is common in screening studies, which are in essence a diagnostic test performed in a "low prevalence" setting. This is not a major concern with depression, as further clarification can be obtained by asking more questions (the reference standard) or referral to another health professional.

Our study was conducted in a community setting by general practitioners and analysed after exclusion of patients taking psychotropic drugs. It is the first assessment of the questions administered verbally rather than in written form. A weakness of our study is that there was no non-screened group as a comparator.

The prevalence for screening studies for depression in general practice is usually low (8% for major depression); hence the likelihood ratio for a negative test does not need to be low to rule out depression when the test is negative (in this sample a patient with a negative test would have a 0.3% chance of being depressed). Also, when compared with the 41 studies evaluated by the US Preventive Services Task Force, the two questions (verbally asked) had a similar likelihood ratio for a positive test compared with most studies in that review.[15] The two questions were, however, considerably shorter than the shortest (seven questions)



Flow of participants through trial

screening questionnaire.[16] They are thus a good compromise between the time required to administer the screen and the likelihood ratio. The additional benefit is that general practitioners are more likely to prescribe drugs to patients in whom they have made the diagnosis.[17]

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Curiouser and curiouser

Last week we buried my father in law, David. He was 92 and had had a full life. We put him to rest in a natural woodland site, and it was a joyful day.

His three sons each spoke beside his coffin. Curiosity was a strong theme. He had a never ending curiosity for how things worked—engines, boats, paints, clays, instruments. For about the past 20 years he had professed not to be able to see or hear, yet he skillfully made and mended clocks. Curiosity, apparently, overcame his disabilities. (Selective deafness was also a hypothesis.) He accepted what he could do and not do and went ahead and did what he could with great tenacity and perseverance.

He had a healthy irreverence, a naughtiness, which his grandchildren loved. Adults also benefited from it. A retired hill farmer friend who came to the funeral remembered how David had wanted to build a still on his land. "But that's illegal." "So?" He had wanted to know how it would work.

People's curiosities vary. This year's Reith lecturer, the neuroscientist Vilinor Ramachandran, speaking on "The emerging mind" showed a passion, not for the wiring of boat engines but for the wiring of the human brain. An intense curiosity about what goes wrong with the wiring to produce sensory anomalies, such as synaesthesia, drives him on to know more and more and to inspire others to know more and more.

Curiosity about people and how they work—physically, mentally, emotionally, spiritually—is at the heart of what doctors do. It drives us. Yes, other "C" words—communication, collaboration, consultation, computers even—are also important. But in a culture increasingly oriented towards data collection and management, this people curiosity is precious. There are nine general practitioners in my practice, and we spend a lot of time discussing chronic disease management protocols and care management screens. Nine doctors, nine views. The optimistic view is that all the energy and time diverted into this will create efficient systems that will liberate time for being curious about people, for being a family doctor. The less optimistic view is that, once the climate has been changed to the extent that it has, cultivating the curiosity strain of the species may become more difficult. Yet this is the strain the consumers want and the health service needs, the one most likely to produce good crops (of GPs) in the future. (Gardening was another of David's hobbies.)

Feeding the fire of curiosity, about engines and clocks and how machines work, gave my father in law a long and happy life. Sorry, another horticultural analogy: the healthy growth of general practice depends on keeping the balance of the soil right, on feeding the curiosity. And perhaps the naughtiness?

Lesley Morrison *general practitioner principal, Teviot Medical Practice, Hawick*

We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. Please submit the article on http://sdubmit.bmj.com Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.

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Shift-work disorder

The social and economic burden of shift-work disorder

Larry Culpepper, MD, MPH

The characterization and pathology of circadian rhythm sleep disorders

Christopher L. Drake, PhD

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Managing the patient with shift-work disorder

Michael J. Thorpy, MD

Shift-work disorder

CONTENTS AND FACULTY

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Disclosures

Dr Culpepper reports that he serves as a consultant to AstraZeneca, Eli Lilly and Company, Pfizer Inc, Wyeth, sanofi-aventis, and Takeda Pharmaceuticals North America, Inc, and on the speakers bureau of Wyeth.

Dr Drake reports that he has received research support from Cephalon, Inc., Takeda Pharmaceuticals North America, Inc, and Zeo, Inc., and has served on the speakers bureaus of Cephalon, Inc., and as a consultant to sanofi-aventis.

Dr Schwartz reports that he serves as a consultant to and on the speakers bureaus of AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Inc., Cephalon, Inc., Pfizer Inc, Sepracor Inc., Takeda Pharmaceuticals North America, Inc, and GlaxoSmithKline.

Dr Thorpy reports that he serves as a consultant to and on the speakers bureaus of Cephalon, Inc., and Jazz Pharmaceuticals, Inc.

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The social and economic burden of shift-work disorder

Larry Culpepper, MD, MPH
Department of Family Medicine
Boston University Medical Center
Boston, Massachusetts

Practice recommendations

- Shift-work disorder (SWD) and its defining symptoms can negatively affect health, quality of life, and work performance. The gravity of these consequences necessitates vigilance for the symptoms of SWD by primary care physicians (**SOR: B**).
- The threshold for treatment intervention for emergency service workers, such as firefighters, who make crucial decisions under shift-work conditions and who are experiencing SWD should be lower than for shift workers in general (**SOR: B**).
- The economic costs of untreated SWD are likely to be high. Early diagnosis and treatment of SWD may reduce these costs in addition to reducing the human burden of this circadian rhythm sleep disorder (**SOR: C**).

Dr Culpepper reports that he serves as a consultant to AstraZeneca, Eli Lilly and Company, Pfizer Inc, Wyeth, sanofi-aventis, and Takeda Pharmaceuticals North America, Inc, and on the speakers bureau of Wyeth.

Shift work is a fundamental component of working patterns across the US workforce and is therefore an integral part of the lifestyle of a large proportion of the population. However, shift workers are at risk of developing the circadian rhythm sleep disorder shift-work disorder (SWD), a clinically recognized condition that develops in some individuals who work at night, start work early in the morning (4 to 7 AM), or work according to a rotating-shift schedule. SWD is more severe than—and distinct from—the sleep disturbances commonly associated with shift work. Provided other sleep/wake disorders can be discounted, SWD is diagnosed by the presence of excessive sleepiness (ES) and/or insomnia for ≥1 month during which the individual is performing shift work.[1]

Shift work poses a serious public health risk, as it can impair an individual's ability to perform effectively and may lead to occupational or traffic accidents. Furthermore, shift work has numerous negative health effects and infringes on an individual's ability to sleep, eat normally, exercise, and develop relationships. However, SWD is underrecognized in the clinical setting,[2] and data regarding its epidemiology and etiology are scarce in the scientific literature. Published information regarding shift work in general has therefore been used as the foundation for informing the clinical community on the potential burden of SWD. It is incumbent on primary care physicians to be vigilant for SWD in shift workers, make an accurate diagnosis, and initiate appropriate treatment in order to relieve—and prevent—the acute consequences and long-term health sequelae of this disorder, as well as to ensure public safety.

This supplement describes the burden of SWD, discusses the current understanding of the processes that cause this and other circadian rhythm sleep disorders, and describes the recognition and available management strategies for SWD. This article reviews the prevalence of SWD and examines the scale of its social and economic burden, including associated comorbidities. In the second article, Dr Chris Drake explains the causes of SWD and other circadian rhythm sleep disorders by describing the circadian and homeostatic systems and detailing how lifestyle factors, individual susceptibility, morbidity, and genetic components can result in circadian rhythm pathology.

The diagnosis of SWD is particularly challenging because its defining symptoms of ES and/or insomnia are demonstrated by numerous morbidities, including other sleep disorders. Furthermore, normal and abnormal responses to the challenge of shift work are not easily differentiated, and current diagnostic criteria require additional validation.[3] Identification of SWD relies on detailed discussion of a patient's medical history, knowledge of relevant risk factors, and differential diagnosis to rule out other potentially causative medical conditions. Dr Jonathan Schwartz provides a comprehensive guide to recognizing and diagnosing patients with SWD in the third article of this supplement. In the final article, Dr Michael Thorpy discusses the behavioral and pharmacologic options available for patients with SWD in order to address ES and insomnia as well as comorbidities. He also supplies a useful algorithm to assist with the treatment of SWD in the primary care setting.

Epidemiology of SWD, insomnia, and ES in shift workers

For approximately 22 million US adults, shift work is an integral part of their professional life.[4] Of these individuals, about 3.8 million regularly work night shifts, and an additional 3.3 million perform night-shift work on a rotating basis.[5]

Drake and colleagues[6] used a telephone questionnaire to conduct a study of the prevalence of SWD in the general population of Detroit, MI; 2036 day-shift, 360 rotating-shift, and 174 night-shift workers participated. This study used minimum *International Classification of Sleep Disorders 2* (ICSD–2) criteria to define SWD[1]; namely, subjects with ES and/or insomnia who had been working either a night-shift or a rotating-shift schedule for the past 2 weeks were diagnosed with SWD. In this study, ES was defined by an Epworth Sleepiness Scale (ESS)[7] score of the total sample mean + 1 standard deviation (effectively, an ESS score of ≥13, compared with the more commonly applied ES diagnostic score of ≥10). Insomnia was diagnosed using *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* criteria,[8] ie, the subject had experienced periodic recurrences of difficulty in falling asleep, staying asleep, or nonrestorative sleep for at least 1 month, with a self-reported severity of at least 6 points out of a possible score of 10 on a visual analog scale.

Drake and colleagues[6] reported that 32.1% and 26.1% of night-shift and rotating-shift workers, respectively, met their prespecified ES and/or insomnia criteria, compared with 18.0% of day workers. The differential "true" prevalence of ES and insomnia—and therefore SWD—in night-shift and rotating-shift workers was reported to be approximately 14.1% and 8.1%, respectively. When it is considered that approximately 6% of all workers in the United States perform night- or rotating-shift work, the overall prevalence of SWD in the general population was estimated to be approximately 1%.[6] This result is lower than the 2% to 5% estimated in the ICSD–2 coding manual,[1] and some sleep specialists have argued that the figure put forward by Drake and colleagues[6] is conservative.[3] However, Drake and colleagues[6] also applied the more usual ES diagnostic measure of an ESS score of ≥10 and, using this criterion, found a much higher prevalence of ES in their study population: 44.8% of night-shift workers and 35.8% of rotating-shift workers were found to have ES and therefore would also be considered to have SWD, provided their symptoms persisted for ≥1 month.

A recent study of 4471 US police officers reported that 2.0% of this population had SWD, which was defined by the occurrence of both insomnia and ES in association with a recurrent schedule of work that overlapped the normal rest period.[9]

Epidemiologic data for SWD are sparse and additional studies are warranted. Few overt data exist for the prevalence of SWD. Although the occurrence of insomnia and/or ES has been studied in various shift-working populations, frequently only one symptom is analyzed. Shift-working individuals who have either symptom for ≥1 month should be regarded as meeting the diagnostic criteria for SWD even if this is not stated explicitly by the respective study investigators.

For example, the Helsinki Heart Study examined the occurrence of insomnia and/or ES over a 3-month period in a population of approximately 3000 middle-aged men participating in a coronary heart disease prevention trial.[10] Persistent insomnia was reported by approximately 50% of rotating- and night-shift workers, whereas persistent ES was reported by approximately 25% of shift workers overall; those with ES and/or insomnia therefore met the diagnostic criteria for SWD.[10]

By contrast, a study using the Multiple Sleep Latency Test in a population of shift-working, long-haul bus drivers reported that the criteria for ES were met by 38% to 42% of subjects.[11] However, as the time frame over which patients experienced ES was not measured in this study, these patients should be viewed as being at risk of developing SWD, as opposed to having SWD per se.[11]

Similarly, in a study of police officers, insomnia or hypersomnia were reported by a significantly higher proportion of shift-working personnel compared with

their day-working colleagues (insomnia, 25.9% vs 15.8% [$P < .001$]; hypersomnia, 4.9% vs 2.2% [$P < .02$]).[12] The absence of data regarding persistence of these symptoms precludes diagnosis of SWD in these patients.

Other studies have reported the prevalence of unplanned napping at work, which may be indicative of ES or sleep deprivation. For example, in a study of almost 700 registered female nurses, approximately 35% and 32% of participants working rotating or night shifts, respectively, reported episodes of unplanned sleep at work and may therefore have been at risk for developing SWD.[13]

Comorbidities associated with shift work and SWD

There are few reported studies regarding comorbidities in patients with SWD, although a large epidemiologic study has reported that patients with SWD are significantly more likely to experience comorbidities than are day workers or shift workers without SWD ($P < .05$).[6] Shift work has adverse effects on health even in the absence of SWD, although to date there is no evidence that shift work directly affects longevity.[14,15]

Metabolic disturbance and gastrointestinal issues

The relationship between sleep disturbance and obesity is well documented but poorly understood due to its complexity.[16] Sleep deprivation in particular has been implicated in the pathogenesis of weight gain and diabetes, and it may be that recognition and treatment of sleep disorders in general may assist with curtailing the current obesity epidemic.[17]

In a study of 500 male municipal workers in Italy, 3 of the 5 diagnostic symptoms of metabolic syndrome—obesity, elevated cholesterol, and raised triglyceride levels—were found significantly more frequently in night-shift workers than in day workers ($P < .001$, $P < .01$, and $P < .001$, respectively), indicating that shift work is associated with significant metabolic disturbance.[18] This report extended the findings of an earlier study that demonstrated that shift workers at a chemical plant in Italy had a significantly higher mean body mass index (BMI) than their day-working colleagues (27.7 kg/m^2 vs 26.5 kg/m^2, respectively; $P < .01$).[19] In addition, the prevalence of diabetes increased with duration of exposure to shift work, and markers of insulin resistance were more common in shift workers than in day workers.[20,21]

Compared with day workers, shift workers also have higher rates of peptic ulcers and gastrointestinal problems, such as constipation and diarrhea.[22,23] These findings were confirmed by a large trial of US workers, which reported that night-shift workers (odds ratio [OR], 3.13; 95% confidence interval [CI], 1.62-6.05), rotating-shift workers (OR, 2.32; 95% CI, 1.32-4.06), and subjects diagnosed with symptoms of SWD (OR, 4.55; 95% CI, 2.47-8.37) experienced increased rates of peptic ulcers compared with day workers ($P < .001$ for all comparisons).[6] Furthermore, both the effects of shift work and the symptoms of SWD contributed cumulatively to the increased likelihood of developing an ulcer among patients with SWD.[6]

Metabolic disturbance and gastrointestinal symptoms in shift workers and patients with SWD may arise in response to eating at unusual times of day, as food intake acts as a cue for the synchronization of the circadian clock. Moreover, gastric secretions in the middle of the night oppose the intrinsic circadian rhythm of enzymatic activity set by the light/dark cycle. The increased consumption of caffeine and alcohol used as coping strategies by many shift workers may also lead to gastrointestinal sequelae.[24]

Cardiovascular issues

Heart rate and blood pressure vary throughout the day due to circadian control; however, persistent nocturnal activity due to night work reportedly limits or abolishes the normal nocturnal reductions in blood pressure and decreases heart rate variability.[25,26] Individuals who do not experience circadian-driven fluctuations in blood pressure are likely to develop hypertension, which may lead to further cardiovascular sequelae.[27] In addition, there is some evidence that ES may be a risk factor for hypertension.[28] Shift workers have a 40% increased risk of developing cardiovascular disease compared with day workers.[29] Interestingly, a large study of the general population in Detroit, MI, reported that while night-shift (OR, 2.57; 95% CI, 1.24-5.30) and rotating-shift work (OR, 2.01; 95% CI, 1.06-3.83) were associated with an increased risk of heart disease ($P = .01$), the symptoms of SWD per se did not additionally exacerbate heart disease.[6] However, a cohort study of nearly 6000 participants (the Cardiovascular Health Study) reported that ES is linked with increased rates of myocardial infarction, total and cardiovascular mortality, and congestive heart failure,[30] although differences between the study populations in this and the study by Drake and colleagues[6] preclude direct comparison of their results.

Changes in hormone secretion, autonomic and sympathetic cardiac control, metabolism, and heart rate while working at night are implicated in shift-work-related cardiovascular problems.[18,31] Other factors, such

as heightened levels of stress relating to work dissatisfaction and an absence of social support, may also play a part.[29,32] Furthermore, increased rates of smoking and more frequent rates of overweight contribute to the increased risk of developing cardiovascular problems in this patient population.[18,29]

Cancer

Increased rates of breast, prostate, and colorectal cancer have been reported in occupations typically associated with night-shift work, such as firefighting, health care, and law enforcement.[33-39] For example, a study of long-term shift-working nurses reported that this population was at a moderately increased risk of breast and colorectal cancer. Nurses who had worked for ≥20 years on a rotating night-shift schedule had a relative risk of breast cancer of 1.79 (95% CI, 1.06-3.01) compared with non–shift-working nurses.[39] The risk of developing breast cancer increased with longer working hours and increased duration of night-shift working.[34] The relative risk of colon cancer in nurses who had worked a rotating night-shift for ≥15 years compared with nurses who never worked night shifts was 1.35 (95% CI, 1.03-1.77).[38]

Women who are awake during what would normally be the period of peak melatonin production (ie, at night) due to work commitments or poor sleep habits have been shown to have an increased risk of developing breast cancer (OR, 1.14 for each night per week; 95% CI, 1.01-1.28).[34] It may be that increased rates of cancer in shift-working populations are due to a reduction in night-time melatonin production, which has been shown to increase the incidence of tumors in animal models.[40,41] Dysregulation of circadian genes in cancer-related pathways or altered hormone production have also been implicated in raising the risk of cancer in shift-working individuals.[42,43]

Reproductive health

In addition to an increased risk of developing breast cancer, shift-working women are also more likely than day workers to experience irregular menstruation, reduced fertility, and problems during pregnancy.[44-46] Moreover, women working rotating shifts have more difficulty becoming pregnant than night-shift working women.[47,48]

Sleep disorders

The chronic sleep deprivation experienced by individuals with insomnia, including shift workers and those with SWD, is linked to reduced serum iron levels, which in turn leads to additional sleep problems such as restless legs syndrome or periodic limb movement disorder.[12,49] Periodic limb movement disorder occurs in 8.5% of shift workers, compared with 4.2% of non–shift workers ($P < .005$).[12] Fatigue (weariness without feeling sleepy) is frequently reported by shift workers and is often a manifestation of an underlying sleep disorder that is disrupting sleep quality.[50] The reported prevalence of sleep disorders other than SWD in shift workers is approximately 30%.[51]

Mood and anxiety disorders

High rates of depression have been reported in shift workers, particularly in women.[52] Furthermore, depression and SWD can both manifest as impairment in memory and concentration and may also result in apathy and lethargy. It is therefore vital that shift-working patients who present with symptoms of depression are asked about their sleep habits in order to avoid misdiagnosis of a mood disorder.

Shift work is thought to exacerbate existing mood disorders; this may be due to a lack of bright light exposure, as is the case with patients who experience seasonal affective disorder.[53] A large epidemiologic study has reported that symptoms of SWD were associated with elevated rates of depression (OR, 2.57; 95% CI, 2.01-3.27).[6] Interestingly, rates of depression did not differ between day, night-shift, and rotating-shift workers who did not have SWD. The findings indicate that, although SWD may be associated with depression, shift work alone does not elevate the risk of developing this mood disorder.[6] Assessment of shift-working radar controllers in the US Air Force using the Zung Anxiety and Depression Scales showed that shift workers with SWD had a greater likelihood of experiencing anxiety than did their shift-working colleagues without SWD ($P < .01$), and they were also significantly more prone to depression ($P < .01$).[54]

Cognitive effects associated with shift work and SWD

Memory consolidation, learning, alertness, and performance are severely affected by sleep deprivation, even in the absence of circadian misalignment.[55,56] Moreover, ES has detrimental effects on memory, impedes concentration, and impairs learning and work performance, regardless of its etiology.[57-59] A recent study has assessed learning in healthy patients who lived under shift-work conditions in a laboratory devoid of time cues by measuring improvements in the Mathematical Addition Test

and the Digit Symbol Substitution Task.[60] Circadian misalignment was found to be detrimental to learning in subjects who failed to adapt to their imposed schedule of sleep and wake.[60] Thus individuals who experience ES, sleep deprivation, and sleep/wake synchronization issues as a result of SWD are likely to be particularly affected in this respect.

ES can be severe in night-shift workers (defined by an ESS score ≥18)[7] and becomes most pronounced in terms of impaired performance between 3 and 6 AM.[55] Reductions in sleep duration of between 1 and 4 hours per day have been reported in night-shift populations, and this sleep deprivation may account for a large proportion of the ES associated with SWD.[61-63] Moreover, the quality of night-shift workers' sleep is often poor due to premature awakening and reductions in rapid eye movement and stage 2 slow wave sleep, which is associated with memory consolidation and learning.[62-66] Restriction of sleep time by as little as 2 hours per night for 1 week has been shown to significantly affect scores on vigilance tasks.[67] Furthermore, the persistent sleep debt incurred by shift workers may lead to reduced attention and performance equivalent to that demonstrated by intoxicated persons or study subjects required to remain awake continuously for 24 hours.[67,68] Of concern, significantly lower levels of alertness and performance have been recorded in nuclear power plant night-shift workers vs day- and evening-shift workers.[69,70]

Alertness and cognitive processes may be especially impaired during the transition from day work to a series of night shifts, as many individuals will attempt to stay awake throughout the whole first day and night.[71] Response times in tests of visual selective attention were significantly ($P < .05$) affected on the first night shift in a shift-work simulation study.[71] These results indicate that the potential for accidents is increased in affected night-shift workers from as early as their first shift; productivity is also likely to be affected almost immediately in such workers.[71]

Social and quality of life burden of SWD

Shift work negatively affects quality of life. In a study of Air Force radar controllers, shift workers in general experienced higher levels of anxiety ($P < .001$) and irritability ($P < .05$) and demonstrated a greater tendency to ignore stress ($P < .001$) than did day workers.[54] Importantly, this study also demonstrated that SWD imparts a significantly greater detriment to quality of life than does shift work alone. Quality of life for shift workers with SWD was significantly poorer than that of shift workers without this disorder for the Sickness Impact Profile domains of sleep and rest ($P < .001$), emotional behavior ($P < .001$), home management ($P < .05$), mobility ($P < .05$), social interaction ($P < .01$), ambulation ($P < .05$), alertness behavior ($P < .001$), work ($P < .05$), and recreational pastimes ($P < .01$).[54] Subjects with SWD also experienced greater impairments, compared with other shift workers, for the Illness Behavior Questionnaire domains of general hypochondriasis ($P < .001$), disease conviction ($P < .001$), affective inhibition ($P < .001$), affective disturbance ($P < .001$), and the Whiteley Index of Hypochondriasis ($P < .001$).[54]

Moreover, a large epidemiologic study of the general US population found that individuals with SWD are more likely to be unable to attend social and family interactions due to sleep problems than those without SWD.[6] Permanent night workers with SWD missed 8.6 days of family or social activity per month compared with 1.5 days in those without SWD; rotating-shift workers with SWD missed 10.1 days of family or social activity each month vs 1.0 day in their colleagues without SWD.[6]

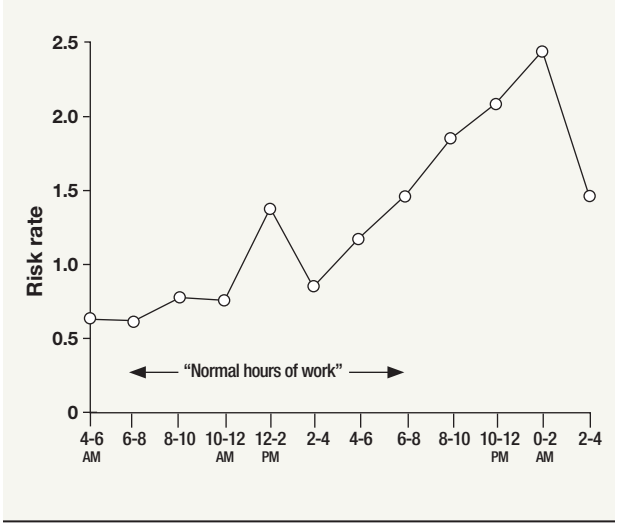
A set of self-report questionnaires—the Standard Shiftwork Index (SSI)—was developed specifically to monitor problems relating to shift work, including changes in alertness, coping, job satisfaction, sleep, psychological well-being, and physical health.[72] A number of studies have used the SSI in shift-work populations and have demonstrated that this measure can differentiate between shift schedules of differing types and length.[73-79] However, a number of analyses have intimated that several of the scales incorporated in the SSI are psychometrically weak, and further evidential support for this set of questionnaires may be required.[80,81]

Accidents

Shift workers are more likely to have work-related accidents than are day workers.[82] Considering that the shift-work population includes nurses, physicians, firefighters, police officers, military personnel, pilots, and drivers, the potential ramifications of SWD are disconcerting. Early treatment intervention should be considered in emergency workers presenting with SWD symptoms so that they can continue to perform their roles safely. Transportation accidents due to ES, suboptimal treatment of patients under the care of shift-working clinicians, and injuries to the clinicians themselves are commonplace, yet SWD remains a poorly documented condition.[2]

The likelihood of a medical resident experiencing a percutaneous injury (with a scalpel or needle) was

FIGURE 1 Risk rate and periods of driving



The risk of a truck driver experiencing a traffic accident is high during times of postprandial drowsiness but is greatest outside normal working hours and, in particular, at the end of the night.

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found to be twice as high during a night shift than during a day shift (OR, 2.04; 95% CI, 1.98-2.11).[83] The odds of reporting an accident or error due to ES were twice as high among nurses on a rotating-shift schedule compared with nurses on a fixed day or evening shift.[13]

Other workers with vital roles are also affected by the demands of shift work. Police officers required to work shifts were reported to be significantly more likely to experience a sleep-related accident at work or at home than were their non–shift-working colleagues (OR, 2.24; $P < .0005$); data concerning the types of accidents experienced by these police officers were not collected in this study.[12]

More accidents are reported by workers commuting home after the night shift than by day workers.[84,85] For example, 40% of motor vehicle accidents experienced by medical residents in their first postgraduate year occurred during the commute home after shift work.[86] Moreover, 74% of motor vehicle crashes involving emergency medicine residents occurred after they had worked a night shift, compared with 12% after a day shift.[85] Among night-shift working nurses, 79% reported experiencing at least one episode of drowsiness on the commute home in a 4-week study.[87]

Driving as part of a shift-based occupation also presents risks for accidents, with approximately 25% of police officers reporting that they have fallen asleep at the wheel while driving at work.[88] It is not surprising that the vast majority of single-vehicle accidents occur early in the morning, when drivers are sleepiest[89,90] (**FIGURE 1**).

Early-morning sleepiness is also thought to be responsible for the increased rate of military flight accidents at this time of day.[91] Twelve percent of US Air Force non-aircrew shift workers admit that they have experienced a fatigue-related operational error, although only 31% of those affected officially reported such an event. Of concern, work/rest guidelines used by shift-working US Air Force aircrew do not appear to greatly improve matters, as fatigue was found to be a factor in 13% of serious aviation mishaps recorded between 1972 and 2000.[92]

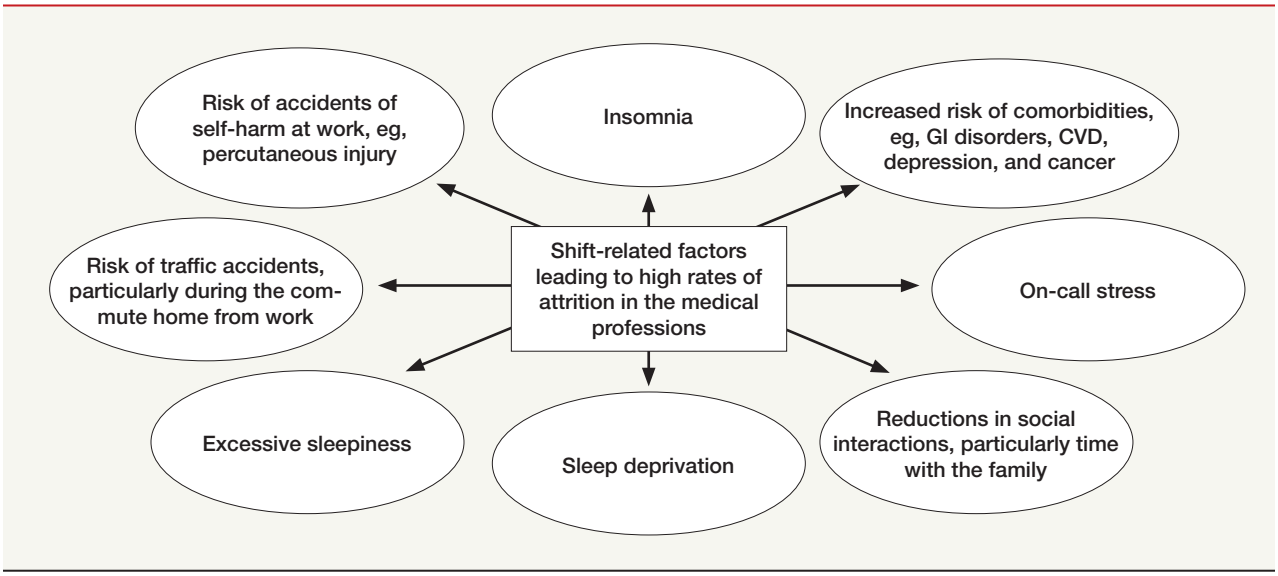
Although these data are illuminating, it is apparent that very few studies have been published on the rate of accidents specifically caused by SWD. Considering that patients with SWD are particularly vulnerable to the circadian issues created by shift work, it seems likely that they must make up a significant proportion of the shift-working population that experiences work-related and traffic accidents. However, until further studies are performed that specifically analyze accidents involving patients with SWD, we can only anticipate that the incidents that these individuals experience are more harmful and occur more frequently compared with the general shift-working population.

Economic impact of SWD

As described in "Cognitive effects associated with shift work and SWD" on page S6 of this article, shift work is associated with significant neurocognitive deficits and reduced efficiency at work. The costs due to lost productivity and accidents associated with shift workers performing at suboptimal level are, therefore, likely to be substantial. To date, studies of the direct and indirect costs of shift work and SWD have not been published; however, an indication of the scale of the economic burden can be gained by looking at the costs associated with the 2 key symptoms of SWD: ES and insomnia.

A study of the economic consequences of ES (performed using 1988 data) reported that ES of any etiology was responsible for motor vehicle accidents costing between $29 billion and $38 billion annually ($53 billion and $69 billion, when adjusted to 2009 values) and work-related accidents (including deaths and disabling injuries) costing between $10 billion and $13 billion annually ($18 billion and $24 billion when adjusted to 2009 values).[93]

FIGURE 2 Shift-related factors likely to affect attrition in the emergency medical professions



CVD, cardiovascular disease; GI, gastrointestinal.

Studies of patients with insomnia of unspecified etiology reveal the extent of the cost burden of this symptom. An observational US study found that average 6-month total costs (ie, direct and indirect costs) were approximately $1253 higher for an adult (age 18–64 years) with insomnia than for a matched control without insomnia.[94]

A recently reported Canadian study highlighted the large contribution of indirect costs to the total costs associated with insomnia.[95] Direct costs included those for doctors' visits, transportation to the visits, and prescription and over-the-counter drugs. Indirect costs associated with insomnia included those for lost productivity and job absenteeism; these accounted for 91% of all costs. On average, the total annual costs incurred by a patient with insomnia syndrome (defined as those who used a sleep-promoting agent ≥3 nights per week and/or were dissatisfied with sleep, had insomnia symptoms ≥3 nights per week for ≥1 month, and experienced psychological distress or daytime impairment)[95] were C$5010 (C$293 direct and C$4717 indirect). For a patient with insomnia symptoms, average annual total costs were calculated to be C$1431 (C$160 direct and C$1271 indirect). By comparison, a good sleeper (ie, a study subject who reported being happy with his or her sleep, did not report symptoms of insomnia, and did not use sleep-promoting medication) was found to incur average annual costs of C$421.[95]

More detailed assessment is required of the costs incurred specifically in patients with SWD, but there is clearly an economic rationale for early diagnosis and treatment of the symptoms of SWD.

Summary

What is clear from this review is that, while information on shift work is relatively abundant, data concerning SWD are meager. For example, epidemiologic data on SWD are sparse, in part because many investigators in studies of shift workers do not take the seemingly logical step of assessing SWD in their subjects. However, differentiating between shift workers who experience transient symptoms associated with adapting to a new shift schedule and individuals with SWD is complex and may lead to underrecognition of this condition. Similarly, there are few data on the comorbidities experienced by individuals diagnosed with SWD and further studies are warranted. The increased risk of illness demonstrated by shift-working individuals may be even greater in patients with SWD due to their intrinsic—and poorly understood—vulnerability to the effects of shift work.

The studies described here show that the burden of SWD is multifactorial, and it includes impairment of patients' relationships and health and reduces their efficiency at work.[6] Again, there are very few data on the economic burden of SWD, although reduced productivity and the cost of accidents in the workplace and while driving are likely to be high. Additional research is needed in this area.

Shift workers, including public service workers, must make difficult decisions during times of day when they

are not functioning optimally. Emergency clinicians in particular have great responsibility and must work under these trying conditions. In addition to the increased rates of traffic and workplace accidents encountered by such clinicians, many will also have difficulty adapting to shift and on-call work, lose recreation time with their families, and experience insomnia, ES, sleep deprivation, and comorbidities (**FIGURE 2**). Not surprisingly, these factors lead to high rates of dissatisfaction and attrition in specialized roles,[96] including health care workers, air traffic controllers, and power-plant workers. A lack of support for shift workers dealing with such issues has economic and safety consequences for society in general; recognition and treatment of SWD are therefore vital. n

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The characterization and pathology of circadian rhythm sleep disorders

Christopher L. Drake, PhD
Henry Ford Hospital
Sleep Disorders and Research Center
Detroit, Michigan

Practice recommendations

- Being alert to excessive sleepiness and/or insomnia in shift workers may prevent comorbidities and accidents that can occur as a consequence of shift-worker disorder (SWD) (**SOR: B**).
- Not all shift workers develop SWD. Thus, identification of sensitivity to shift work may be facilitated by asking patients whether they find it difficult to function in the absence of consolidated sleep, prefer to be active early in the day, or have previously experienced insomnia due to sleep challenges (**SOR: B**).

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Organisms demonstrate predictable daily patterns in neuroendocrine function and behavior. The archetypal example is the sleep/wake cycle, although daily fluctuations are evident in nearly all physiological processes, including heart rate, blood pressure, and the release of digestive enzymes.[1,2] Such characteristics are controlled by circadian rhythms under the command of the organism's circadian pacemaker, also referred to as the "biological clock." The word *circadian* is taken from the Latin *circa dies*, meaning "around a day" and, in this instance, refers to the endogenous free-running clock within the hypothalamus. This clock functions on a cycle of approximately 24.2 hours,[3] although daylight and social cues serve to entrain (synchronize) the circadian pacemaker to the 24-hour day ascribed by the rotation of the Earth. This article aims to characterize the current understanding of the mammalian circadian system and describes the features of the 6 recognized circadian rhythm sleep disorders (CRSDs), including shift-work disorder (SWD).

The circadian system

The circadian system consists of 3 parts: (1) input pathways, (2) a central oscillator, and (3) output pathways.[4] The mammalian sleep/wake cycle is governed by the circadian clock as follows: (1) light is transferred from the retina via melanopsin in ganglion cells of the retinohypothalamic tract to (2) the 2 suprachiasmatic nuclei (SCN) in the hypothalamus, which interpret these data regarding day length and signal them to (3) the pineal gland, which secretes melatonin nocturnally for a duration corresponding to the habitual period of darkness (scotoperiod) experienced by the organism[5-8] (**FIGURE 1**). The SCN also activate further output pathways, including the adrenal gland, which releases the stress hormone cortisol in the morning prior to waking; production of cortisol assists with arousal from sleep.[9]

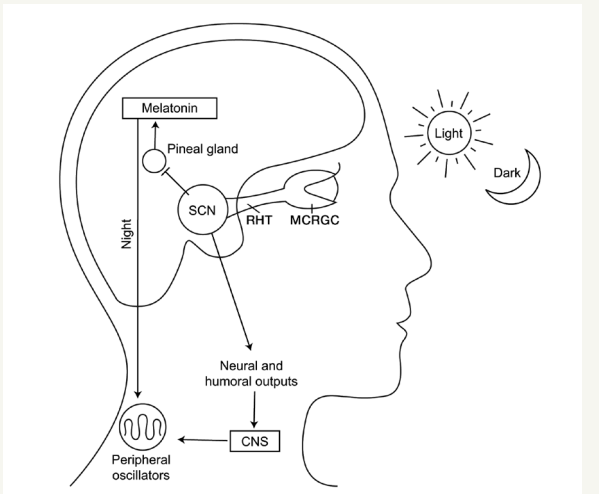
The SCN are capable of maintaining oscillatory patterns of rhythmic gene expression and electrical and metabolic activity even when cultured in vitro.[10-13] Ablation of the SCN results in disruption of activity/rest cycles in some mammals.[14] These findings demonstrate the robustness of the central oscillator and its vital role in preserving important mammalian behaviors such as the sleep/wake cycle. Each of the 2 SCN comprises approximately 10,000 neurons, a proportion of which fire rhythmically to synchronize cellular activity throughout the body via the neuroendocrine and autonomic nervous systems.

Target cells and the SCN rhythmically transcribe clock genes. Expression of such genes is controlled by autoregulatory feedback, ensuring that the circadian rhythm of each cell can work autonomously while remaining capable of responding to entrainment from extrinsic cues—predominantly the light/dark cycle. Examples of clock genes that have been characterized in humans are *hPer* (period homolog)*1*, *hPer2, hPer3, hCLOCK* (circadian locomotor output cycles kaput), *hCK* (casein kinase)*1*δ, and *hCK1*ε. Mutations in these genes are thought to be responsible for a variety of intrinsic CRSDs and also confer individual preferences for activity early or late in the day (morningness or eveningness, respectively). For example, a single nucleotide polymorphism in the *hCLOCK* gene is associated with a more delayed, evening-type, individual-phase preference, whereas a polymorphism in the *hPer2* gene is associated with more of an advanced-phase preference characterized by going to sleep and awakening earlier.[15,16]

The homeostatic system

The sleep/wake cycle is not governed solely by the circadian system; successive hours of wakefulness produce an increasing sleep pressure referred to as the homeostatic sleep drive. These 2 systems typically interact in a synergistic way, with the homeostatic system increasing the drive to sleep as the day progresses, while the circadian signal counteracts this process by promoting wakefulness (**FIGURE 2A**). The circadian alertness signal dissipates in the evening, making way for homeostatic sleep pressure to give rise to sleep onset.[17,18] However, when the internal circadian phase is shifted or behaviors change relative to circadian timing—as occurs in individuals with a CRSD—the homeostatic and circadian systems no longer interact synergistically to maintain appropriate sleep/wake behavior. For example, shift workers may struggle to stay awake at night in the face of increased homeostatic pressure for sleep, without the benefit of a wake-promoting signal from the SCN (**FIGURE 2B**) (see "Shift-work disorder" on page S15 of this article for a more detailed explanation of the sleep challenges that give rise to this CRSD).[19] This situation is diametrically opposed to normal sleep/wake behaviors in terms of the circadian timing of physiological processes and has potentially dire consequences. Indeed, circadian desynchronization in animals has been shown to decrease survival rate,[20] and numerous studies in humans have demonstrated increased morbidity associated with circadian misalignment (see "The social and economic burden of shift-work disorder" on page S3 of this supplement).

FIGURE 1 **Entrainment of the sleep/wake cycle by light**



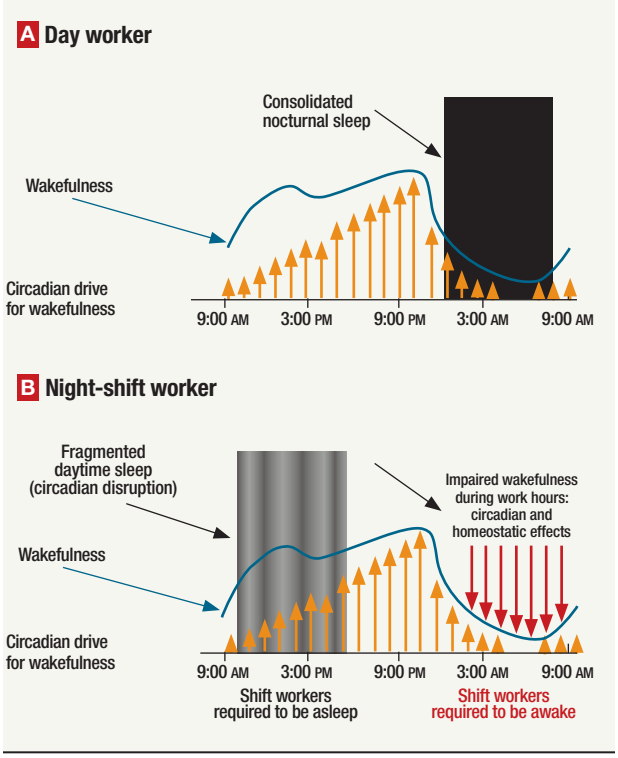
CNS, central nervous system; MCRGC, melanopsin-containing retinal ganglion cells; RHT, retinohypothalamic tract; SCN, suprachiasmatic nuclei.

Types of circadian rhythm sleep disorder

The 6 main CRSDs can be broadly classified into 2 types: intrinsic and extrinsic (**TABLE 1**).[21] Intrinsic CRSDs are characterized by asynchrony between the patient's sleep/wake cycle and the external day/night cycle, due to dysregulation within the internal circadian system. Some intrinsic CRSDs have a heritable component, while other intrinsic CRSDs are caused by the absence of the transmission of light/dark signals to the brain or by maturational changes.[22-25]

Extrinsic CRSDs result from an imposed change in the behavioral timing of sleep and wakefulness relative to internal circadian timing. Not everyone who is

FIGURE 2 Sleep/wake patterns of day and night-shift workers



(A) A schematic of the typical sleep/wake patterns in a diurnally entrained day worker. The circadian drive for wakefulness increases throughout the day to maintain alertness and then declines with the start of melatonin secretion in the early evening, facilitating sleep onset. Here circadian and homeostatic factors work synergistically to promote the normal cycle of sleep and wakefulness. **(B)** A schematic of a diurnally entrained night-shift worker. Sleep that is initiated during the day is in conflict with the internally generated circadian signal for wakefulness, thereby producing fragmented daytime sleep. During night-time work hours, the circadian signal for wakefulness dissipates in conjunction with an increasing homeostatic drive for sleep. Thus, in the shift worker, both circadian and homeostatic factors that promote sleep occur at times when the worker is attempting to remain awake and alert. Maladjustment to these challenges contributes to the occurrence of shift-work disorder.

exposed to changes in their sleep/wake pattern will develop an extrinsic CRSD; rather, these conditions act as a trigger for individuals who are susceptible to the circadian challenges of shift work or jet lag. (Factors that may cause a vulnerability to extrinsic CRSDs are discussed in detail in "Shift-work disorder" on page S15 of this article.)

In addition to the CRSDs listed above, the second edition of the *International Classification of Sleep Disorders* also recognizes CRSDs that occur due to a medical condition, or drug or substance abuse, or are not otherwise specified.[21] Potential causes/triggers of CRSDs include stroke, depression, intracranial infection, or head injury. Central nervous system stimulants and depressants may also contribute to drug-induced circadian phase disturbances.[22]

Intrinsic circadian rhythm sleep disorders

Delayed sleep-phase disorder

Delayed sleep-phase disorder leads to a postponement of the rest period and a late awakening compared with societal norms, and is the most common intrinsic CRSD.[23] An overwhelming majority (90%) of these patients report that the onset of their symptoms occurred before or during adolescence.[23] Functional alterations in some clock genes may lead to maladaptation of the sleep/wake cycle to entrainment by light,[26] and several different mutations in the *hPer3* gene have been found to result in the delayed sleep-phase disorder phenotype.[27,28] Individuals with this heritable form of delayed sleep-phase disorder may have a lengthened intrinsic circadian period even in the presence of normal entrainment cues. Other patients with delayed sleep-phase-disorder demonstrate hypersensitivity to light.[29]

Advanced sleep-phase disorder

Individuals with advanced sleep-phase disorder experience a circadian pressure for early initiation of sleep and early awakening.[30] This disorder is uncommon, being diagnosed in <2% of patients with an intrinsic CRSD.[23] Patients with advanced sleep-phase disorder tend to be elderly.[23,24] As sleeping and awakening early are less likely to interfere with work and social interactions than consistently sleeping and rising later in the day, it may be that advanced sleep-phase disorder is underreported. Advanced sleep-phase disorder has a heritable pathology in some individuals (familial advanced sleep-phase disorder). Two different gene mutations (in *hPer2* and *hCK1δ*) in separate families have been reported to result in a shortened circadian pacemaker oscillation period in the presence of normal entrainment, resulting in advanced melatonin, temperature, and sleep/wake rhythms.[31-34]

Free-running disorder

Patients with free-running disorder—also referred to as non–24-hour sleep/wake syndrome—demonstrate a progressive pattern of 1- to 2-hour delays in the onset of sleep and the subsequent waking time. Free-running disorder is diagnosed in <2% of individuals with an intrinsic CRSD[23] and most often occurs in totally blind individuals with no light perception due to the absence of photoentrainment of the sleep/wake cycle.[25] Without entrainment, the behavioral sleep/wake cycle persists with a period similar to that of the internal circadian period of slightly more than 24 hours, resulting in a small but continual off-setting of sleep/wake times compared with the 24-hour day/night cycle.[35]

Irregular sleep/wake rhythm

Individuals with irregular sleep/wake rhythm experience disorganized and variable rest and wake times, sleeping multiple times throughout the day and night. This disorder is diagnosed in 12% of patients with an intrinsic CRSD and occurs most frequently in the neurologically impaired who have damage to the SCN.[23,30] In addition, older age is associated with irregular sleep/wake rhythm due to the increasing prevalence of neurologic conditions such as dementia.[30]

Extrinsic circadian rhythm sleep disorders

Jet lag disorder

The circadian clock cannot adjust quickly enough to accommodate long-distance travel across multiple time zones, often leading to jet lag disorder. Symptoms of jet lag disorder include difficulty in initiating or maintaining sleep, excessive sleepiness, and gastrointestinal disturbances, as the body struggles to accommodate sudden shifts in the timing of activities relative to internal circadian rhythms.[21] Because environmental cues at the flight destination support phase adaptation of the circadian clock to local time, symptoms of jet lag disorder are usually transitory; however, objective measurements of hormone levels, sleep architecture, and body temperature have indicated that a complete phase shift after a long-haul flight can take up to 2 weeks.[36]

The characteristics and severity of jet lag disorder are largely dependent on the direction of travel and the number of time zones crossed.[37] Westward travel is more easily accommodated by the circadian system, as it allows the passenger to delay the onset of sleep instead of advancing sleep times, as required when traveling east. This occurs because the human circadian system runs at an internal period (tau) of slightly longer than 24 hours, a period that is conducive to phase delays in circadian timing.[3] Older age and individual vulnerability to phase shifts also affect sensitivity to jet lag disorder.[37,38]

Shift-work disorder

SWD is an extrinsic circadian rhythm sleep disorder with far-reaching implications in terms of associated morbidity, occupational and traffic accidents, and reduced work productivity (see "The social and economic burden of shift-work disorder" on page S3 of this supplement).[39] SWD occurs when an individual's occupation requires that he or she function at times that are in opposition to the body's normal circadian-controlled periods of sleep and wake. Most individuals will experience some degree of difficulty in attempting to work at unusual times within the 24-hour day, and current diagnostic criteria do not clearly differentiate this group from individuals who have a pathologic response to shift work and develop SWD.[37] Broadly, workers with SWD can be defined as those experiencing persistent insomnia when trying to sleep and/or excessive sleepiness when trying to remain awake. Sleep in patients with SWD is typically fragmented, with frequent awakenings during the daytime rest period. Although appropriate scheduling of light exposure can improve circadian adaptation, even permanent night workers find it difficult to adapt their

TABLE 1 Circadian rhythm sleep disorders (CRSDs) recognized in the ICSD-2[21]

Intrinsic	Extrinsic
• Delayed sleep-phase disorder • Advanced sleep-phase disorder • Free-running disorder (non–24-hour sleep/wake syndrome) • Irregular sleep/wake rhythm	• Shift-work disorder • Jet lag disorder

ICSD–2, International Classification of Sleep Disorders, 2nd edition.

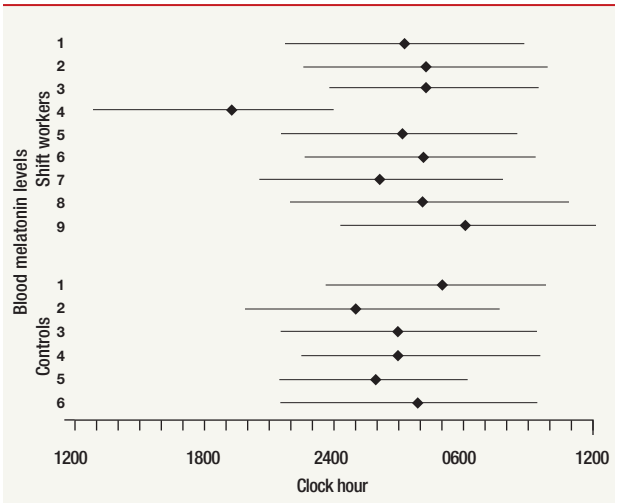
The ICSD–2 also recognizes CRSDs that are secondary to medical conditions and drug or substance abuse as well as CRSDs that are not otherwise specified.

TABLE 2 Innate factors that may trigger shift-work disorder

Factor	Supporting evidence
Predisposition to developing insomnia	An increased chance of developing insomnia has been shown to have a heritable component; this vulnerability to insomnia is then unmasked by sleep challenges such as shift work.[42-44]
Genetic vulnerability to sleep-loss induced performance decrement	Reductions in waking performance as a result of sleep loss vary in healthy individuals with different polymorphisms of the *hPer3* gene.[45]
Circadian variation	Genetic polymorphisms result in individual morningness or eveningness preferences; morning-type individuals are more likely to develop SWD.[15,16] Wide intersubject variation has been reported in the expression of genes related to the circadian system after a simulated night shift.[46]

SWD, shift-work disorder.

FIGURE 3 Blood plasma levels of melatonin in individual shift workers and control subjects



Lines indicate nocturnal melatonin elevation (onset, offset, and duration) and diamonds represent the peak of the rhythm (acrophase) in individuals.

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internal circadian rhythms to the timing of their new sleep/wake schedule.[40]

Accumulated sleep loss over successive nights as a result of shift work creates a growing sleep debt that increases the homeostatic sleep drive.[41] Over a series of night shifts, the natural circadian drive for sleep during the night interacts with this increasing sleep debt (**FIGURE 2B**), resulting in further exacerbation of excessive sleepiness, impaired work performance, and increased risk of accidents in individuals with SWD.[19] Thus, both sleep loss as well as circadian pressure for sleep independently contribute to excessive sleepiness in patients with SWD.

Although a change in sleep/wake relative to circadian timing can trigger SWD, not all shift workers develop this CRSD. The high degree of variation between individuals in terms of the severity of symptoms associated with shift work is a complex issue that has not yet been fully elucidated. However, it seems likely that there are a number of innate factors that may increase an individual's susceptibility to SWD, including vulnerability to insomnia, sensitivity to sleep loss, or variation within the circadian system (**TABLE 2**).[15,16,42-46]

Studies of melatonin rhythms in night-shift workers have shown that many workers do not completely adapt their circadian rhythms to their new pattern of sleep and wake[47,48] (**FIGURE 3**). This may be due to an inherent inability to adapt their circadian rhythms or due to behaviors that preclude adaptation. A recent study has shown that a significantly greater ($P < .0001$) number of shift-intolerant vs shift-tolerant workers have a circadian period that is longer or shorter than 24 hours, indicative of circadian desynchronization and an inability to adapt to their new work schedule.[49] In addition, adaptation cannot occur in night-shift workers who persistently revert to a night-time sleep schedule on their days off and who, therefore, do not experience consistent circadian sleep/wake alignment with the light/dark cycle. Night-shift workers who do not adapt to their new shift schedule have been reported to experience reduced sleep during the daytime, putting them at increased risk of developing SWD compared with colleagues who demonstrated a rapid phase shift to accommodate their new work schedule.[50]

The presence of noise in the home, poor sleep hygiene, and social obligations may make it difficult for some shift workers to obtain a sufficient amount of sleep. In these instances, it may be that shift work is incompatible with the patient's lifestyle, resulting in behaviorally induced insufficient sleep syndrome. In patients with SWD, however, insomnia and/or excessive sleepiness persist despite attempts to fully accommodate the altered work schedule.

Summary

The mammalian circadian clock is complex and is responsible for ensuring the rhythmic nature of numerous behaviors and processes. In recent years, there have been frequent and impressive advances in our understanding of the structure and properties of the mammalian central circadian oscillator—the SCN—and the molecular machinery that it controls.

Of the 6 main CRSDs recognized by the *International Classification of Sleep Disorders* (**TABLE 1**),[21] 4 are due to intrinsic problems with the circadian pacemaker, caused by damage to the SCN, maturational changes, lack of appropriate entrainment, or genetically inherited traits. The 2 remaining CRSDs—jet lag disorder and SWD—are triggered by behavioral changes, as they occur as a direct result of human activity, ie, long-distance air travel in a short time and working outside usual hours, respectively. However, not everyone develops jet lag disorder or SWD under these conditions, and the interindividual variation in susceptibility to intrinsic and extrinsic CRSDs is an area of ongoing research.

In a round-the-clock, global society, shift-working individuals perform vital tasks, so it is imperative to find simple ways to diagnose and treat SWD. The following articles discuss how this may be achieved. n

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Recognition of shift-work disorder in primary care

Jonathan R. L. Schwartz, MD
University of Oklahoma Health Sciences Center
INTEGRIS Sleep Disorders Center of Oklahoma
Oklahoma City, Oklahoma

Practice recommendations

- To recognize shift-work disorder (SWD), primary care physicians can screen for persistent excessive sleepiness (ES) and insomnia in patients who work night or rotating shifts (**SOR: B**).
- If SWD is suspected, a differential diagnosis should be generated, as ES and insomnia are commonly associated with other morbidities. Ask patients about symptoms of other common sleep/wake disorders, such as obstructive sleep apnea and periodic limb movement disorder (**SOR: B**).
- The Epworth Sleepiness Scale is a useful tool for subjectively evaluating ES (**SOR: A**).

Dr Schwartz reports that he serves as a consultant to and on the speakers bureaus of AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Inc., Cephalon, Inc., Pfizer Inc, Sepracor Inc., Takeda Pharmaceuticals North America, Inc, and GlaxoSmithKline.

Shift-work disorder (SWD) is experienced by individuals whose work schedule overlaps with the normal sleep period, causing misalignment between the body's endogenous circadian clock and the time at which the worker is able to rest. The *International Classification of Sleep Disorders, 2nd edition* (ICSD-2) defines SWD as the presence of excessive sleepiness (ES) and/or insomnia for at least 1 month, in association with a shift-work schedule.[1]

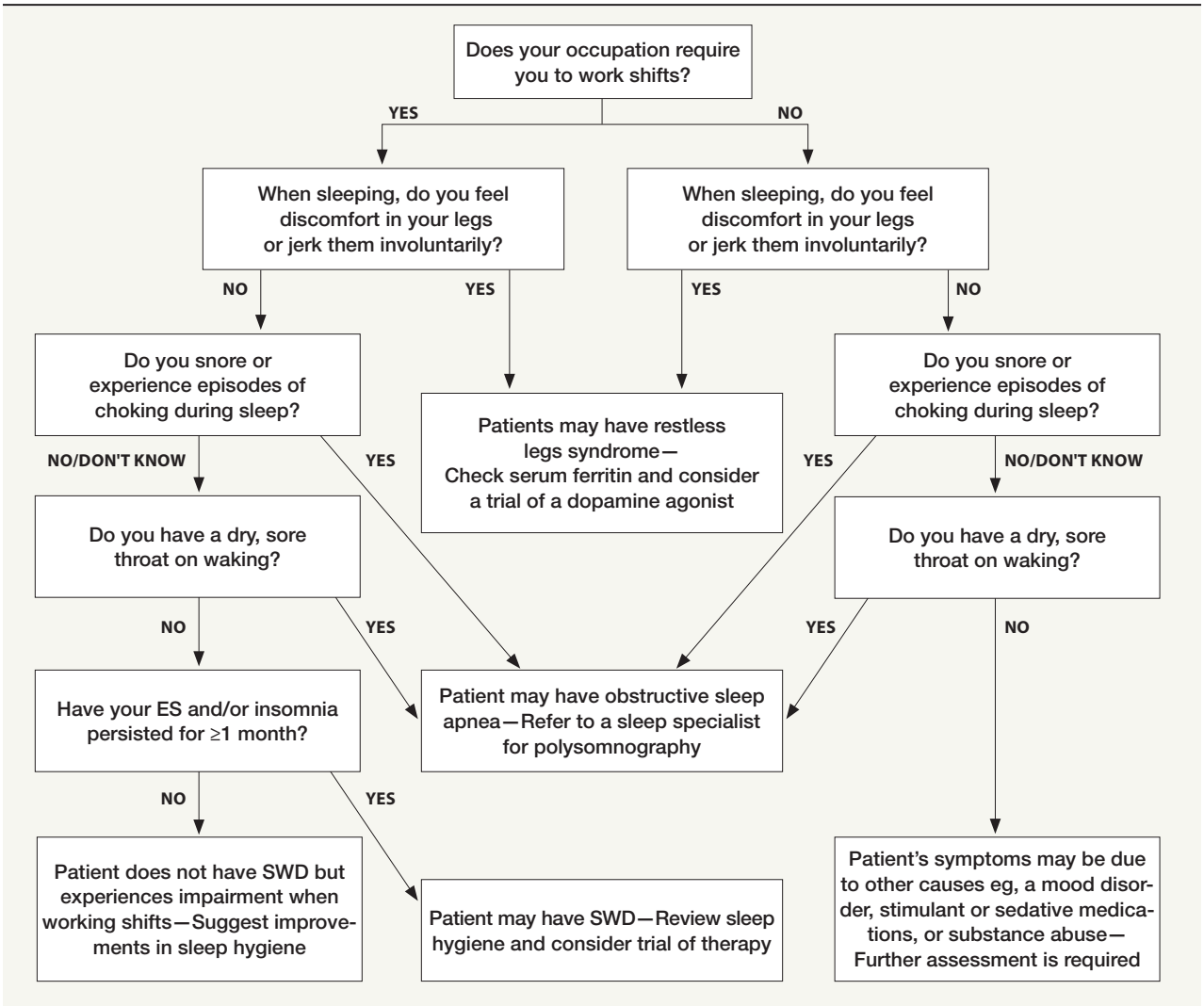
This classification results in the shift-work population being separated into 3 distinct groups: those who have no impairment; those who have impairment but do not meet the ICSD-2 criteria for the diagnosis of SWD; and those who have SWD. Individuals in the last 2 groups are less likely to be able to meet the demands of shift work and, therefore, often return to non–shift-work schedules or retire from the workforce. This creates a "healthy worker effect," whereby workers remaining on night- or rotating-shift patterns are the best suited for this type of work.[2,3] However, retirement or changes to shift-work schedules are not an option for many workers, and patients with SWD must be recognized and treated in order to preserve their health and livelihood.

This article aims to characterize the symptoms and risk factors associated with SWD, with a view to assisting primary care physicians in the diagnosis and recognition of this consistently underrecognized sleep/wake disorder.[4]

Symptoms of SWD

Insomnia and ES (drowsiness and a propensity to sleep) are the defining symptoms of SWD and can result in fatigue (weariness and depleted energy), difficulty concentrating, reduced work performance, headache, irritability or depressed mood, and feeling unrefreshed after sleeping.[4,5] The consequences of insomnia and ES may, therefore, also be useful warning signs for SWD, and patients presenting with one or more of these sequelae should be evaluated for risk factors for SWD and asked about their symptoms using the differential diagnosis described below and in the **FIGURE**.

FIGURE Questions to ask patients who present with insomnia and/or ES (as assessed by an ESS score ≥10)



ES, excessive sleepiness; ESS, Epworth Sleepiness Scale; SWD, shift-work disorder.

These questions aim to aid in differentiating between common sleep/wake disorders in shift-working patients who present with sleepiness or have trouble sleeping and should not be viewed as an exhaustive or definitive list of potential questions or potential diagnoses.

Risk factors for SWD

Vulnerability to SWD is dependent on certain predisposing and precipitating factors, including shift characteristics, circadian preference, job satisfaction, and susceptibility to sleep disturbance (see "The characterization and pathology of circadian rhythm sleep disorders" on page S12 of this supplement). The effects of some physiological and lifestyle factors, such as age and gender, on an individual's propensity to develop SWD have not been well quantified to date.

Shift type and pattern

Night-shift workers are reportedly most susceptible to SWD, with an estimated 32.1% of this group experiencing symptoms that meet the minimum diagnostic criteria for SWD compared with 26.1% of rotating-shift workers.[6] A recent study by Waage and others[7] found that 23.3% of oil rig swing-shift workers (2 weeks working 12-hour day/night shifts followed by 4 weeks off) met ICSD-2 criteria for SWD. The relatively high prevalence of SWD in night-shift workers is thought to be due to exposure to light during rest periods and dark during the hours when the workers are attempting to be most productive.[6] Morning-shift workers are more susceptible to SWD than evening-shift workers, as delaying sleep appears to be more easily achieved than attempting to advance the rest period.[8]

The timing of shifts and changes to the shift schedule have been shown to significantly affect sleep, with individuals on rotating shifts experiencing the greatest detriments to their sleep quality.[8] In one study, workers on rotating shifts experienced significantly more difficulty sleeping than those on a stable shift schedule: 20.4% of rotating-shift workers reported a sleep latency >30 minutes vs 11.5% of fixed- or night-shift workers ($P < .001$).[8] Furthermore, while rotating-shift workers experienced a similar frequency of disrupted nights' sleep to that of other shift workers, they also reported a significantly higher number of night-time awakenings during each disrupted night's sleep ($P < .05$). In addition, approximately one-third of rotating-shift workers reported experiencing ES compared with 19% of night- or other shift workers and 12% of daytime workers ($P < .001$). Therefore, it is probably not surprising that rotating-shift workers were absent from work significantly more often than individuals on fixed day-shift schedules (62.8% vs 38.5%, respectively; $P < .001$) and had a significantly higher annual frequency of work-related accidents (19.5%) than those on fixed daytime (8.8%) or night-time shifts (9.6%) ($P < .001$).[8]

Advancing the rest period is reportedly more difficult than delaying sleep and is thought to be responsible for making counterclockwise shift rotation a risk factor for maladaptation to shift-work conditions.[9] Forward-rotating shift patterns have long been considered more beneficial to workers than backward-rotating patterns.[9] A rapidly forward-rotating shift system has been shown to have positive effects on sleep, to reduce ES, and to improve overall perceptions of general well-being compared with a slower backward-rotating shift pattern.[10] However, this study did not elucidate whether the new shift pattern reduced the negative effects of shift work to the level of those experienced by day workers.[10] The forward-rotating system was found to be particularly helpful to older workers, who experienced larger improvements in ES compared with younger workers.[10]

Shift timing in relation to "zeitgebers"

Bright light is the strongest "zeitgeber"—a cue responsible for the entrainment (synchronization) of the circadian clock. The body's natural circadian rhythms, and therefore the likelihood of developing ES and/or insomnia, will persist as long as shift workers continue to expose themselves to light at times that are inappropriate for re-entrainment (for example, exposure to light in the morning in night-shift workers).[11,12] One study found that workers who ensured that they slept in a darkened bedroom, wore dark glasses when commuting home, and avoided bright light on their days off were least affected by a night-shift schedule.[13] There is some evidence that shift workers respond to relative changes in light intensity over a 24-hour period rather than absolute light intensity, and bright light on the commute home in the morning from a night shift is enough to prevent re-entrainment of the circadian clock toward night working.[13] Interestingly, any degree of re-entrainment to the new rhythm is sufficient to confer significant benefits. Patients who either completely or partially re-entrained their circadian phase with respect to their night shift through the use of a fixed dark daytime sleep episode, sunglasses, melatonin, and bright light at night experienced substantial benefits in ES, performance, and mood (see "Managing the patient with shift-work disorder" on page S24 of this supplement).

Job satisfaction

Poor job satisfaction is associated with higher levels of ES in shift workers[14,15] and may therefore predispose an individual to SWD. Workers on rapidly rotating shifts who had poor job satisfaction did not have shorter sleep times but were sleepier at work compared with their satisfied colleagues ($P < .001$) and had poorer quality of sleep.[14] In a 3-year study, workers on a backward-rotating shift schedule who had poor job satisfaction had a higher likelihood of experiencing ES than individuals who were satisfied with their work ($P = .026$).[15] In addition, ES significantly increased in dissatisfied workers ($P < .05$) over the duration of the study compared with workers who were content with their jobs.[15]

Individual physiological and lifestyle factors

AGE. There is some disagreement in the literature as to the degree to which age affects adjustment to shift-work conditions, but the weight of current evidence suggests that advancing age is a risk factor for developing an intolerance to shift work.[2,3,16-19] Older individuals (ages 53–59 years) appear to adapt better initially to acute sleep deprivation than younger individuals (ages 19–29 years); however, older individuals show a reduced capacity for circadian adaptation when exposed to a series of night shifts.[17] Thus, although younger individuals are initially sleepier in response to a new shift pattern, they are capable of rapidly adapting to these changes. After 3 consecutive night shifts, younger workers were less sleepy than older workers[17]; therefore, older workers are more likely to experience impairment while working night shifts even if they do not meet all of the ICSD-2 criteria for a diagnosis of SWD.

GENDER. Shift work may affect men and women differently. In a study of crane operators, women working night shifts or afternoon shifts slept approximately 30 minutes less than their male counterparts,[20] although this is unlikely to translate into an increased propensity to develop SWD in women. However, less sleep in female shift workers may reflect differences in the familial and/or social obligations of the male and female members of this worker population. The tendency for female shift workers to sleep less also emphasizes that extrinsic factors, such as childcare requirements, may have an impact on sleep during a shift-work schedule even in the absence of any innate circadian issues.[20] A more recent study found few gender-related differences in sleepiness and performance in workers on rapidly rotating shifts.[14] More detailed epidemiologic data are needed before any firm conclusions can be drawn on the influence of gender in SWD; currently it does not appear that gender is a risk factor for SWD.

CIRCADIAN PREFERENCE. It has been suggested that adults can be divided into "morning" or "evening" types[21] and the Morningness–Eveningness Questionnaire (MEQ) can be used to assess into which category an individual falls.[21] Morning-type individuals, or "larks," are most alert early in the day and are thought to be more susceptible to SWD, as they obtain less sleep (on average 86.8 minutes fewer) after a night shift than evening-type workers, or "night owls."[22] However, use of the MEQ is unproven in the evaluation of SWD.[23] Currently, there are no studies regarding whether there is a genetic component to SWD susceptibility[19]; however, a number of reports have indicated that a preference for "morningness" or "eveningness" is genetically determined (see "The characterization and pathology of circadian rhythm sleep disorders" on page S12 of this supplement). In addition, an inherent vulnerability to insomnia or sensitivity to sleep loss may also lead to an innate susceptibility to SWD.

LIFESTYLE FACTORS. A number of lifestyle factors and choices can cause ES and insomnia in shift workers. These include the presence of other people in the home who may disrupt the attempted rest period; social obligations during the normal waking day that require the patient to be awake when he or she should be resting; patients attempting to sleep at "normal" times during days off and the weekend, thus lowering the chances of adapting to the shift-work pattern during the week; and deliberately staying awake or being unable to sleep during transitions between shift patterns, leading to sleep deprivation. These factors should be discussed with the patient at presentation, with a view to improving sleep hygiene. Such factors may trigger SWD in patients who are predisposed to developing this sleep/wake disorder; addressing poor sleep habits in patients who do not have SWD may help resolve their sleep problems.

Shift work can prevent individuals from enjoying a healthy lifestyle, with lower levels of physical exercise and higher levels of smoking seen in shift workers compared with non–shift workers.[15,24] Poor diet and lack of exercise as a result of social constraints or coping mechanisms associated with shift work may lead to metabolic imbalance, which can exacerbate symptoms of ES and insomnia.[24]

Habits adopted to cope with shift work may actually exacerbate the problems associated with night- or rotating-work schedules. For example, consumption of caffeinated drinks to enhance wakefulness or napping at inappropriate times may worsen insomnia when trying to rest.[25] Consumption of alcohol to induce sleep may increase ES during the next shift.[25] Alcohol also interacts with certain shift characteristics to increase the risk of developing SWD and was found to be particularly detrimental to workers on a 3-shift rotation, with 51% vs 42% of regular alcohol consumers and nondrinkers experiencing insomnia, respectively. Although alcohol did exacerbate insomnia in the other shift workers studied, the effect was not as pronounced, with 48% of workers on a 2-shift rotation who consumed alcohol experiencing insomnia compared with 46% of their nondrinking counterparts.[24]

Differential diagnosis of SWD in the primary care setting

The American Academy of Sleep Medicine notes that the boundary between a "normal" response and a pathologic response to shift work is not clearly defined and that the validity and reproducibility of diagnostic criteria need testing.[19] To add to the challenges inherent in defining SWD, ES, insomnia, and a number of their sequelae (see "Symptoms of SWD" on page S18 of this article) are also indicative of a variety of disorders other than SWD. For example, ES and/or insomnia are also symptoms of other sleep/wake disorders, sleep deprivation, pre-existing medical conditions (including mood disorders and central nervous system issues such as narcolepsy and brain injury), the use of sedative or stimulant medications, and substance abuse. The discussion of a patient's full medical history should assist in ruling out other potential causes for his or her symptoms, but it is also vital to generate a differential diagnosis to exclude

the other potentially causative conditions. (Examples of how mood disorders and other sleep/wake disorders can be differentiated from SWD appear below.)

Mood disorders and sleep/wake disorders often present in the primary care setting and can at first seem indistinguishable. For example, patients with ES as a result of a sleep/wake disorder may superficially appear to have depression, as a lack of energy, poor memory, reduced concentration, and a loss of interest in life are common features of both ES and mood disorders. In such instances, asking the patient about his or her sleep habits and the use of simple depression questionnaires such as the Patient Health Questionnaire-9 (www.patient.co.uk/showdoc/40025272/) are vital to avoid misdiagnosis and prescription of inappropriate medication.

ES is also a symptom of the sleep/wake disorders obstructive sleep apnea (OSA) and restless legs syndrome (RLS), which are commonly reported in shift workers.[26,27] Patients with OSA have poor quality sleep, as they experience repeated full or partial blockages of their airway, resulting in snoring and episodes of choking or gasping during sleep.[28] Recurrent partial or complete obstruction of the upper airway leads to repeated arousals and disturbed sleep, which can cause ES.[29,30] Night-shift work has been shown to aggravate OSA,[31] possibly due to the increased potential for weight gain and metabolic disturbance in this population[24]; overweight and metabolic syndrome are risk factors for and comorbidities associated with OSA.[28] It is imperative that patients with suspected OSA are referred to a sleep specialist as well as counseled about appropriate therapies and lifestyle changes.[32]

RLS may develop in shift workers due to low serum iron levels induced by chronic sleep deprivation.[33] Patients with symptoms of RLS should have their serum ferritin levels checked and, if found to be <50 mcg/mL, a trial of oral iron therapy may be of benefit.[34] If serum ferritin is normal or symptoms of RLS persist, patients can be treated with a dopamine agonist such as pramipexole or ropinirole.[34] If therapy with a dopamine agonist is not successful, the patient should be referred to a sleep specialist for further treatment and given guidance regarding sleep hygiene. The **FIGURE** provides a suggested set of questions that could form the basis of a differential diagnosis of sleep/wake disorders in shift-working individuals presenting with symptoms of ES and/or insomnia.

Further assessment of patients with suspected SWD

Further assessment for SWD is advised if the patient works shifts, has been experiencing symptoms of ES and insomnia for ≥1 month, and does not have the signs and symptoms of other sleep/wake disorders. Recent practice parameters from the American Academy of Sleep Medicine recommend the use of a sleep diary for ≥7 days to aid in the diagnosis of SWD and to rule out other sleep/wake disorders.[19,23] At present, there are no standard sleep diaries, and many clinicians create their own so that patients can capture data on the quantity and quality of their sleep.

The Epworth Sleepiness Scale (ESS) is helpful in measuring ES in the primary care setting.[35] This brief questionnaire, which can take as little as 2 minutes to complete, asks the patient about his or her chances of dozing in 8 sedentary situations, such as when reading a book or sitting in a meeting. A score of ≥10 out of a possible 24 is indicative of clinically significant ES.[35] However, as the situations described in the ESS are more oriented toward activities of day to day living, they may not be completely appropriate for the measurement of ES in a shift-work situation. Furthermore, the ESS is not validated in night- or rotating-shift workers. Nonetheless, the ESS is useful both as a screen for ES and for follow-up of therapy.

Because the diagnosis of SWD is based on patient history, it does not require confirmation with a sleep study. However, if the patient has symptoms suggestive of OSA or another sleep/wake disorder, then further evaluation, including a sleep study or polysomnogram, is warranted.

Summary

The difference between a "normal" and a pathologic response to shift work is not clearly defined. As a result of this uncertainty, SWD is underrecognized, underdiagnosed, and underrepresented in published clinical studies. The main symptoms of SWD—ES and insomnia—are also characteristic of a number of other conditions, including a variety of sleep/wake disorders. For this reason, exclusion of other potential causes of ES and insomnia is necessary before a firm diagnosis of SWD can be given. Further research is required to establish the physiologic basis of individuals' vulnerability to SWD. Such studies would be helpful in identifying risk factors for SWD and delineating normal and pathologic responses to shift-work conditions. n

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Managing the patient with shift-work disorder

Michael J. Thorpy, MD
Director of the Sleep-Wake Disorders Center
Montefiore Medical Center
Bronx, New York

Practice recommendations

- Behavioral measures, eg, exercise and improved sleep hygiene, can enhance sleep quality and combat insomnia and excessive sleepiness (ES) in shift workers and individuals with shift-work disorder (SWD) (**SOR: B**).
- Napping before a shift followed by consumption of a caffeinated drink and, if appropriate, scheduled naps at work, may improve ES in patients with SWD (**SOR: C**).
- Use of bright light therapy to partially re-entrain the circadian clock should be explored for all night-shift workers—particularly those with SWD (**SOR: B**).
- The wakefulness-promoting agents armodafinil and modafinil are FDA approved for the treatment of ES in patients with SWD. Alongside nonpharmacologic interventions, they can be included in a comprehensive management plan for SWD (**SOR: A**).
- Melatonin or other sleep-promoting agents may help shift workers achieve sleep during required rest periods and when adjusting to night-shift work; studies are needed in patients with SWD to better evaluate the utility of these agents in this population (**SOR: C**).

Dr Thorpy reports that he serves as a consultant to and on the speakers bureaus of Cephalon, Inc., and Jazz Pharmaceuticals, Inc.

The goals of treatment for individuals with shift-work disorder (SWD) are to ensure sustained wakefulness when wakefulness is required and to facilitate restorative sleep when sleep is required. Several nonpharmacologic interventions are available for the treatment of SWD, such as the improvement of sleep hygiene, exercise, and timed exposure to light. Although these treatments are recommended as part of the Practice Parameter Guidelines for the Evaluation and Treatment of Circadian Rhythm Sleep Disorders from the American Academy of Sleep Medicine,[1,2] most have been evaluated in shift workers generally, rather than specifically in those with SWD. However, the current definition of SWD requires further validation, and while the delineation between workers who do not thrive under shift-work conditions and individuals who develop SWD remains indistinct, it is likely that literature specific to SWD will remain sparse.[2]

Regardless, such nonpharmacologic interventions should be introduced for all individuals presenting with SWD. Pharmacotherapy may also be required. Two pharmacologic agents—modafinil and its *R*-enantiomer armodafinil—have been evaluated specifically in patients with excessive sleepiness (ES) associated with SWD and are approved as wakefulness-promoting agents for this indication by the US Food and Drug Administration (FDA).

This article reviews appropriate management strategies and specific interventions—both nonpharmacologic and pharmacologic—that primary care physicians can offer to individuals diagnosed with SWD.

Addressing comorbid conditions

For the individual presenting with SWD, it is essential to identify and address any comorbid conditions that might contribute to poor sleep hygiene and/or cause ES or fatigue during required periods of wakefulness. Perhaps the most relevant comorbidities are other sleep disorders, such as obstructive sleep apnea (OSA), and mood disorders, such as depression. Referral to a sleep specialist may be necessary for individuals

with a suspected or confirmed comorbid sleep disorder (see "Recognition of shift-work disorder in primary care" on page S18 of this supplement). An algorithm for the management of SWD in the primary care setting, including steps to evaluate comorbid disorders, appears in **FIGURE 1**.

Nonpharmacologic interventions

A range of nonpharmacologic options have been evaluated to relieve the ES often reported by shift workers. These interventions include steps to improve sleep hygiene, scheduled nap times, exercise, and timed exposure to light. Although not all of these interventions have been specifically evaluated among individuals with SWD, such approaches may prove useful as part of a wider management program alongside pharmacotherapy.

Evaluating the work pattern

Certain shift patterns have been shown to be more detrimental than others in terms of their effects on performance.[3] For example, Folkard and Tucker[3] analyzed data from 7 studies that evaluated the risk for incidents (including accidents and injuries) during successive night shifts. They found that the risk approximately doubled with each shift worked, from ~6% during the second night shift to 17% during the third night shift and 36% during the fourth night shift (**FIGURE 2**). Additional studies evaluating the effects of >4 consecutive night shifts, which were not included in the analysis by Folkard and Tucker,[3] confirm the risk for decreased cognitive performance and increased severe ES.[4,5] The observed marked increase in the risk for incidents during working hours suggests that working more than 4 consecutive 12-hour night shifts should be avoided. Individuals should also be counseled to avoid work shifts that are longer than 12 hours due to the risk accumulated on an hourly basis.[3] Individuals on a rotating shift schedule should be encouraged to rotate their shifts in a clockwise rather than a counterclockwise manner (morning to evening to night shift as opposed to night to evening to morning shift) (**FIGURE 3**). It is easier to change the sleep/wake cycle to a clockwise shift rotation, as this follows the natural adaptive pattern of delaying the sleep period.[6,7] However, a change of rotation direction does not eliminate the risks associated with SWD.

FIGURE 1 **Primary care management algorithm for the individual with shift-work disorder**

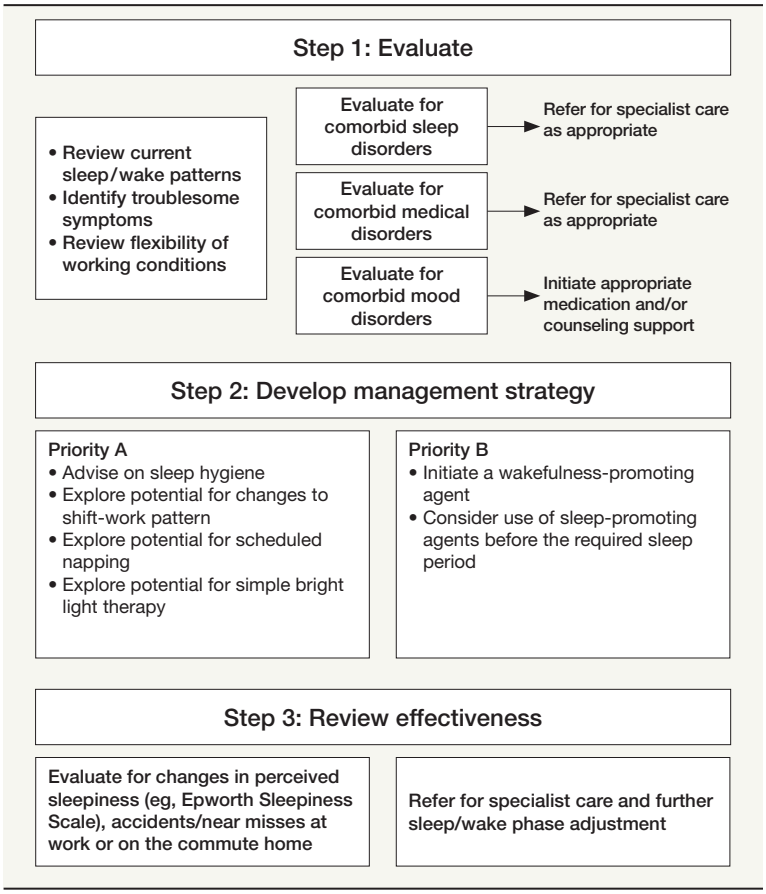
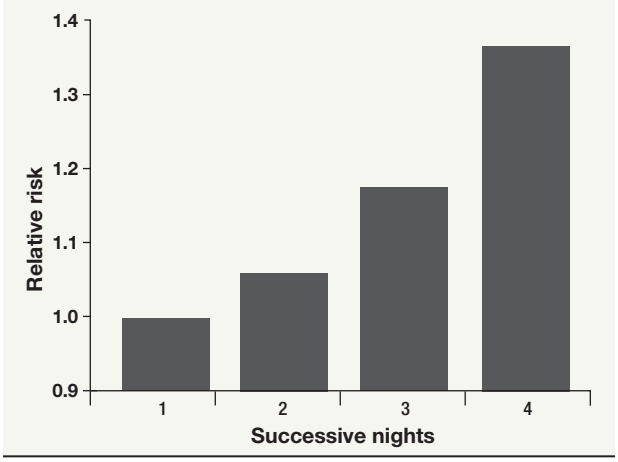


FIGURE 2 **Risk for incidents during successive night shifts**



Reprinted from Occupational Medicine (London), Volume 53, Issue 2, Folkard S and Tucker P. Shift work, safety and productivity; pp 95–101, Copyright © 2003, with permission from Oxford University Press.[3]

FIGURE 3 Optimal and least beneficial shift rotation patterns

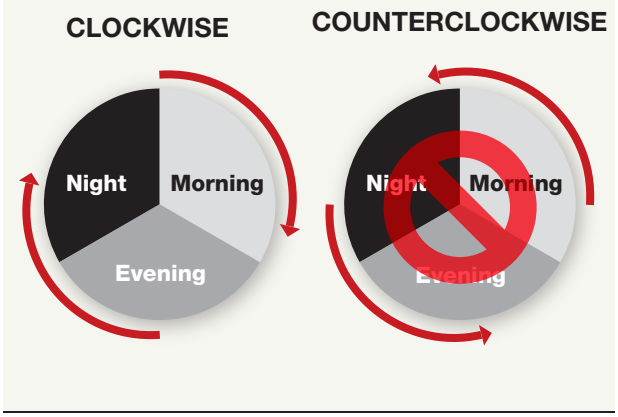


TABLE 1 Steps to achieve an appropriate environment for restorative sleep

Step	Practical advice
Ensure the room is dark if sleep is required during daylight	• Ensure the room has sufficiently well-lined curtains, or install black-out blinds on all windows
Ensure a constant temperature in the bedroom	• Aim for a temperature of around 20°C (68°F) • Avoid too many bedclothes
Reduce noise exposure before and during the required sleep period	• Avoid watching television or listening to loud music immediately before the required sleep period • Use a room at the rear of the house if near a busy road • Consider ear plugs if the ambient noise is intrusive • Put telephones on an answering machine • Ask family members to be quiet
Avoid large meals, caffeine-containing drinks, smoking, and alcohol before the required sleep period	• Schedule meal times so that the main meal of the day is eaten during or before the work period • Consider having a warm, milky drink before the required sleep period

Improving sleep hygiene

Insomnia during periods when sleep is required is a key feature of SWD. When persistent, the chronic sleep debt such individuals incur may contribute to long-term health detriments, eg, cardiovascular disease and ongoing ES, during periods when wakefulness is required. (See "The social and economic burden of shift-work disorder" on page S3 of this supplement.)

Advice on steps to improve sleep hygiene is relevant to all shift workers—including those with and those without SWD—and should be among the first steps in managing any individual presenting with sleep disturbances. Individuals should be advised on how to create an appropriate environment for sleep in terms of noise, temperature, and mental preparation for sleep (**TABLE 1**). They should also be encouraged to ensure a single 7- to 8-hour sleep episode during a 24-hour period, as opposed to, for example, two 4-hour sleep periods.[8,9] There is now good evidence to suggest that sleep fragmentation of this type can adversely affect sleep architecture (ie, the natural stages of sleep), which leads to an accumulated sleep debt.[10] Incurring a sleep debt can exacerbate the negative effects of shift work on cognitive performance and may also aggravate any underlying sleep disorder by adding to the ES experienced during periods of wakefulness.

Exercise

Exercise has been shown to be helpful in promoting sleep onset and improving the perceived quality of sleep.[11] Exactly how exercise promotes sleep remains unclear, but the beneficial effects of exercise on mood and anxiety may contribute.[11,12] In addition, exercise has been shown to facilitate phase shifting of the circadian system[13] and thus may help in the adaptation process to shift work.[14] The most appropriate timing and type of exercise to support individuals with SWD remain to be defined, although there is no evidence to suggest that short bouts of exercise during a work period would be beneficial. In one study of 12 volunteers undergoing a period of sleep deprivation, short bouts of exercise increased alertness for a short time, but this benefit was lost in less than an hour.[15]

Further research is needed to fully define the benefits of exercise among individuals with SWD and to define the optimal timing and regimen to facilitate phase adaptation and reduce the symptom burden among this population.

Scheduled naps

Several studies have indicated that scheduled napping for shift workers may be useful in relieving ES during work periods.[16-22] The optimal duration and timing of such naps have yet to be defined, although one study suggested a longer nap during a night shift (120 minutes vs 60 minutes) was better in terms of sustaining cognitive performance in the early hours of the morning

TABLE 2 Reducing the risk for motor vehicle accidents during the commute home

Steps to recommend	To be avoided
• Consider using a taxi service and/or car pooling, preferably with a driver who has not just completed a night shift • Consider taking a nap before driving home • Try to minimize the commute time, eg, move closer to the workplace • Consider using public transportation • If sleepy while driving, pull over at a rest stop and take a nap	• Avoid traveling at high speeds on highways • Do not rely on rolling down the window and turning up the radio—these actions will only relieve sleepiness very briefly • Do not continue to drive when feeling sleepy; pull over at a rest stop and take a nap

and that sleep efficiency was greater when the nap was taken later in the work shift.[18] Even short naps of <1 hour appeared to improve alertness among experienced night-shift workers.[21] Finally, napping before a night shift may also be beneficial in improving performance, particularly when combined with subsequent caffeine intake.[22]

No studies to date have evaluated napping in subjects with SWD. Furthermore, introducing such an intervention may not be practical for all individuals with SWD. Appropriate facilities may not be generally available in the workplace, and napping while "on duty" may be considered unprofessional or ethically unacceptable in some work settings. For example, concerns regarding continuity of care for patients may impede the implementation of scheduled napping among health care workers.[16]

Additional studies evaluating the health, safety, and performance benefits of scheduled nap times for shift workers and among those with a diagnosis of SWD will be required if any cultural change to allow napping is to be achieved.

Light exposure

The human endogenous circadian rhythm is closely linked to the external light/dark cycle; this interaction involves the receipt of daylight-stimulated nerve activity via the retinal ganglion and the retinohypothalamic tract and is controlled by the suprachiasmatic nuclei of the hypothalamus (see "The characterization and pathology of circadian rhythm sleep disorders" on page S12 of this supplement).[23] Consequently, bright light can incrementally reset (re-entrain) the innate sleep/wake cycle[24,25] and can promote wakefulness by suppressing the production of the sleep-mediating hormone melatonin.[26,27] The interaction between light exposure and the endogenous circadian rhythm forms the basis for bright light therapy as a countermeasure for sleep disturbance among night-shift workers.[28]

Evidence suggests that light therapy can entrain the circadian pacemaker to suit night-shift work and so can be used to support night-shift workers in adapting to their shift pattern.[29,30] Bright light (~2500 lux vs normal lighting of ~150 lux) during the work period, combined with regular sleep periods in a darkened room between shifts, significantly ($P < .05$) delayed the dim-light melatonin-onset response in 54 subjects undergoing a simulated night-shift work pattern, indicating a physiologic phase shift.[31] Such partial re-entrainment improved performance, alertness, and mood during the work period among healthy adults.[32]

A separate study, again using a simulated night-shift work pattern, suggested that brief (1-hour) bright light (~3000 lux) exposure combined with caffeine intake during a night shift maintained cognitive performance throughout the work period in 11 subjects, but that brief bright light exposure alone could, in fact, degrade performance.[33] Reducing light exposure on the commute home from work using sunglasses (or goggles) has been shown to assist with achieving sleep when the worker arrives home[34,35] and to support the partial circadian re-entrainment attained with bright light therapy.[34,36]

The optimal bright light exposure to facilitate partial re-entrainment of the circadian rhythm among night-shift workers has yet to be established. The above studies used a variety of regimens, from constant bright light throughout the work period[31] to intermittent delivery of bright light.[32] A recent study has suggested that a combination of afternoon/evening sleep (between 2 PM and 10 PM) and phase-advancing light therapy (between 3 AM and 7 AM) may be optimal for maintaining alertness in individuals undergoing a simulated night-shift (11 PM to 7 AM) work pattern comprising 4 day and 3 night shifts over 10 days.[37] However, none of these studies have been conducted specifically in patients with SWD.

Reducing the effects of ES when commuting

ES is a well-established risk factor for motor vehicle accidents.[38,39] The potential for motor vehicle accidents on the commute home from work is of considerable concern among shift workers, as they are at greater risk for such an event following a night shift.[40-43] Individuals with SWD should be counseled to minimize their risk

for a motor vehicle accident during the commute home. Practical steps are summarized in **TABLE 2**.

Attention to diet

One study has suggested that attention to dietary composition may have an impact on alertness and performance among individuals working night shifts in a hospital setting.[44] The study suggested that a diet with a carbohydrate-to-protein ratio of around 3:1 is optimal in terms of benefits for both mood and psychometric performance.

Pharmacologic interventions

Wakefulness-promoting agents

The wakefulness-promoting agents modafinil and armodafinil (the *R*-enantiomer of modafinil) are currently the only agents specifically approved by the FDA for the treatment of ES associated with SWD. Approval of modafinil for this indication was based on the results of 2 controlled clinical trials (**TABLE 3**).[45,46] Modafinil significantly improved wakefulness, as measured using patient-reported diary data and changes on the Multiple Sleep Latency Test ($P < .001$ and $P = .002$, respectively) in those who had ES as a consequence of SWD.[45] Attention was also significantly improved in the modafinil group compared with placebo ($P < .001$), and significantly fewer participants treated with modafinil reported accidents or near misses during the commute home than did those who received placebo ($P < .001$).[45] Additionally, modafinil significantly improved self-reports of functioning (in terms of productivity and vigilance; $P < .05$) and quality of life ($P < .05$) in individuals with SWD.[46]

In these 2 studies, headache was the most commonly reported adverse event, and nausea was the next most prominent adverse effect with modafinil. In the study by Czeisler and colleagues[45] more modafinil-treated patients experienced insomnia compared with the placebo group (6% vs 0%, respectively; $P < .01$).

Armodafinil has been shown to improve wakefulness in individuals with ES associated with SWD in a controlled clinical trial (**TABLE 3**).[47,48] This study showed armodafinil to be significantly better than placebo at improving wakefulness, reflected by a significantly prolonged sleep latency throughout the night among night-shift workers with SWD ($P < .0001$). Compared with placebo, treatment with a single dose of armodafinil 150 mg, 30 to 60 minutes before the start of the shift, significantly reduced ES at work ($P < .0001$) and during the commute home ($P = .0027$) and did not adversely affect daytime sleep.[47,48] As observed for modafinil, headache and nausea were the most common treatment-emergent adverse events in patients with SWD who took part in these 2 studies.

To date, no studies have been performed that directly compare the efficacy of armodafinil and modafinil; however, the 2 wakefulness-promoting agents do have different pharmacokinetic profiles.[49,50] Compared with modafinil, armodafinil takes longer to reach its peak plasma concentration and is present at higher concentrations for a longer period after administration, resulting in its wakefulness-promoting effects lasting throughout the day.[49,50] The longer duration of armodafinil's effects and its potential for once-daily dosing make it an appropriate and convenient choice for patients with SWD.

Stimulants

Stimulants, such as methamphetamine, have been shown to enhance wakefulness in individuals undergoing simulated night-shift work.[51,52] However, amphetamines can induce rebound insomnia and this, combined with their adverse cardiovascular effects and their abuse potential, makes them less than ideal options for an often chronic condition such as SWD.[53] Methamphetamine has not been evaluated as an intervention for individuals with a diagnosis of SWD and, although it is effective at improving performance and mood during one or more night shifts after single doses, its usefulness in managing SWD on numerous sequential nights is questionable.

A number of studies among individuals undergoing simulated night-shift work suggest that caffeine may be useful to promote wakefulness during the work period, although there may be some residual effects on daytime sleep depending on the caffeine drink selected.[54-56] One study suggested that low-dose repeated caffeine administration may improve performance at the expense of increasing subjective ES during periods of extended wakefulness.[57] As discussed above, caffeine in combination with other wakefulness-promoting strategies, including scheduled napping and bright light therapy, has proved to be a promising intervention under simulated shift-work conditions.[22,23] However, the appropriate dose and timing of caffeine intake to optimize performance and mood during a night shift have not yet been determined. Higher caffeine doses may induce a state of hyperstimulation and can even be toxic.[58] Moreover, habitual caffeine intake can lead to the development of tolerance to its effects,[59] abrogating the efficacy of caffeine intake in the long-term management of an often chronic condition such as SWD. To date, regular

TABLE 3 Improved wakefulness and reduced ES associated with FDA-approved wakefulness-promoting agents[45-48]

Citation	Population	Regimens	N (evaluable efficacy population)	Key findings
Modafinil				
Czeisler et al[45]	Adults (18-60 years) with SWD working ≥5 night shifts/month with ≥3 worked consecutively	Modafinil 200 mg Placebo *Taken 30-60 minutes before the start of the work shift for 12 weeks*	89 104	• Mean sleep latency change from baseline ± SD: – Modafinil: 1.7 ± 0.4 minutes – Placebo: 0.3 ± 0.3 minutes (P = .002) • Change from baseline in the median frequency of reported attention lapses: – Modafinil: Reduced by 2.6 – Placebo: Increased by 3.8 (P < .001) • Reported accidents/near accidents while commuting home: – Modafinil: 29% – Placebo: 54% (P < .001)
Erman et al[46]	Adults (18-60 years) with SWD working ≥5 night shifts/month with ≥3 worked consecutively	Modafinil 200 mg Modafinil 300 mg Placebo *Taken 30-60 minutes before the start of the work shift for 12 weeks*	87 90 86	• Modafinil 300 mg significantly improved overall patient functioning vs placebo as measured using the FOSQ: – Increase from baseline in FOSQ score: 2.3 vs 1.6 points, respectively (P < .05) • Modafinil 200 mg and 300 mg both significantly improved quality of life vs placebo as measured using the SF-36 mental health component score: – Mean change from baseline of 3.2, 3.7, and 0.7 points, respectively (P < .05 for both doses vs placebo)
Armodafinil				
Drake et al,[47] **Roth et al**[48]	Adult permanent or rotating night-shift workers with SWD working ≥5 night shifts/ month	Armodafinil 150 mg Placebo *Taken 30-60 minutes before the start of the work shift for 12 weeks*	112 104	• Mean sleep latency change from baseline: – Armodafinil: 3.1 ± 4.5 minutes – Placebo: 0.4 ± 2.9 minutes (P < .0001) • Reported ES levels on the KSS were significantly reduced with armodafinil vs placebo (P < .005). • Change in the maximum level of sleepiness (electronic diary data) – During the work shift: 2.0 vs 1.1 points, respectively (P < .0001) – During the commute home: 1.2 vs 0.6 points, respectively (P = .0027)

ES, excessive sleepiness; FOSQ, Functional Outcomes of Sleep Questionnaire; KSS, Karolinska Sleepiness Scale; SD, standard deviation; SF-36, Medical Outcomes Study Short-Form (36-item) Health Survey; SWD, shift-work disorder.

moderate caffeine intake has not been specifically assessed among individuals with SWD.

Other pharmacologic options for SWD

Administration of the sleep-mediating hormone melatonin can promote daytime sleep.[60] However, while some studies have reported that melatonin is helpful for inducing daytime sleep in simulated and real-world shift-work conditions,[61-64] others have failed to demonstrate any objective or subjective benefit.[65] Single doses of melatonin taken before the required sleep period in simulated shift-work studies of healthy subjects have been shown to decrease sleep latency and increase sleep duration.[62] Melatonin may be most beneficial as part of a phase-advancing program to support individuals in adjusting to night-shift work rather than as a chronic therapy for SWD.[61,63,64,66]

Hypnosedatives, or sleep-promoting agents, taken before required sleep periods have also been evaluated in simulated shift-work conditions. Zolpidem, zopiclone, triazolam, and temazepam have all been shown to increase sleep duration during the day and to improve wakefulness during the night shift.[52,67-70] Only zopiclone has been evaluated among shift workers.[70] In a study of 12 healthy male volunteers working 12-hour shifts, a single dose of zopiclone 7.5 mg taken before the required sleep period significantly improved sleep at night, but this improvement did not reach statistical significance when the required sleep period was during the day. No studies of hypnosedatives have been conducted among individuals with SWD. The greater effect of hypnotics on night-time sleep suggests that they are less efficacious at improving disturbed sleep when given out of phase with the usual sleep period.

Summary

Although few interventions have been studied specifically among individuals with SWD, there are a range of practical steps that clinicians can offer to relieve its adverse effects and to reduce a patient's risk of experiencing the potentially fatal consequences of this disorder.

Appropriate interventions include steps to improve sleep hygiene, and evaluation and appropriate referral for comorbid conditions, with particular emphasis on comorbid sleep disorders. Strategies to promote adaptation to the required sleep/wake cycle should also be implemented. These can include bright light therapy (before or during a night shift), reduction of exposure to daylight on the commute home from work, and/or medication with melatonin before a required sleep period, or combinations thereof.[32,34,36,66] These strategies have proved useful among shift workers in general, and further investigation of such strategies would be valuable among those with SWD. Steps to improve shift schedules (eg, the use of clockwise-rotating shifts and avoiding shifts longer than 12 hours), and measures to improve shift-work conditions, such as bright light exposure and appropriately timed naps, may also be helpful.

The wakefulness-promoting agents modafinil and armodafinil are the only interventions with FDA approval for use in patients with SWD and have been evaluated specifically among individuals with ES associated with SWD. These agents have been proven to reduce ES during the work period, with associated benefits in terms of a reduced incidence of accidents or near misses during the commute home. Initiation of wakefulness-promoting therapy should be considered early in the management of individuals with SWD.

Future research should focus on the potential of interventions known to promote wakefulness or sleep specifically among individuals with SWD. In the meantime, clinicians caring for individuals with SWD should develop individualized management strategies that incorporate both nonpharmacologic interventions and pharmacologic therapies, such as a wakefulness-promoting agent before the work period with or without a sleep-promoting agent before the required sleep period. n

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SHIFT-WORK DISORDER

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Armodafinil for Treatment of Excessive Sleepiness Associated With Shift Work Disorder: A Randomized Controlled Study

Charles A. Czeisler, PhD, MD, James K. Walsh, PhD, Keith A. Wesnes, PhD, Sanjay Arora, PhD,† and Thomas Roth, PhD

From the Division of Sleep Medicine, Harvard Medical School, and Division of Sleep Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (C.A.C.); Sleep Medicine and Research Center, St Luke's Hospital, Chesterfield, MO (J.K.W.); Cognitive Drug Research Ltd, Goring-on-Thames, UK (K.A.W.); Sleep Disorders and Research Center, Henry Ford Hospital, Detroit, MI (T.R.). The participating investigators are listed on page 969
†Died March 1, 2007; was an employee of Cephalon Inc.
Individual reprints of this article are not available. Address correspondence to Charles A. Czeisler, PhD, MD, Division of Sleep Medicine, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Ave, Ste 438A, Boston, MA 02115 (; Email: charles_czeisler/at/hms.harvard.edu).

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See "Fatigue, Countermeasures, and Performance Enhancement in Resident Physicians" on page 955.

Abstract

OBJECTIVE: To assess the effect of armodafinil, 150 mg, on the physiologic propensity for sleep and cognitive performance during usual night shift hours in patients with excessive sleepiness associated with chronic (≥3 months) shift work disorder (SWD) of moderate or greater severity.

PATIENTS AND METHODS: This 12-week, randomized controlled study was conducted at 42 sleep research facilities in North America from April 2 through December 23, 2004, and enrolled 254 permanent or rotating night shift workers with SWD. Entry criteria included excessive sleepiness during usual night shifts for 3 months or longer (corroborated by mean sleep latency of ≤6 minutes on a Multiple Sleep Latency Test), insomnia (sleep efficiency ≤87.5% during daytime sleep), and SWD that was judged clinically to be of moderate or greater severity. Patients received armodafinil, 150 mg, or placebo 30 to 60 minutes before each night shift. Physiologic sleep propensity during night shift hours, clinical impression of severity, patient-reported sleepiness, and cognitive function were assessed during laboratory night shifts at weeks 4, 8, and 12.

RESULTS: Armodafinil significantly improved mean (SD) sleep latency from 2.3 (1.6) minutes at baseline to 5.3 (5.0) minutes at final visit, compared with a change from 2.4 (1.6) minutes to 2.8 (2.9) minutes in the placebo group ($P<.001$). Clinical condition ratings improved in more patients receiving armodafinil (79%) vs placebo (59%) ($P=.001$). As reported by patients' diaries, armodafinil significantly reduced sleepiness during laboratory nights ($P<.001$), night shifts at work ($P<.001$), and the commute home ($P=.003$). Armodafinil improved performance on standardized memory ($P<.001$) and attention (power, $P=.001$; continuity, $P<.001$) tests compared with placebo. Armodafinil was well tolerated and did not affect daytime sleep, as measured by polysomnography.

CONCLUSION: In patients with excessive sleepiness associated with chronic SWD of moderate or greater severity, armodafinil significantly improved wakefulness during scheduled night work, raising mean nighttime sleep latency above the level considered to indicate severe sleepiness during the daytime. Armodafinil also significantly improved measures of overall clinical condition, long-term memory, and attention.

Trial Registration: clinicaltrials.gov Identifier: NCT00080288

CDR = Cognitive Drug Research; CGI-C = Clinical Global Impressions of Change; CGI-S = Clinical Global Impressions of Severity of Illness; KSS = Karolinska Sleepiness Scale; MSLT = Multiple Sleep Latency Test; nCPAP = nasal continuous positive airway pressure; OSA = obstructive sleep apnea; SWD = shift work disorder

Approximately 15% of employed adults in the United States work during nighttime hours.[1] Night work induces a misalignment between the sleep-wake schedule and sleep and wake propensity that is controlled by the hypothalamic circadian pacemaker.[2,3] In most people who work and/or commute during the night and early morning, circadian misalignment results in impaired wakefulness while working or commuting and, despite prior sleep deprivation, insomnia during daytime sleep.[2,4,6] These are the symptoms of shift work disorder (SWD).[7,8] In the recently revised *International Classification of Sleep Disorders: Diagnostic and Coding Manual,*[7] the American Academy of Sleep Medicine changed the name of the condition formerly known as *shift work sleep disorder* to "*circadian rhythm sleep disorder, shift work type (shift work disorder)*." The patients in the current study meet the criteria of what is now called *shift work disorder*.

For editorial comment, see page 955

The most severely affected individuals may report falling asleep while working or commuting. In fact, one-third of night workers admit to regularly nodding off or falling asleep at least once per week while working, and half admit to falling asleep while commuting.[9] Mitler et al[10] reported that 56% of professional truck drivers experienced episodes of drowsy driving, 80% of which occurred during night driving. Moreover, 54% of the drowsy driving episodes involved just 10% of the drivers.[10] A recent study of 2570 working adults found that 44.8% of night shift workers and 35.8% of rotating shift workers reported excessive sleepiness (ie, an Epworth Sleepiness Scale score of ≥10), and 18.5% of night shift workers and 15.7% of rotating shift workers reported moderate to severe insomnia during daytime sleep.[4]

Shift work can impair individuals' health status, occupational performance, and social well-being.[1,11,13] These impairments appear to be greatest among those meeting diagnostic criteria for SWD. Patients with SWD are also at greater risk of cardiovascular disease, ulcers, depression, sleepiness-related accidents, and absenteeism compared with shift workers without SWD.[4] Excessive sleepiness associated with SWD has been shown to have other effects, including impairments in cognition and psychomotor performance, which in turn may

contribute to increased accidents during work and motor vehicle crashes during the morning commute.[4,14,15]

A randomized controlled study showed that the wakefulness-promoting agent modafinil (200 mg) improves wakefulness and the ability to sustain attention in patients with SWD.[16] Despite the drug's 15-hour half-life, these effects were not sustained vs placebo throughout the entire night.[16] Modafinil is a racemic compound that contains equal amounts of 2 enantiomers with different terminal half-lives: *R*-modafinil (armodafinil) is eliminated more slowly than *S*-modafinil and has a half-life of approximately 15 hours compared with a half-life of approximately 3 to 4 hours for *S*-modafinil. Preliminary data in healthy volunteers revealed that armodafinil, 200 mg, enabled individuals to sustain wakefulness and neurobehavioral performance more effectively in the final third of a simulated night shift compared with modafinil, 200 mg.[17] We anticipated that elevated plasma concentrations of armodafinil later in the overnight shift and on the commute home would benefit patients with SWD because they are substantially impaired at those times.[16] The current study assessed the efficacy and safety of armodafinil in patients with excessive sleepiness associated with chronic SWD of moderate or greater severity.

PATIENTS AND METHODS

This 12-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study was conducted with a common protocol at 42 centers in the United States (37) and Canada (5) from April 2 through December 23, 2004 (a center in Australia planned to but did not enroll any patients), in compliance with the International Conference on Harmonization's Good Clinical Practice Consolidated Guidance. An independent ethics committee or institutional review board at each center approved the protocol.

Patients participated in a screening visit, during which the Clinical Global Impressions of Severity of Illness (CGI-S) scale[18] was completed and electronic diaries were dispensed. After a sequence of 3 or more consecutive night shifts, patients returned for an overnight sleep laboratory night shift to undergo baseline assessments and daytime polysomnography. Patients who met inclusion and exclusion criteria received study medication or placebo at a subsequent randomization visit. After this, patients were evaluated at weeks 4, 8, and 12 during an overnight laboratory night shift scheduled immediately after a sequence of 3 or more consecutive work night shifts.

Men and women between the ages of 18 and 65 years who worked 5 or more night shifts per month (each shift ≤12 hours, with ≥6 hours worked between 10 pm and 8 am and with ≥3 shifts occurring on consecutive nights) and planned to maintain this schedule for the duration of the treatment were screened for inclusion. Only individuals who exhibited signs and symptoms of SWD of moderate or greater severity, as documented by a CGI-S rating of 4 or higher[18] for sleepiness on work nights, including the commute to and from work, were enrolled in the study. During screening, patients were assessed for SWD according to the *International Classification of Sleep Disorders* criteria.[7] Inclusion criteria included a diagnosis of SWD according to the *International Classification of Sleep Disorders*; a complaint of chronic (≥3 months) excessive sleepiness during night shifts, which was corroborated by a mean sleep latency of 6 minutes or less on a nighttime Multiple Sleep Latency Test (MSLT); and insomnia, as indicated by daytime sleep efficiency of 87.5% or less (determined by 8-hour polysomnography). Patients with a history of substance abuse or medical or psychiatric disorders[8] that could account for excessive sleepiness during the night shift were excluded, as were patients with any disorder that might interfere with drug pharmacokinetics or a known sensitivity to stimulants or modafinil. Female patients of childbearing potential were required to have a negative serum pregnancy test result at screening and to use a medically accepted method of birth control. Steroidal contraceptives had to be used in combination with a barrier method. Patients who consumed on average more than 600 mg/d of caffeine during the 7 days preceding the baseline visit were excluded from the study. In addition, patients were excluded if they took prescription drugs disallowed by the protocol or consumed clinically important amounts of nonprescription drugs within 7 days of the screening visit. Before study enrollment, all patients gave written informed consent.

Study participants were randomly assigned (1:1) to receive armodafinil, 150 mg (Cephalon Inc, Frazer, PA), formulated as 50-mg tablets or matching placebo 30 to 60 minutes before each night shift and no later than 11 pm. The study sponsor generated and maintained the randomization code, and all clinical personnel from the sponsor, investigators, and patients remained blinded to the identity of the study drug for the duration of the study. A central interactive voice response system for the randomization process ensured an overall balance among treatment groups within each country.

Patients received a dose of 50 mg on the first night, 100 mg on the second and third nights, and 150 mg on all subsequent nights. Patients took study medication only on nights when they worked the night shift or attended the sleep laboratory. During laboratory night shifts, study medication was administered at 10 pm (±30 minutes). The investigator reviewed patient diaries, work schedules, and drug accountability records for compliance at all postbaseline visits.

Efficacy Measures

Sleep propensity during laboratory night shifts was evaluated electrophysiologically using 20-minute MSLT[19] sessions at midnight and at 2, 4, 6, and 8 am. Sleep latency was measured as the time from lights out to the first 30-second epoch scored as sleep according to standard criteria.[20] If a patient fell asleep during the session, he or she was awakened and kept awake while remaining in bed for the remainder of the 20 minutes. If a patient did not fall asleep during the session, the test was terminated and sleep latency recorded as 20 minutes. The MSLT scoring was conducted blind to study condition at a central scoring site by 1 of 4 trained registered polysomnographic technologists (supervised by J.K.W.) according to standard criteria for research studies.[21] All recordings for which mean sleep latency was distinct (61%) were scored by 1 technologist; the remainder were evaluated by 2 scorers. If mean latency differed by 1 minute or more between those 2 scorers, the assessment of a third technologist resolved the difference.

Investigators used the Clinical Global Impressions of Change (CGI-C) scale[18] to assess changes from baseline in symptom severity during the night shift and the commute (established using the investigator-rated CGI-S) according to 7 categories ranging from “very much improved” to “very much worse.” Patient-estimated sleepiness was evaluated using the Karolinska Sleepiness Scale (KSS).[22] Patients completed the KSS before every MSLT session. Patients completed daily electronic diaries that contained questions related to sleepiness and sleep, mistakes or accidents, and caffeine use during the night shift and the commute home, as well as questions concerning sleep on the days after night shifts. The diaries were reviewed monthly.

The computerized Cognitive Drug Research (CDR) system[23,25] was administered at 12:30, 2:30, 4:30, 6:30, and 8:30 am of each laboratory night shift. The CDR battery included tests of memory (eg, numeric working memory test, word recognition test, immediate word recall test, delayed word recall test, and picture recognition test) and attention (eg, simple reaction time test, choice reaction time test, and digit vigilance task). Composite factors derived from the CDR included quality of episodic secondary memory (ability to encode, store, and retrieve verbal and pictorial information of an episodic nature), speed of memory (time required to retrieve information from episodic and working memory), power of attention (ability to focus attention), and continuity of attention (ability to sustain attention). Cognitive Drug Research Ltd was contracted to provide the CDR computerized assessment system to conduct the psychomotor and cognitive tests for this study. The CDR computerized system was delivered to each site, and the site staff were trained by qualified personnel. All data were captured electronically, except word recall, for which the patients wrote the words on recall sheets. The electronic data and recall sheets were returned to CDR Ltd, where the data were processed using validated procedures by qualified personnel (supervised by K.A.W.). After processing the data, CDR Ltd completed a quality assurance procedure on the dataset and transferred it to the study sponsor.

Safety and Adverse Effect Assessments

Adverse events were monitored throughout the study. Clinical laboratory tests, vital sign measurements, and 12-lead electrocardiography were conducted at screening, baseline, and the 4-, 8-, and 12-week visits. Vital signs were measured at approximately 3 and 11 hours after dosing at each laboratory visit, as well as at 6:15 pm after the daytime polysomnography at baseline and the final visit (approximately 20 hours after the dose). Electrocardiography was conducted at approximately 3 hours after dosing. Physical examinations were conducted at screening, baseline, and the final visit.

Daytime polysomnography was conducted for 8 hours starting at 10:15 am during the baseline screening and final laboratory night shifts to assess the effect of armodafinil on daytime sleep. Patients were scheduled to sleep in a dark, sound-attenuated, temperature-controlled room and were instructed to remain in bed even if they awakened before the end of the scheduled sleep episode. Sleep was scored according to standard criteria[20] at the Henry Ford Hospital Sleep Disorders and Research Center. The scorers were all trained on the Rechtschaffen and Kales scoring system (supervised by T.R.). All potential scorers were required to score a series of standardized polysomnograms. The standardized polysomnograms that were used for determining scorer qualification had been staged by a consensus scoring of 3 sleep specialists accredited by the American Board of Sleep Medicine. Scorers were not qualified to score polysomnograms for this study until they obtained a 90% epoch-by-epoch agreement between their scoring and the consensus scoring on 3 consecutive standardized polysomnograms. During the study, all recordings were scored blind as to the study, site, treatment condition, and study night. Ten percent of these polysomnograms were selected to be scored a second time as a reliability check. Scorers performing the reliability checks were not aware that this was a reliability check (ie, it was presented as another study polysomnogram). These records were selected on a quasi-random basis. That is, records were selected randomly with the constraints that the number of records from each site be proportional to their enrollment of individuals into the study and that an equal number of records be selected from each treatment condition. Sixty-seven records were scored as a quality check. On the basis of epoch-by-epoch scoring of wake; sleep stages 1, 2, 3, and 4; and rapid eye movement; a percent agreement of epoch-by-epoch scoring was obtained. The mean percent agreement was 89.6%, with a range of 81.6% to 95.6%. Diary data related to the effect of study medication on daytime sleep were reviewed monthly.

Statistical Analyses

Sample size estimates were based on the results of data from previous clinical studies with armodafinil and modafinil. This analysis showed that a sample size of 108 patients per treatment arm would provide 85% power to detect a 1.5-minute difference in mean sleep latency on the MSLT between the armodafinil, 150 mg, group and the placebo group, assuming a common SD of 3.65 minutes. This sample size would have at least 90% power to detect a difference of 25% in the proportion of patients reporting at least minimal improvement in the CGI-C ratings between the armodafinil group and the placebo group, assuming a 37% rate in the placebo group. The planned enrollment was approximately 250 patients to ensure that 216 had at least 1 postbaseline MSLT assessment.

Demographic and baseline characteristics were summarized using descriptive statistics. Between-group comparisons of continuous demographic variables were conducted using analysis of variance with treatment group as a factor. Categorical variables were compared using the Pearson χ^2 test or Fisher exact test.

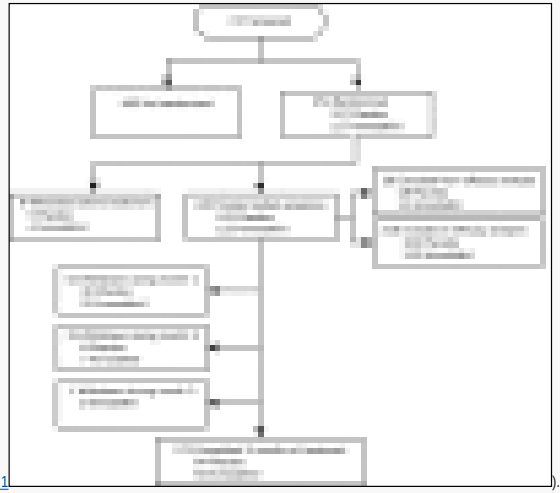
The prespecified primary hypothesis was that armodafinil would increase mean sleep latency and improve the overall clinical condition in patients with excessive sleepiness associated with SWD. Two primary efficacy analyses were prespecified to test this hypothesis. The first was the change from baseline to final visit (12-week or last postbaseline measurement) in overall mean sleep latency (averaged across the last 4 nighttime sessions at 2, 4, 6, and 8 am) compared with placebo as assessed by the MSLT. The second was the proportion of patients who showed at least minimal improvement in the CGI-C rating for overall clinical condition during the night shift and commute to and from work at the final visit (12-week or last postbaseline measurement) compared with placebo.

Safety analyses were conducted using data from randomized patients who received at least 1 dose of study medication or placebo. Efficacy analyses were performed on data from randomized patients who had received at least 1 dose of study medication or placebo and had a baseline and at least 1 postbaseline assessment on the MSLT and CGI-C. Analyses of all efficacy variables at weeks 4, 8, and 12 used observed cases, and the final visit analyses were performed using the last postbaseline observation carried forward.

To analyze the KSS scores, data from the 4 tests associated with the MSLT naps at 2, 4, 6, and 8 am were averaged; and to analyze factor scores on memory and attention from CDR data, tests at 2:30, 4:30, 6:30, and 8:30 am were averaged. Mean sleep latency, mean KSS score, and CDR factor and component scores were assessed using analysis of variance with treatment group and country as factors. The CGI-C data were analyzed using a Cochran-Mantel-Haenszel χ^2 statistic, adjusted for country. All tests of significance were 2-tailed, and the .05 level of significance was used.

Diary data were summarized using descriptive statistics. The comparison of treatment groups for the data from electronic diaries and polysomnographic recordings was performed using the Wilcoxon rank sum test. Safety data, as well as diary data related to the effect of study medication on daytime sleep, were summarized using descriptive statistics.

RESULTS



Of the 747 adults screened, 254 met entry criteria. Of these, 245 (96%) received at least 1 dose of study medication and were included in the safety analysis (Figure 1). At baseline, the armodafinil and placebo groups were similar in demographic variables and illness severity ratings (Table 1). Overall, 138 (56%) of 245 patients were rated by the investigator as moderately ill, and 107 (44%) of 245 patients were rated as markedly, severely, or extremely ill. Most patients (212/245; 87%) were permanent night shift workers. The largest area of industry represented was health care and social assistance, which accounted for 98 (40%) of 245 patients in the safety population.

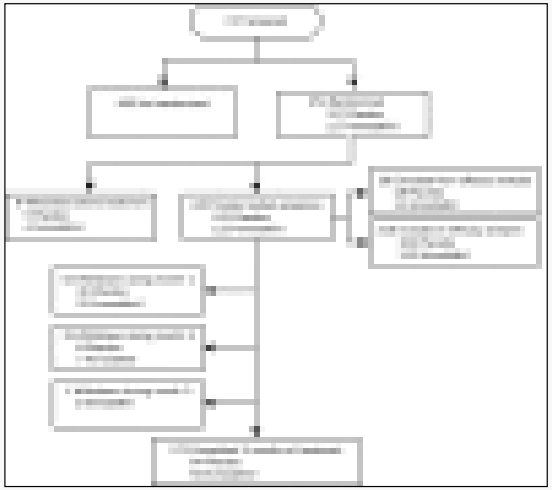


FIGURE 1.

Patient disposition. Screened patients include patients referred from central advertising, investigators' advertising effort, and investigators' patients. Reasons patients were not randomized include the following: sleep efficiency of more than 87.5%, (more ...)

TABLE 1.

Baseline Characteristics of Patients Diagnosed as Having Shift Work Disorder Who Received 150 mg of Armodafinil or Placebo

The mean (SD) number of nights that patients received study medication was 42.4 (19.3) for the armodafinil group and 39.2 (18.2) for the placebo group. Sixty-eight (28%) of 245 patients withdrew from the study (30 in the armodafinil group and 38 in the placebo group). Reasons for discontinuing were adverse events (7 in the armodafinil group and 4 in the placebo group), consent withdrawn (3 in the armodafinil group and 16 in the placebo group), loss to follow-up (3 in the armodafinil group and 5 in the placebo group), nonadherence with study procedures (6 in the armodafinil group and 2 in the placebo group), and other (11 in the armodafinil group and 11 in the placebo group). No patients discontinued participation because of lack of efficacy.

The efficacy analysis included 216 (85%) of 254 patients. Patients were severely sleepy at baseline, with mean (SD) sleep latencies on the MSLT of 2.3 (1.6) minutes for the armodafinil group and 2.4 (1.6) minutes for the placebo group. For patients' own estimates of their sleepiness at baseline, the mean (SD) KSS score was 7.4 (1.4) in the armodafinil group and 7.3 (1.3) in the placebo group, and 97 (87%) of 112 patients in the armodafinil group and 87 (84%) of 104 in the placebo group had a KSS score of 6 or higher.

Primary Efficacy Measures

Armodafinil improved mean (SD) nighttime sleep latency (2-8 am) by 3.1 (4.5) minutes to 5.3 (5.0) minutes at the final visit, compared with an increase of 0.4 (2.9) minutes to 2.8 (2.9) minutes at the final visit in patients receiving placebo (difference between groups in change from baseline, *P*<.001; Figure 2

, left). Of 112 patients who received armodafinil, 89 (79%) were rated as improved in the CGI-C ratings at the final visit compared with 61 (59%) of the 104 patients who received placebo (*P*=.001).

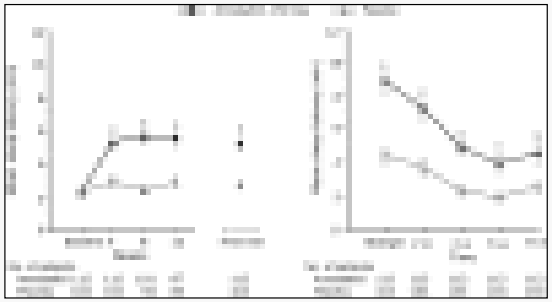
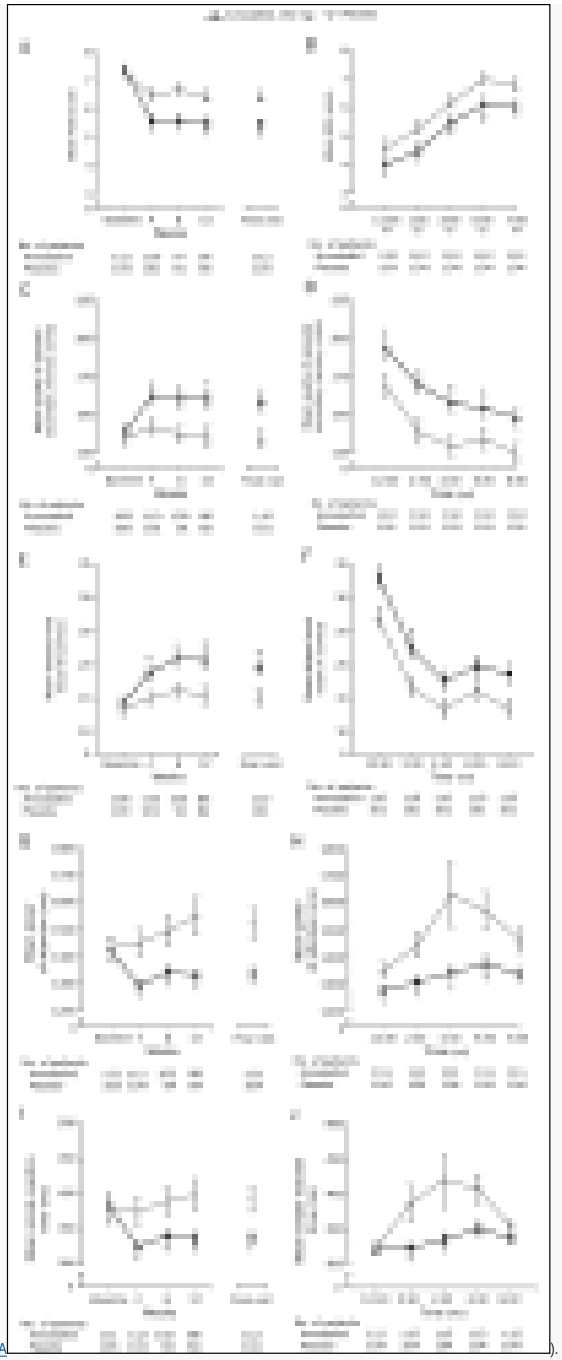


FIGURE 2.

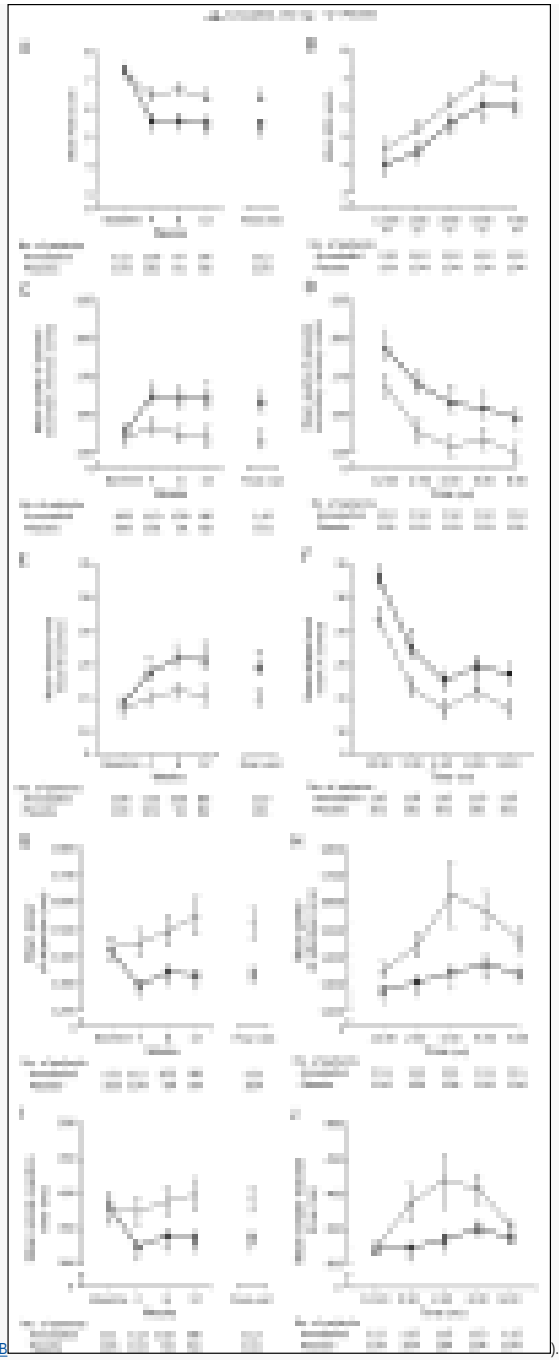
Mean sleep latency on the Multiple Sleep Latency Test (MSLT). Sleep latency by visit for the last 4 tests (2-8 am) (left) and during the final visit night shift (midnight to 8 am) (right). Error bars indicate SEM. *P* values are based on the change from (more ...)

Secondary Efficacy Measures

Wakefulness Assessments. The significant increase from baseline in mean nighttime sleep latency in the armodafinil group relative to the placebo group was evident at the 4-, 8-, and 12-week assessments (Figure 2, left). The sleep latency for individual MSLT sessions at all 5 time points (midnight to 8 am) at the final visit was greater for patients who received armodafinil than for patients who received placebo (*P*<.001 at midnight, 2 am, 4 am; *P*=.007 at 6 am; *P*=.02 at 8 am (Figure 2, right). For the armodafinil group, 64 (57%) of 112 patients were “very much improved” or “much improved” at the final visit compared with 37 (36%) of 104 patients in the placebo group (*P*=.002). The proportion of patients with at least minimal improvement on the CGI-C rating of sleepiness was significantly greater for armodafinil than for placebo at the 4-week (armodafinil, 89/110 patients [81%]; placebo, 59/100 [59%]; *P*<.001), 8-week (armodafinil, 77/99 [78%]; placebo, 45/93 [48%]; *P*<.001), and 12-week (armodafinil, 75/96 [78%]; placebo, 50/89 [56%]; *P*=.001) assessments.



Patient-reported levels of sleepiness during the night shift on the KSS were significantly reduced for the armodafinil group compared with the placebo group at all visits (Figure 3, A



Patient-reported sleepiness at the first 4 time points at the final visit was significantly improved for patients who received armodafinil vs that for patients who received placebo (Figure 3, B

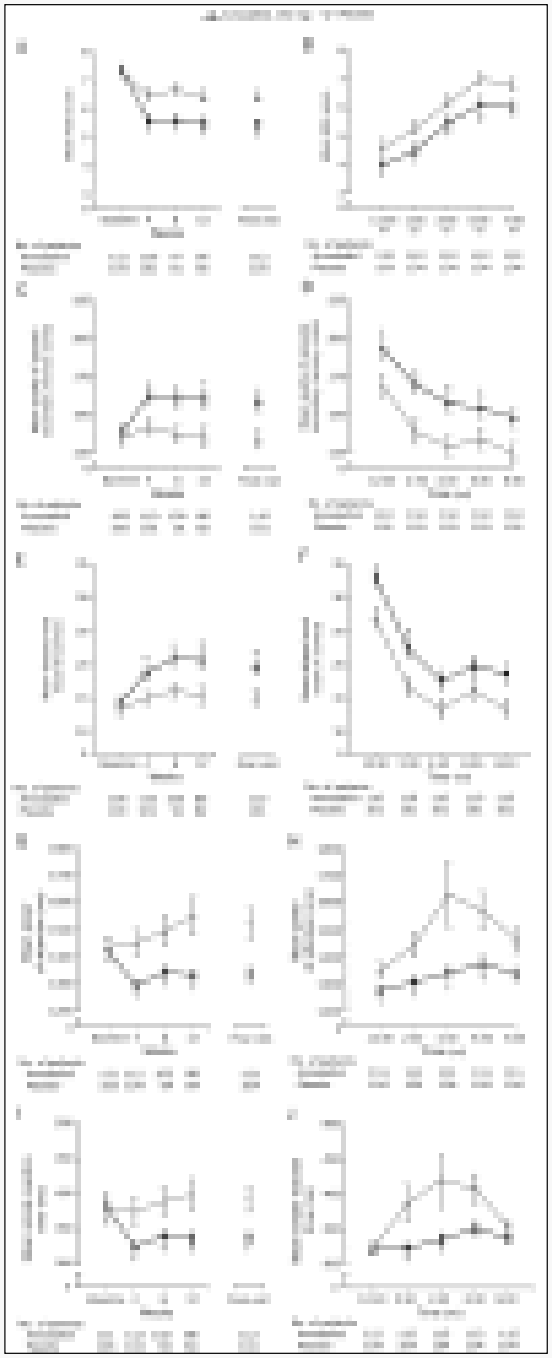
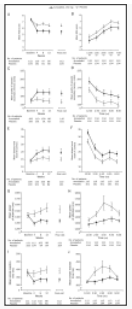


FIGURE 3.

Mean Karolinska Sleepiness Scale (KSS) scores. Scores are by visit (A) and during the final visit night shift (midnight to 8 am) (B); for quality of episodic secondary memory by visit (C) and during the final visit night shift (midnight to 8 am) (D); (more ...)

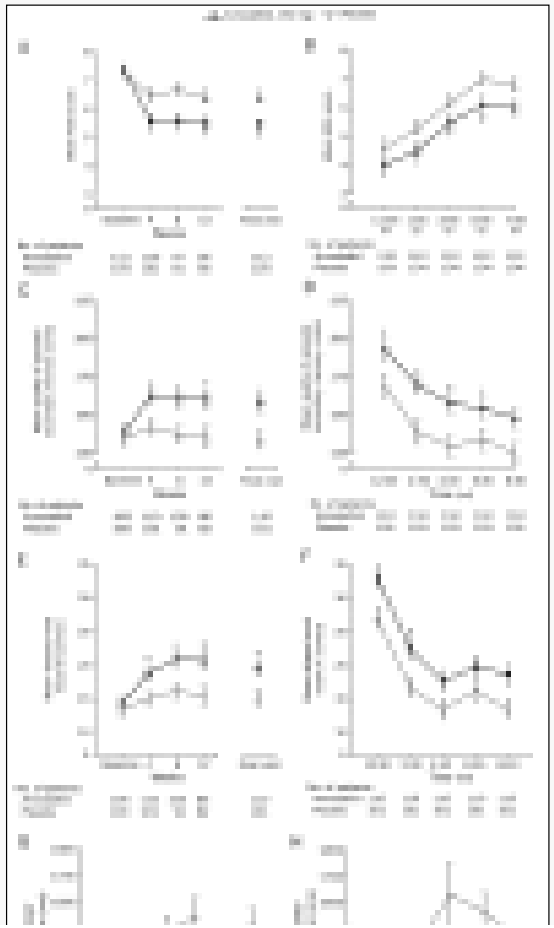


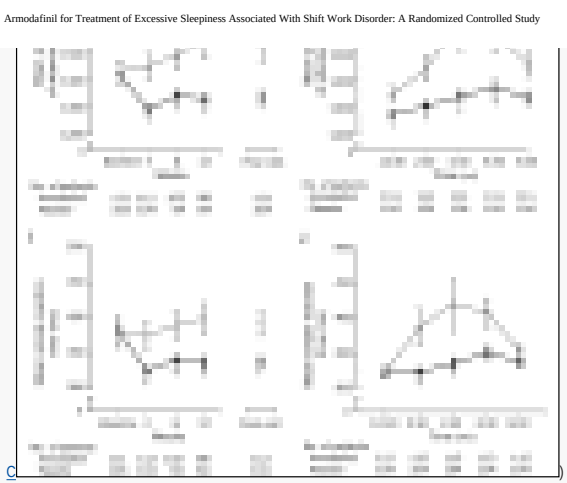
At the final visit, armodafinil was associated with significant improvement in most items assessed in the electronic diaries, including maximum level of sleepiness during the night shift and commute home and the mean number of mistakes, accidents, or near misses compared with placebo (Table 2).

TABLE 2.

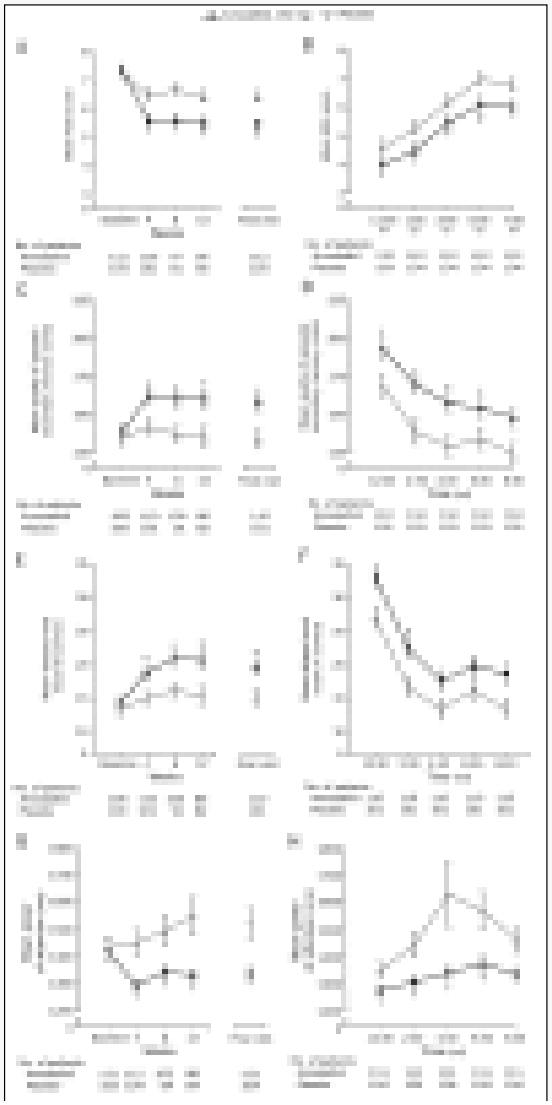
Baseline and Change From Baseline in Ratings of Sleepiness on the Electronic Daily Diaries for Patients Diagnosed as Having Shift Work Disorder Who Received Armodafinil, 150 mg, or Placebo

Memory Assessments. Armodafinil significantly improved the mean score for the quality of episodic secondary memory factor compared with placebo at each visit (*P*<.001 at weeks 4 and 8; *P*=.002 at week 12; *P*<.001 at final visit; Figure 3.

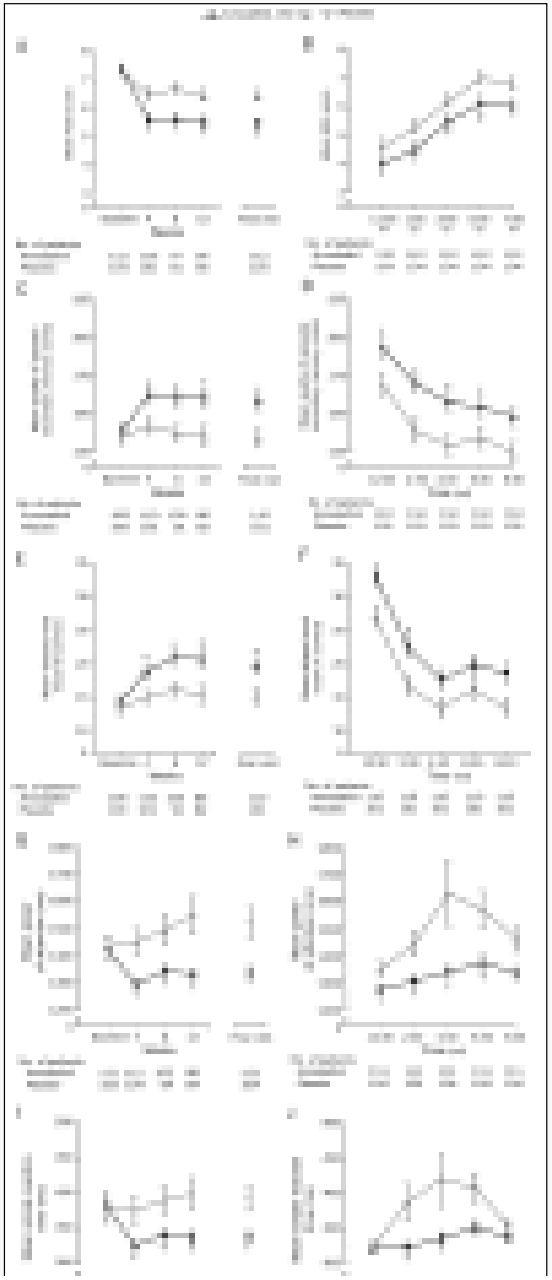




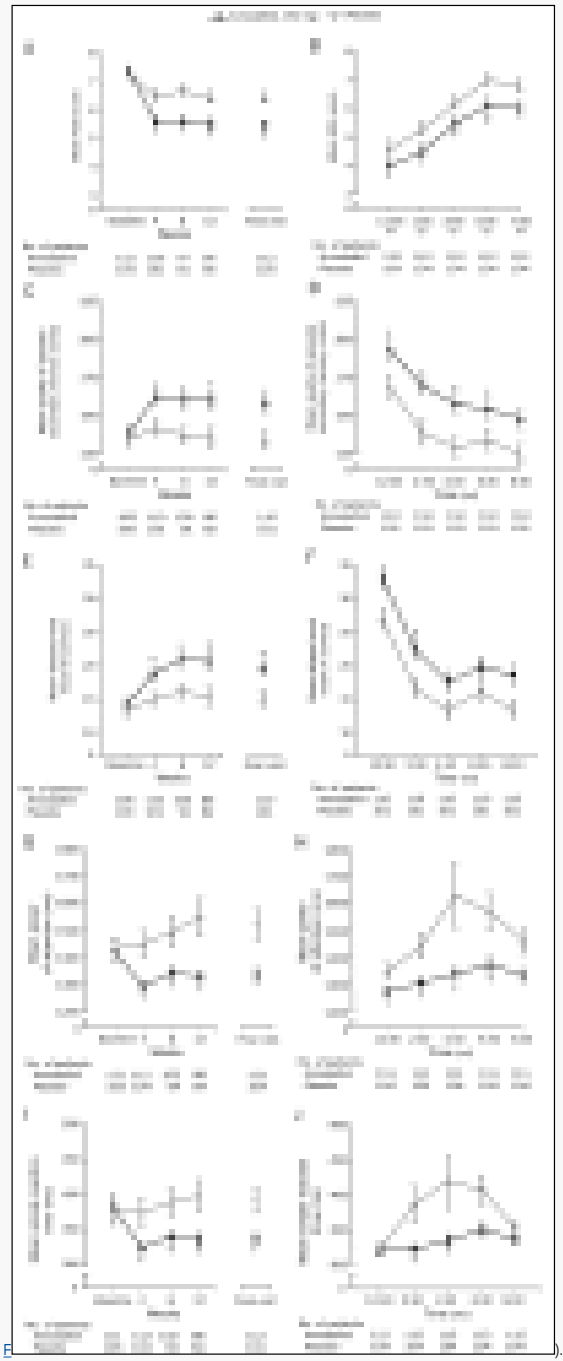
C) and during the first 4 tests on the final night shift (*P*=.002 at 12:30 am; *P*<.001 at 2:30 am; *P*=.02 at 4:30 am; *P*=.006 at 6:30 am; Figure 3,



D). Within this factor score, armodafinil significantly improved the accuracy of delayed word recall compared with placebo at each visit (*P*=.02 at week 4; *P*=.006 at week 8; *P*=.02 at



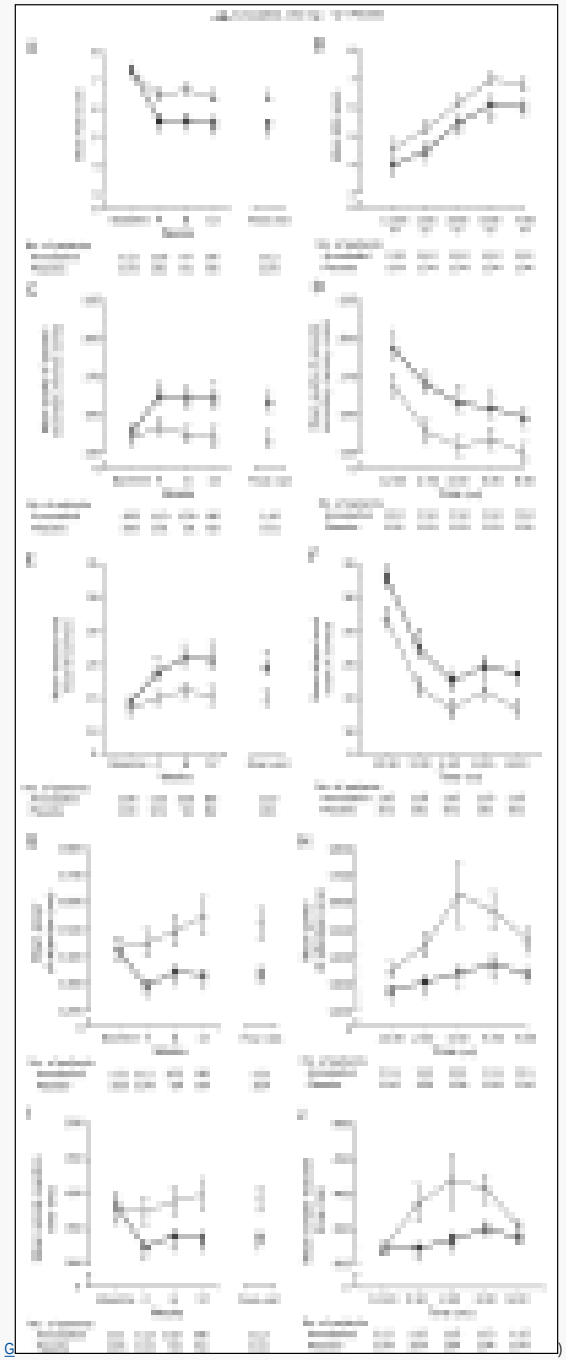
week 12 and at final visit; Figure 3, E) and during the first 2 tests on the final night shift (*P*<.001 at 12:30 am; *P*=.02 at 2:30 am; Figure 3,



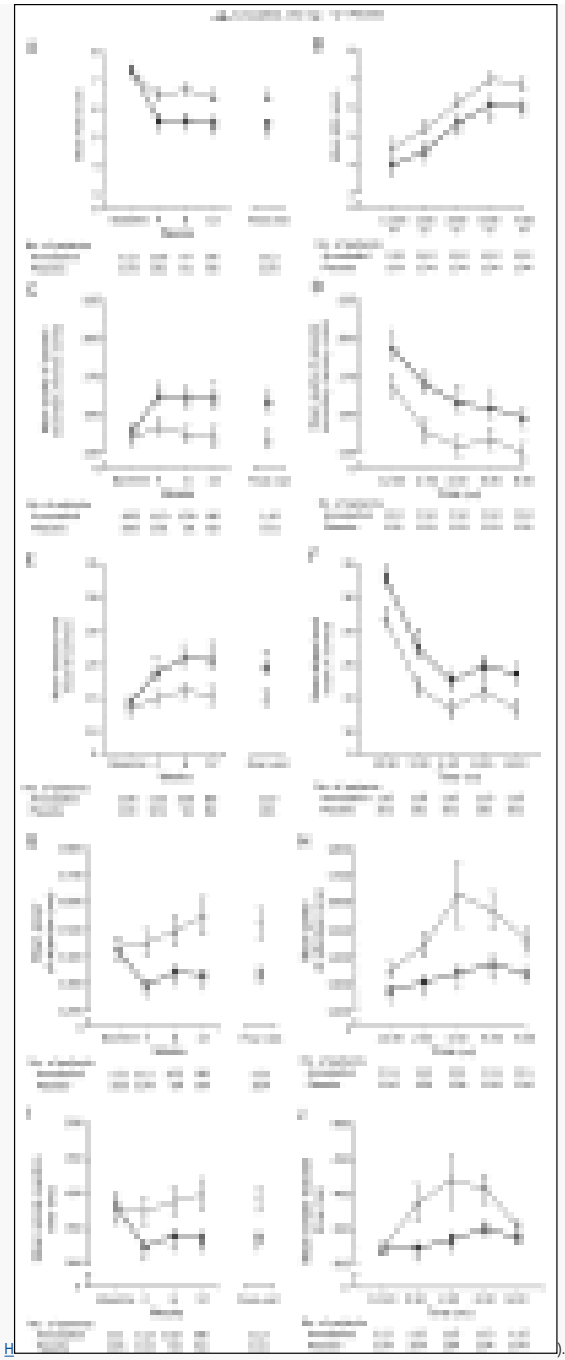
F).

The mean (SD) times for speed of memory were similar at baseline for armodafinil (2877.9 [666.5] milliseconds) and placebo (2914.0 [896.8] milliseconds). Armodafinil significantly improved speed of memory from baseline compared with placebo at week 8 (armodafinil, −240.9 milliseconds; placebo, −46.5 milliseconds; *P*=.02) and week 12 (armodafinil, −307.7 milliseconds; placebo, −115.2 milliseconds; *P*=.01), with a change at the final visit (armodafinil, −257.2 milliseconds; placebo, −140.4 milliseconds) that was not statistically significant (*P*=.09).

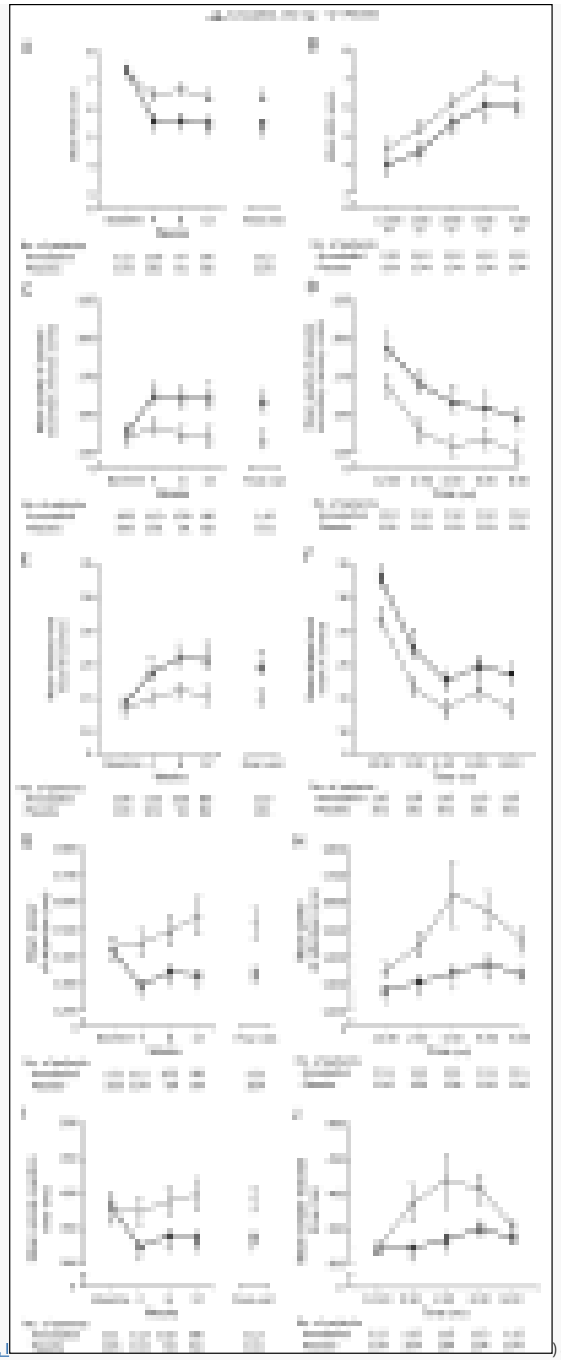
Attention Assessments. Armodafinil significantly improved mean power of attention from baseline at each study visit (*P*=.005 at week 4; *P*=.006 at week 8; *P*=.005 at week 12; *P*=.001 at final visit; Figure 3,



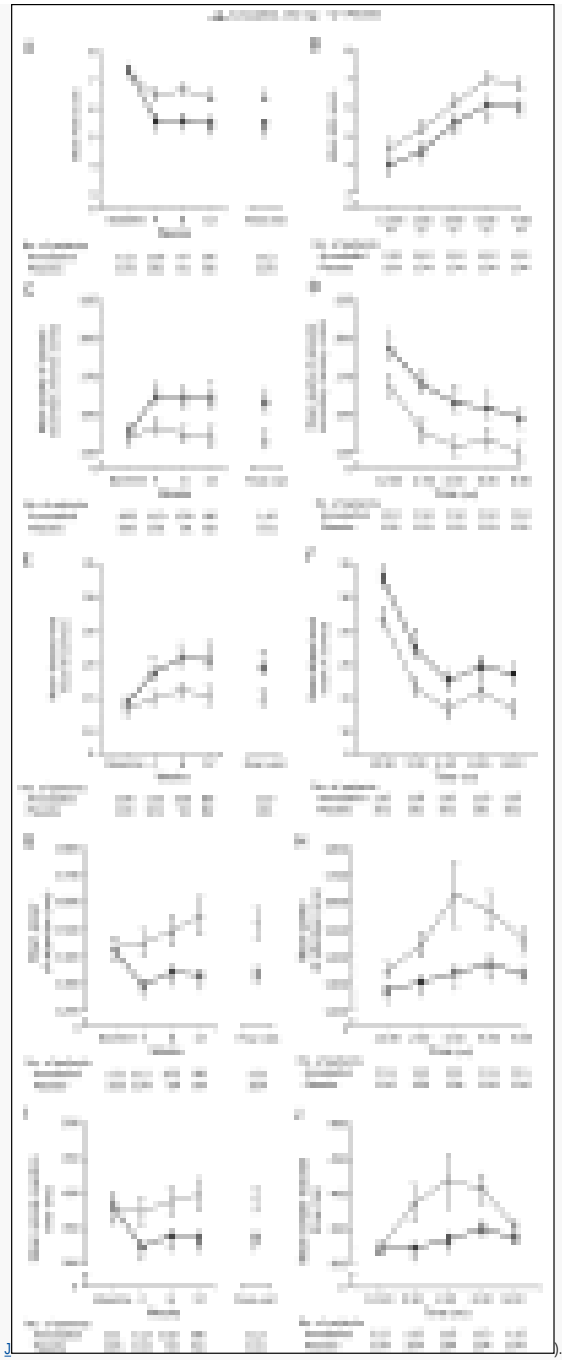
G) and during the first 4 tests on the final night shift compared with placebo (*P*=.002 at 12:30 am; *P*=.006 at 2:30 am; *P*=.004 at 4:30 am; *P*=.03 at 6:30 am; Figure 3,



H). Within this factor score, armodafinil significantly improved simple reaction time compared with placebo at all visits (*P*=.02 at week 4; *P*=.04 at week 8; *P*=.045 at week 12; *P*=.01 at



final visit; Figure 3, I) and during the second and third tests on the final night shift (*P*=.02 at 2:30 am; *P*=.03 at 4:30 am) (Figure 3.



J).

Continuity of attention improved at the final visit in patients who received armodafinil (increase in mean [SD] score, 2.9 [5.5] units) compared with those who received placebo (increase in mean [SD] score, 0.2 [5.7] units) (difference between groups in change from baseline, *P*<.001). The difference in change between the groups was significant at weeks 8 (*P*=.03) and 12 (*P*=.002).

Tolerability

The adverse events reported by 5% or more of patients who received armodafinil and reported more frequently than by patients who received placebo were headache (15/123 [12%] in the armodafinil group and 12/122 [10%] in the placebo group), nausea (9/123 [7%] in the

armodafinil group and 4/122 [3%] in the placebo group), nasopharyngitis (7/123 [6%] in the armodafinil group and 4/122 [3%] in the placebo group), and anxiety (6/123 [5%] in the armodafinil group and 2/122 [2%] in the placebo group). Most adverse events were considered mild or moderate by the investigator. Severe adverse events, as determined by the site investigator, occurred more frequently in patients who took armodafinil (n=12) than in those who took placebo (n=3), with diarrhea (n=2) and low back pain (n=2) being the most common events in this category in the armodafinil group. Two serious adverse events were reported, 1 for the armodafinil group (suicidal ideation in a patient with a history of depression), which was considered by the investigator to be possibly related to the study medication, and 1 for the placebo group (viral meningitis), which was considered by the site investigator not to be related to study medication. No single adverse event led to withdrawal of more than 1 patient.

Changes from baseline to the final visit in mean laboratory parameters, mean vital signs, physical examination findings, and concomitant medication use were comparable for both groups, except for small increases in mean γ-glutamyltransferase values (mean [SD] change: armodafinil, 5.6 [30.8] U/L; placebo, 0.9 [7.5] U/L; *P*=.10) and a decrease in mean uric acid values (mean [SD] change: armodafinil, −4.38 [9.02] mg/L; placebo, −2.28 [10.33] mg/L; *P*=.10). The mean changes in laboratory parameters were not considered clinically meaningful, and the mean values remained within the reference ranges. Shifts in serum chemistry laboratory values from the reference range at baseline to values outside the reference range for at least 1 time point during the study occurred at comparable frequency in the armodafinil and placebo groups; none were considered clinically meaningful by the site investigators. For serum hematology laboratory values, slightly more shifts in lymphocyte and platelet values above the reference range were reported among patients who took armodafinil than among patients who received placebo, and there were slightly more shifts in neutrophil values below the reference range among patients who took armodafinil than among patients who received placebo. None of these changes were considered clinically meaningful by the site investigators.

Differences in vital sign parameters were not statistically significant for measurements taken approximately 3 hours after dosing, approximately 11 hours after dosing (Table 3), or at 6:15 pm after the daytime polysomnogram at the final visit.

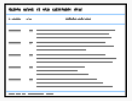


TABLE 3.

Vital Sign Measurements for Patients Diagnosed as Having Shift Work Disorder Who Received Armodafinil, 150 mg, or Placebo[a]

Armodafinil did not adversely affect daytime sleep variables (eg, sleep latency, sleep duration, and sleep-stage distribution) compared with placebo (Table 4). These findings were consistent with results from patient diaries.

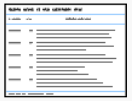


TABLE 4.

Daytime Polysomnographic Characteristics at Baseline and the Final Visit in Patients Diagnosed as Having Shift Work Disorder Who Received Armodafinil, 150 mg, or Placebo[a]

DISCUSSION

Treatment with armodafinil, 150 mg, significantly reduced sleep propensity and subjective ratings of sleepiness and improved aspects of attention and memory in patients with SWD during usual night shift hours. These differences were associated with significantly greater improvement in the severity of patients' overall clinical condition compared with those who received placebo. Armodafinil increased nighttime mean sleep latency to greater than 5 minutes, although a proportion of individuals remained sleepy; patients who fall asleep in 5 minutes or less are often considered severely sleepy.[26] This improvement was demonstrated at the first laboratory night shift and was sustained throughout the 12-week study. The findings confirm our hypothesis that armodafinil would significantly increase mean sleep latency and improve the overall clinical condition in patients with excessive sleepiness associated with SWD.

In a previous study in a similar population, modafinil, 200 mg, significantly improved overall mean nighttime sleep latency as measured by the MSLT by a mean of 1.7 minutes, with statistically significant increases in sleep latency vs placebo at the 2 and 4 am MSLT naps.[16] In the current study, armodafinil, 150 mg, significantly improved the overall mean nighttime sleep latency as measured by the MSLT by a mean of 3.1 minutes at the final visit, with statistically significant increases in sleep latency at all 5 MSLT sessions from midnight to 8 am. A direct comparison study is necessary to compare the efficacy and safety of these agents.

The MSLT has also been used to assess sleepiness in other disorders for which excessive sleepiness is a cardinal symptom—narcolepsy and obstructive sleep apnea (OSA). The improvement in the mean sleep latency for patients with narcolepsy who received modafinil, 200 mg/d, for 9 weeks in a placebo-controlled clinical study was approximately 1.8 minutes vs baseline.[27] A meta-analysis revealed that the summary estimate of improvement in mean sleep latency for patients with OSA who were successfully treated with nasal continuous positive airway pressure (nCPAP) was 0.74 minutes.[28] Both modafinil and nCPAP are recognized as standard treatments for individuals with excessive sleepiness associated with narcolepsy[29] or OSA,[30] respectively, and the effects of these interventions on mean sleep latency have been shown to be associated with significantly improved health-related quality of life.[31,32] Moreover, nCPAP treatment significantly reduces the elevated risk of motor vehicle crashes in patients with nontreated OSA.[33,34] These findings suggest that an improvement in objective sleep latency comparable with that shown in the current study is sufficient to ameliorate the burden of illness and may be considered clinically relevant; our conclusion is similar to that reached in the meta-analysis mentioned herein, which showed a less than 1-minute mean improvement in objective sleep latency from nCPAP therapy in patients with OSA.[28] Considering the nonlinear relationship between MSLT scores and sleepiness, a given numerical improvement in mean sleep latency at the low end of the scale is more clinically relevant than the same numerical improvement at the high end of the scale.[35] The proportion of patients in the placebo group who were rated by the investigator as at least minimally improved on the CGI-C, the other coprimary outcome measure, was higher than what was anticipated and observed in a previous study[16] of modafinil in patients with excessive sleepiness associated with SWD, for reasons that are not understood.

Excessive sleepiness impairs performance on various tasks, including those involving psychomotor performance or cognitive functions such as attention and memory.[36-41] In the current study, attention was comprehensively enhanced as assessed by the CDR system with administration of armodafinil: the ability to both focus and sustain attention was improved compared with placebo, as shown by improvements in both speed and accuracy measures from an attention task (simple reaction time). Furthermore, armodafinil significantly improved long-term memory (quality of episodic secondary memory) and speed of memory compared with placebo, with significant improvements in the accuracy of delayed word recall. This improvement in accuracy was accompanied by an improvement in speed.

In the armodafinil group, reductions in patients' subjective ratings of sleepiness throughout the laboratory night shift were consistent with their ratings during actual work shifts and during the commute home. Furthermore, treatment with armodafinil was associated with significant reductions in reports of intended and unintended sleep episodes and mistakes, near misses, or accidents during the night shift. A similar magnitude of improvement was demonstrated for the commute home, although this effect was not statistically significant compared with placebo. Long-term, prospective studies of the impact of armodafinil on work performance and safety in patients with SWD are necessary to confirm the effects observed in the current 3-month trial.

Before treatment, our patients with SWD were severely sleepy, as shown by mean nocturnal sleep latencies of approximately 2 minutes, which are comparable to the latencies observed in patients with narcolepsy during the daytime.[27] Patients with reports of excessive sleepiness associated with SWD are at substantially greater risk of impaired physical and mental well-being and performance.[4] These risks constitute a public health concern. Untreated OSA and narcolepsy and working more than 24 consecutive hours[42] can increase the risk of motor vehicle crashes.[43,44] Patients diagnosed as having OSA are at a 2- to 7-fold greater risk of motor vehicle crashes,[33] a risk that can be mitigated with appropriate treatment.[33,34,45,46] Data from the health care field, which represented the largest segment of patients in the current study and

is the largest and fastest growing industry in the United States, show that extended work shifts lasting more than 24 consecutive hours are also associated with increased risk of attentional failures, degraded performance, and increased risk of occupational accidents and serious fatigue-related medical errors and adverse events, resulting in patient injury and even death.[42,47,50] Although the shift durations in these studies differ from those in the current study, SWD can increase the risk of attentional failures and degrade employee performance. To mitigate these risks, health care employers should implement fatigue management programs that include screening programs for the diagnosis and treatment of employees with SWD and other disorders of sleep and wakefulness.

Armodafinil was well tolerated and did not adversely affect scheduled daytime sleep. No clinically important effects on laboratory values, vital signs, polysomnograms, or electrocardiograms were seen. The current study did not find a statistically significant difference for armodafinil vs placebo in mean vital signs; increases in heart rate and blood pressure have been reported in other randomized, double-blind studies of the medication, although not consistently.[51,52]

Our study has several considerations that may limit the interpretation of data. Most patients enrolled were permanent night shift workers. This may limit the generalizability of these results to individuals working alternative shift schedules. This study was performed in SWD patients with both excessive sleepiness and insomnia, who may represent a more severely affected group; therefore, additional studies may be necessary to quantify the effects in a patient population with less severe SWD. The study did not include patients with SWD associated with starting work in the early morning. Although the prevalence of SWD is unknown in this population, approximately 3 times as many individuals work shifts that start in the early morning than night shifts. Further studies are necessary to determine whether these results are generalizable to those who start work in the early morning.

Although the effects of armodafinil were statistically significant and clinically relevant, a proportion of patients remained sleepy on objective assessment at the end of treatment. This finding suggests that armodafinil, 150 mg, is not equally effective in all patients and highlights the importance of ensuring that use of pharmacotherapy to enhance wakefulness is part of a comprehensive program that includes diagnostic screening for sleep disorders, education, and behavioral treatment interventions designed to optimize sleep and wakefulness. Recommended for industries such as the health care field, a comprehensive approach for SWD should address sleep and wake hygiene, strategic napping, appropriate time off between work periods, diet, exercise, appropriately timed light exposure to facilitate circadian adaptation, and work hour limits. Diagnosis and treatment of comorbid sleep disorders, such as OSA, narcolepsy, and restless legs syndrome, are important components of any comprehensive program for SWD.

CONCLUSION

Armodafinil, 150 mg, significantly improved measures of sleep propensity, subjective sleepiness, memory, and attention during scheduled night work hours in patients with excessive sleepiness associated with SWD without disturbing daytime sleep. The effects on wakefulness were apparent during the night shift and the commute home. Concurrent improvements in overall clinical condition were also found. Armodafinil was generally well tolerated. These findings support the inclusion of armodafinil as part of a comprehensive treatment program for excessive sleepiness associated with SWD.

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Footnotes

Cephalon Inc funded the study and developed the protocol in collaboration with the authors. For more information on the role of the funding source, see page 971, and for the financial disclosures of the authors, see page 969.

Participating Investigators

Investigators who participated in this study are as follows: Richard Bogan, MD, Columbia, SC; Gerald Burns, MD, Metairie, LA; Martin Cohn, MD, Naples, FL; James Cook, MD, Danville, IN; Bruce Corser, MD, Cincinnati, OH; Richard Marcus, MD, Hickory, NC; Karl Doghramji, MD, Philadelphia, PA; Cynthia Dorsey, PhD, Belmont, MA; Helene Emsellem, MD, Chevy Chase, MD; Milton Erman, MD, San Diego, CA; James Ferguson, MD, Salt Lake City, UT; Jonathan Flescher, MD, Raleigh, NC; Yury Furman, MD, Los Angeles, CA; Paul Haberman, MD, Santa Monica, CA; Barbara Harris, PhD, Scottsdale, AZ; Dennis Hill, MD, Salisbury, NC; Max Hirshkowitz, PhD, Houston, TX; John Hudson, MD, Austin, TX; Steven Hull, MD, Overland Park, KS; David Laman, MD, Pittsburgh, PA; D. Alan Lankford, PhD, Atlanta, GA; Jed Black, MD, Stanford, CA; Michael Neeb, PhD, Toledo, OH; Vernon Pegram, PhD, Birmingham, AL; Richard Pellegrino, MD, Hot Springs, AK; John Pinto, MD, Las Vegas, NV; Russell Rosenberg, PhD, Atlanta, GA; Murray Rosenthal, DO, San Diego, CA; Markus Schmidt, MD, Dublin, OH; J. Baldwin Smith III, MD, Winston-Salem, NC; James Ware, PhD, Norfolk, VA; Kenneth Wright, PhD, Boulder, CO; James Wyatt, PhD, Chicago, IL; Gary Zammit, PhD, New York, NY; Henry Lahmeyer, MD, Northfield, IL; Siriwan Kriengkairut, MD, Bismarck, ND; William Leeds, DO, Topeka, KS; Francisco Candal, MD, Slidell, LA; Derek Loewy, MD, Tucson, AZ; Michael Alexander, MD, Niagara Falls, Ontario, Canada; Leonid Kayumov, PhD, Scarborough, Ontario, Canada; Mortimer Mamelak, MD, Toronto, Ontario, Canada; Adam Moscovitch, MD, Calgary, Alberta, Canada; Colin Shapiro, MD, Toronto, Ontario, Canada; Nick Antic, MD, Daw Park, Adelaide, South Australia, Australia.

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Dr Czeisler has received consulting fees from or served as a paid member of scientific advisory boards for Actelion Ltd, Avera Pharmaceuticals Inc, Cephalon Inc, Delta Airlines, Eli Lilly and Co, Fedex Kinko's, Federal Motor Carrier Safety Administration, US Department of Transportation, Fusion Medical Education LLC, Garda Siochana Inspectorate (Dublin, Ireland), Global Ground Support, Hypnion Inc (acquired by Eli Lilly and Co in April 2007), Johnson & Johnson, Koninklijke Philips Electronics NV, Morgan Stanley, Sanofi-Aventis Groupe, Portland Trailblazers, Respironics Inc, Sepracor Inc, Sleep Multimedia Inc, Sleep Research Society, Somnus Therapeutics Inc, Takeda Pharmaceuticals, Vanda Pharmaceuticals Inc, Vital Issues in Medicine, Warburg-Pincus and Zeo; owns an equity interest in Lifetrac Inc, Somnus Therapeutics Inc, Vanda Pharmaceuticals Inc, and Zeo Inc and receives royalties from McGraw Hill and Penguin Press; has received lecture fees from the Accreditation Council of Graduate Medical Education; Alfresa; American Academy of Allergy, Asthma and Immunology Program Directors; American Physiological Society; Association of University Anesthesiologists; Baylor College of Medicine; Beth-Israel Deaconess Medical Center; Brown Medical School/Rhode Island Hospital; Cephalon Inc; Clinical Excellence Commission (Australia); Dalhousie University; Duke University Medical Center; Harvard University; Institute of Sleep Health Promotion (NPO); London Deanery; Morehouse School of Medicine; Mount Sinai School of Medicine; National Emergency Training Center; National Institutes of Health; North East Sleep Society; Osaka University School of Medicine; Partners HealthCare Inc; Sanofi-Aventis Inc; St. Lukes Roosevelt Hospital; Takeda; Tanabe Seiyaku Co Ltd; Tokyo Electric Power Company; University of Michigan; University of Pennsylvania; University of Pittsburgh; University of Tsukuba; University of Virginia Medical School; University of Wisconsin Medical School; World Federation of Sleep Research and Sleep Medicine Societies; and has received research prizes with monetary awards from the American Academy of Sleep Medicine; American Clinical and Climatological Association; Association for Patient-Oriented Research; Sleep Research Society; National Institute for Occupational Safety and Health and National Sleep Foundation; clinical trial research contracts from Cephalon Inc, Merck & Co Inc, and Pfizer Inc; and an investigator-initiated research grant from Cephalon Inc. Dr Czeisler is the incumbent of an endowed professorship provided to Harvard University by Cephalon Inc and holds a number of process patents in the field of sleep/circadian rhythms (eg, photic resetting of the human circadian pacemaker). Since 1985, Dr Czeisler has served as an expert witness on various legal cases related to sleep and/or circadian rhythms.

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Dr Wesnes is the sole shareholder of Cognitive Drug Research Ltd, which was contracted by Cephalon to provide the cognitive testing system used in this study. Cognitive Drug Research Ltd conducts research for the worldwide pharmaceutical industry and in the last 7 years has worked for the world's largest 17 pharmaceutical companies and numerous other companies. Since 2001 (3 years before the start of this study), Dr Wesnes had been a paid consultant to Eisai, Pharmaton SA, Cephalon, Merck & Co Inc, Novartis, and Roche. He owns no shares or stocks in any pharmaceutical company or other company that may result in any conflict of interest.

Role of the Funding Source

All involved parties were responsible for conducting the study in compliance with the Good Clinical Practice Consolidated Guidance. Cephalon Inc funded the study and developed the protocol in collaboration with the authors. The sponsor was responsible for conduct of the study, including but not limited to selection of qualified investigators, quality control, independent

review board approval, protection of human subjects and informed consent, data collection and management, adverse event reporting, and regulatory reporting. A qualified statistician (S.A.) employed by the study sponsor conducted the statistical analysis of the data. The data analysis presented in this article was also replicated independently by an academic clinical research group (Chalmers Research Group, CHEO RI, Ottawa, Ontario, Canada). Operational management of the study was performed by Covance Inc (Princeton, NJ) and Clinical Trial Services (Audubon, PA) under the direction of the sponsor, and all responsibility for the quality and integrity of the trial data resided with the sponsor. All authors had a lead role in designing the study, developing the protocol, interpreting the data, and writing the manuscript. Authors attended investigator meetings and trained individual site investigators. Lead investigators at each study site were responsible for obtaining informed consent, adherence to the protocol, patient safety, and data collection. All authors had full access to the data and contributed to data interpretation and preparation of this report. The corresponding author had final responsibility for the decision to submit for publication.

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The Epidemiology and Diagnosis of Insomnia

Karl Doghramji, MD

Abstract

Many questions remain unanswered with regard to our understanding of insomnia. Although it is generally believed that 10% to 15% of the adult population suffers from chronic insomnia, and an additional 25% to 35% have transient or occasional insomnia, prevalence estimates vary because of inconsistent definitions and diagnostic criteria. The elderly in particular are affected by insomnia, and it has been shown that women are more likely to have sleep difficulties than men. Although insomnia can be a primary condition, and can coexist with other disorders or be considered secondary to these disorders, the mechanisms producing it are not clearly defined. Additionally, the relationship between insomnia and other disease states is not always clear because it is often not possible to determine the cause-and-effect relationship between disorders. Epidemiologic studies show that abnormal sleep patterns predict lower life expectancy, and that people with insomnia are more likely to develop affective disorders, substance abuse, and other adverse health outcomes. This article will provide an overview of insomnia, its prevalence and epidemiology, and guidelines for clinical assessment.

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Sleep accounts for one third of human life, yet scientific inquiry in this area is limited compared with other aspects of neuroscience.[1] Additionally, studies suggest that poor sleep contributes to ill health. Epidemiologic studies show that abnormal sleep patterns predict lower life expectancy,[2] and that insomnia frequently co-occurs with affective disorders, substance abuse, and other physical and psychological comorbidities.[3,4] However, research into the relationships between these findings is sorely lacking.

The definition of insomnia is a complaint of disturbed sleep, manifested as difficulties in sleep initiation or sleep maintenance, and/or as early awakenings. Many sources also add the presence of associated daytime impairments, such as fatigue, irritability, decreased memory and concentration, and pervasive malaise affecting many aspects of daytime functioning.[5] Although all definitions of insomnia rely on its symptomatic presentation, a standard diagnostic definition does not exist. Three separate texts present diagnostic criteria for insomnia: *The Diagnostic and Statistical Manual of Mental Disorders (DSM)*[6]; *The International Classification of Sleep Disorders*[7]; and *The ICD-10 Classification of Mental and Behavioural Disorders*.[8] Some definitions are based solely on reports of nocturnal sleep disturbances,[9] whereas others include features such as associated daytime impairment (eg, fatigue, irritability, or reduced memory or concentration),[10] self-reported sleep dissatisfaction,[11] or other criteria.[6,12-15]

Attempts have been made to subtype insomnia. One method is based on duration of symptoms, identifying insomnia as either chronic (long-term) or acute (transient). A 2005 National Institutes of Health (NIH) State-of-the-Science statement pointed out that time periods of various durations have been used to define chronic insomnia, ranging from 30 days to 6 months.[5] The transient/chronic distinction can be clinically relevant, inasmuch as transient insomnias often result from specific environmental or social events, such as shift work, death of a loved one, air travel, and noise, and may be more appropriately managed by addressing these stressors and by managing the insom-

Corresponding author: Karl Doghramji, MD, Director, Sleep Disorders Center, Thomas Jefferson University, 1015 Walnut Street, Suite 319, Philadelphia, PA 19107. E-mail: karl.doghramji@jefferson.edu.

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nia directly (and often prophylactically). On the other hand, chronic insomnia may be more often related to intrinsic sleep disorders, primary insomnia, or chronic medical and psychiatric conditions, and may require a more extensive evaluation (including assessment of comorbid conditions) in order to delineate appropriate treatment. However, it should be stressed that the relationships between insomnia duration, etiology, and evaluation implications have not been well investigated.

Insomnia can also be classified on the basis of etiology into primary and secondary subtypes. The term *primary* indicates that the insomnia is not caused by any known physical or mental condition but is characterized by a consistent set of symptoms, a defined disease course, and a general responsiveness to treatment.[16,17] Although the etiology of primary insomnia has yet to be clarified, recent research implicates endocrine, neurologic, and behavioral factors as contributing to its pathogenesis.[18-20] It is estimated that among patients diagnosed with insomnia, 25% to 30% suffer from primary insomnia.[6,21] *Secondary* insomnia, in contrast, has been defined historically as insomnia resulting from other medical and psychiatric illnesses, medication use, or other primary sleep disorders.[5,22] The 2005 NIH State-of-the-Science statement, however, has suggested the use of the term *comorbid insomnia*, instead of *secondary insomnia*, based on a limited level of understanding of the causal relationships which may exist between insomnia and coexisting disorders. Conceivably, primary insomnia could coexist as an independent entity in the context of another disorder, as opposed to being caused by it.[5]

Epidemiology and Natural History of Insomnia

Estimates of the prevalence of insomnia are variable because definitions and diagnostic criteria for insomnia are inconsistent. In addition, the use of baseline and follow-up assessments to establish incidence and remission rates can be problematic because of the wide spectrum of insomnia duration (eg, a positive finding of insomnia at baseline and 1-year follow-up may reflect unremitting chronic insomnia or 2 episodes of transient insomnia).[23] Given these limitations, it is generally believed that 10% to 15% of adults suffer from chronic insomnia,[24] usually regarded as a persistent insomnia lasting more than 1 month, and an additional one third have transient or occasional insomnia.[25]

The elderly in particular are affected, with an estimated prevalence ranging from 13% to 47%.[22,26-31] The National Institute on Aging's Established Populations for Epidemiologic Studies of the Elderly (EPESE) 3-year longitudinal study showed that 42% of community-dwelling seniors who participated in the survey had difficulty falling and staying asleep.[26,32] Sleep difficulties were more prevalent among seniors with physical disability, depressed mood, respiratory symptoms, or fair-to-poor perceived health and among those using anxiolytic and barbiturate prescription medication. At the 3-year follow-up of EPESE, Foley et al estimated incidence and remission rates for insomnia in more than 6000 participants of the original survey.[32] Among 4956 participants who had no symptoms of insomnia at baseline, nearly 15% reported symptoms at the 3-year follow-up, suggesting an annual incidence of 5%.

In the same study, for about 15% of participants, insomnia symptoms resolved each year. Extrapolating these findings to the general population, the authors estimated that 8 million elderly persons nationwide have insomnia on any given day, more than 1 million new cases of insomnia develop each year, and symptoms resolve in nearly 1.3 million elderly persons annually.[32] Disturbed sleep is also associated with impairments in memory and attention, and can be misinterpreted as signs of dementia in the elderly.[33]

Although most epidemiologic studies indicate that women are more likely to have sleep difficulties than men,[27,34] the EPESE study reported comparable rates in both sexes. The exception to this parity occurred in patients 85 years or older, in which the prevalence was higher among men.[32] The EPESE study also showed that women were less likely to achieve remission (46% of women vs 52% of men), suggesting the high-

er prevalence in women reported in other epidemiologic studies may indicate fewer remissions in women, not more new cases.[32] This hypothesis was supported by findings from the Cardiovascular Health Study of 2005, which reported that women with insomnia were less likely than men to remit.[35]

In addition to the EPESE study of elderly patients, several other longitudinal studies have helped clarify the natural history of chronic insomnia. Breslau et al conducted a baseline assessment and 3.5-year follow-up of 1200 young adults (aged 21-30 years) drawn randomly from a health maintenance organization database. The lifetime prevalence of insomnia in this population was 24.6% and was slightly higher in women than men (26.7% and 21.4%, respectively). The 3.5-year incidence of new insomnia among subjects with no insomnia at baseline was 14.8% for women and 10.6% for men; slightly less than the incidence rates reported in the EPESE study.[36]

In a study of 521 healthy middle-aged women near menopause presenting at a clinic, Owens and Matthews found a very high prevalence (42%) of self-reported sleep difficulties. Among those reporting sleep problems, the most prevalent complaint was awakening during the night (reported by 92%), followed by earlier-than-desired awakening (59%) and trouble falling asleep (49%). A cross-sectional analysis failed to identify significant associations between pre-, peri-, or postmenopausal status and general or specific sleep complaints. However, among the subset of women who were premenopausal at baseline and postmenopausal and not using hormone replacement therapy at follow-up, a higher proportion reported sleep difficulties at the postmenopausal than at the premenopausal assessment.[37]

Hohagen et al conducted a study of 2512 patients aged 18 to 65 years presenting to primary care clinics in Germany; a baseline assessment identified 18.7% with severe insomnia (*DSM-III-R* criteria), 12.2% with moderate insomnia (*DSM-III-R* criteria, without impairment of daytime functioning), and 15% with mild insomnia (occasional difficulties in initiating and maintaining sleep). Follow-up assessments were conducted in patients reporting baseline insomnia at 4 months and 2 years. At baseline, mild insomnia was more prevalent among men, but severe insomnia was more common among women by a nearly 2:1 margin (65% vs 35%). More than two thirds of patients with severe insomnia at baseline reported a disease duration of 1 year or more.[38]

At the 4-month follow-up, 75% of those reporting severe insomnia at baseline still reported severe or moderate insomnia, with the remainder reporting either mild symptoms or no symptoms. At 2 years, the persistence of severe or moderate insomnia was 52% among those with severe insomnia at baseline; 42% of these patients reported severe insomnia at all 3 visits.[38] Importantly, despite the overall persistence of sleep complaints among those with severe insomnia, a follow-up study revealed that the symptomatic presentation shifted significantly over time. For example, only half of those reporting exclusively sleep-onset difficulties at baseline did so at 4 months, and the persistency of sleep maintenance and early-awakening complaints was even lower. This symptomatic lability calls into doubt the utility of insomnia classifications based on time of night affected, at least among patients with severe insomnia.[39]

Clinical Correlates of Insomnia

The longitudinal studies described above have also provided insight into the clinical conditions commonly associated with insomnia. Among young adults, prevalent insomnia was associated most strongly with major depressive disorder (MDD), with an odds ratio (OR) for the presence of MDD of 16.6 among subjects with insomnia compared with those without insomnia; the OR was even higher (41.8) among subjects reporting both insomnia and hypersomnia. A number of other psychiatric conditions, including anxiety disorders (ORs, 2.4-7.0), substance abuse disorders (OR, ~2 for both alcohol and illicit substances), and nicotine dependence (OR, 2.8), were also highly correlated with insomnia.[36]

With regard to temporal patterns, a previous history of insomnia at baseline was strongly associated with the incidence of new psychiatric disorders, including MDD, anxiety disorders, substance abuse disorder,

and nicotine dependence. The association with subsequent MDD was attenuated when the presence of other depressive symptoms at baseline was taken into account.[36] However, a potential causative role for insomnia in the development of MDD has been postulated by several researchers.[40,41] Whether insomnia is a precursor to MDD, an early clinical hallmark of MDD, or the result of etiological factors common to MDD remains to be clarified.

Hohagen et al reported that severe and moderate insomnia, but not mild insomnia, were associated with (unspecified) chronic somatic disorders. In addition, when asked to rate their overall health status, patients with severe insomnia rated their health as "moderate" (60%) or "bad" (25%) far more frequently than those with no insomnia (41% and 4%, respectively).[38]

The same study also showed a strong correlation between insomnia severity and psychiatric comorbidities. Among those with severe insomnia, the prevalence of any psychiatric disorder was 37.4% and the prevalence of depression was 21.7%, compared with prevalence rates of 9.9% and 3.7%, respectively, for those reporting no sleep problems.[38]

In addition to the strong correlations between insomnia and psychiatric comorbidities, the prevalence of insomnia is increased relative to healthy controls in the context of several chronic medical conditions, including osteoarthritis[42]; rheumatoid arthritis[43]; coronary artery disease[44,45]; end-stage renal disease[46]; type 1 and type 2 diabetes mellitus[47,48]; and neurologic disorders, such as restless legs syndrome,[49] Parkinson's disease,[50] and Alzheimer's disease.[51] These associations and others are addressed in detail in the following article by Dr Ancoli-Israel ("The Impact and Prevalence of Chronic Insomnia and Other Sleep Disturbances Associated With Chronic Illness").

Clinical Assessment

Although more studies are necessary, evidence indicates that (1) insomnia may coexist with both psychological conditions and physical illness, and (2) left untreated, it may become a long-term, chronic condition, particularly in women. Early intervention and management, therefore, could be beneficial. However, the proportion of insomnia patients who report insomnia to their physicians is quite small, and physicians may not adequately assess it.[36,52] Both patients and physicians may not recognize the impact of poor sleep on daily functioning and the risk of serious accidents and psychological sequelae.[5] Practice guidelines developed by the Standards of Practice Committee of the American Academy of Sleep Medicine strongly recommend routine clinical screening for symptoms of insomnia during health examinations so that treatment can be integrated into the patient's overall care.[53]

As with every illness, the cornerstone of assessment for insomnia begins with a comprehensive history and screening for comorbidities, such as depressive and anxiety disorders, respiratory problems, and substance use, among others.[54] An in-depth sleep history is essential in identifying the cause of insomnia[5] and should include results of previous treatments.[54] Many of the tools that are useful in the assessment of insomnia are subjective questionnaires. Others include sleep logs, symptom checklists, psychological screening tests, and bed partner interviews.[5] The Pittsburgh Sleep Quality Index is a sleep questionnaire that may provide useful information about sleep quality, timing, and duration.[55] The Insomnia Severity Index (**Figure**) is a reliable and valid instrument to quantify perceived insomnia severity, including next-day consequences.[56] Nocturnal polysomnography and daytime multiple sleep latency testing are not recommended for the routine evaluation of insomnia unless other sleep disorders are suspected, such as sleep-related respiratory disturbances or periodic limb movement disorder.

Conclusion

Many questions remain unanswered in our understanding of insomnia. Future research must clarify existing evidence surrounding the exact nature of the relationship between insomnia and psychological and physiologic comorbidities. In the absence of comprehensive knowledge about the active intricacies of the "resting" brain,

Figure. Insomnia Severity Index[57]

Please answer each of the questions below by circling the number that best describes your sleep patterns ***in the past week.*** Please answer all questions.

Please rate the current (past week's) **SEVERITY** of your insomnia problem(s):	None	Mild	Moderate	Severe	Very Severe
Difficulty falling asleep	0	1	2	3	4
Difficulty staying asleep	0	1	2	3	4
Problem waking up too early	0	1	2	3	4

How **SATISFIED/DISSATISFIED** are you with your current sleep pattern?	Very Satisfied 0	Satisfied 1	Neutral 2	Dissatisfied 3	Very Dissatisfied 4

To what extent do you consider your sleep problem to **INTERFERE** with your daily functioning (eg, daytime fatigue, ability to function at work/daily chores, concentration, memory, mood, etc)?	Not at all Interfering 0	A Little 1	Somewhat 2	Much 3	Very Much Interfering 4

How **NOTICEABLE** to others do you think your sleeping problem is in terms of impairing the quality of your life?	Not at all Noticeable 0	A Little 1	Somewhat 2	Much 3	Very Much Noticeable 4

How **WORRIED/DISTRESSED** are you about your current sleep problem?	Not at all Worried 0	A Little 1	Somewhat 2	Much 3	Very Much Worried 4

Total: _____

what *is* known about the high prevalence and socioeconomic burden of insomnia should encourage increased awareness of the prevalence of sleep disturbances and promote effective treatment strategies.

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RAPID PUBLICATION

Shift Work Sleep Disorder: Prevalence and Consequences Beyond that of Symptomatic Day Workers

Christopher L. Drake, PhD[1,2]; Timothy Roehrs, PhD[1,2]; Gary Richardson, MD[1]; James K. Walsh, PhD[3]; Thomas Roth, PhD[1,2]

[1]Henry Ford Hospital Sleep Disorders and Research Center, Detroit, MI; [2]Department of Psychiatry and Behavioral Neurosciences, Wayne State College of Medicine, Detroit, MI; [3]St. Luke's Hospital and Department of Psychology, St. Louis University, St. Louis, MO

Study Objectives: Although there are considerable data demonstrating the impact of shift work on sleep and alertness, little research has examined the prevalence and consequences of shift work sleep disorder in comparison to the difficulties with insomnia and excessive sleepiness experienced by day workers. The present study was designed to determine the relative prevalence and negative consequences associated with shift work sleep disorder in a representative sample drawn from the working population of metropolitan Detroit.

Design: Random-digit dialing techniques were used to assess individuals regarding their current work schedules and a variety of sleep- and non–sleep-related outcomes.

Setting: Detroit tricounty population.

Participants: A total of 2,570 individuals aged 18 to 65 years from a representative community-based sample including 360 people working rotating shifts, 174 people working nights, and 2036 working days.

Measurements and Results: Using standardized techniques, individuals were assessed for the presence of insomnia and excessive sleepiness, based on DSM-IV and ICSD criteria. Those individuals with either insomnia or excessive sleepiness and who were currently working rotating or night schedules were classified as having shift work sleep disorder. Occupational, behavioral, and health-related outcomes were also measured. Individuals who met criteria for shift work sleep disorder had significantly higher rates of ulcers (odds ratio = 4.18, 95% confidence interval = 2.00-8.72), sleepiness-related accidents, absenteeism, depression, and missed family and social activities more frequently compared to those shift workers who did not meet criteria ($P < .05$). Importantly, in most cases, the morbidity associated with shift work sleep disorder was significantly greater than that experienced by day workers with identical symptoms.

Conclusion: These findings suggest that individuals with shift work sleep disorder are at risk for significant behavioral and health-related morbidity associated with their sleep-wake symptomatology. Further, it suggests that the prevalence of shift work sleep disorder is approximately 10% of the night and rotating shift work population.

Key Words: shift work sleep disorder, insomnia, excessive sleepiness, ulcers, heart disease, shift work, night work, rotating work.

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INTRODUCTION

ALTHOUGH MORE THAN 16% OF WAGE AND SALARY WORKERS ARE SHIFT WORKERS,[1] FEW DATA ARE AVAILABLE ADDRESSING THE PREVALENCE OF SHIFT WORK SLEEP DISORDER (SWSD) AND THE FUNCTIONAL IMPAIRMENT THAT IS UNIQUELY ASSOCIATED WITH ITS 2 PRIMARY SYMPTOMS, INSOMNIA AND EXCESSIVE SLEEPINESS.[2] In contrast, there have been a number of laboratory and field studies that have focused on the effects of shift-work schedules on sleep and alertness. Overall, these studies have shown that individuals engaged in shift work experience disturbed sleep and excessive sleepiness relative to day workers.[3-9] These symptoms are likely due to the fact that shift workers' behavioral sleep-wake schedules are out of phase and often in direct opposition to their endogenous circadian rhythms.[9-12]

The human circadian timing system is tightly entrained by exposure to environmental light.[13,14] Normally, environmental light maintains circadian entrainment to the 24-hour day. Late evening light will phase delay rhythms while morning light will advance them.[15,16] However, shifts in endogenous rhythms are difficult to maintain except under laboratory conditions where light exposure is restricted to atypical periods of the day and night.[17-20] Even in tightly controlled experiments using bright light to shift circadian rhythms, more than 30% of shift workers are unable to attain large phase shifts.[21,22] Difficulty limiting light exposure to appropriate times of day is a major reason why most shift workers, even those on permanent night shifts, do not fully

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Address correspondence to: Dr. Christopher Drake, Senior Scientist, Henry Ford Hospital Sleep Disorders and Research Center, CFP-3, 2799 West Grand Blvd, Detroit, Michigan, 48202; E-mail: cdrake1@hfhs.org

adapt to the shifted sleep-wake schedule required of their work shift.[23-27]

Despite presumed universal difficulty in adapting the endogenous circadian pacemaker to the irregular sleep-wake rhythm common in shift work, there are wide individual differences in sleep disturbance and excessive sleepiness among shift workers.[28-32] For instance, studies have found that some, but not all, rotating shift workers experience more sleep disturbance or sleepiness than do day workers.[33] Some of the variability in symptomatology is likely related to differences in the amount and/or quality of sleep obtained by individuals engaged in various types of shift work. For example, night workers report reduced total sleep time as compared to both evening workers and day workers.[34] Given recent data demonstrating consistent individual differences in the response to sleep deprivation,[35,36] it is also likely that there are differences in the way that an individual's sleep-wake system responds to the sleep disruption associated with shift work. There are individuals whose sleep is not substantively impaired by a rotating or night work schedule, while others may find it extraordinarily difficult to obtain adequate sleep while on schedules that require a partial or complete shift of the circadian sleep-wake cycle. Similarly, there may be individual differences in sleepiness-related impairment given a comparable level of sleep loss.[36]

Extreme difficulty maintaining adequate sleep-wake function while on a shift-work schedule is reflected in the current nosologic system as SWSD.[2] Currently, the minimal criteria for SWSD includes a primary symptom of either insomnia *or* excessive sleepiness that is temporally associated with a work period that occurs during the habitual sleep phase. Excessive sleepiness and insomnia are not unique to shift workers and are among the most commonly reported symptoms of patients with a variety of sleep disorders. In order to begin to distinguish the characteristics of SWSD and its associated consequences, research on SWSD would benefit from comparisons with day-work samples experiencing similar symptoms. Accurately making the distinction between shift workers with a sleep disorder independent of their shift-work status and those in whom shift work is the essential component of their sleep disturbance is important.[37] Clinicians are faced with making this distinction for all patients with potential SWSD, but such distinctions are difficult to make. Nonetheless, morbidity associated with the differential or unique presence of insomnia or excessive sleepiness in a shift-work sample relative to a day-work sample would help to elucidate the characteristics of this disorder.

While the diagnostic category of SWSD has been in place for more than a decade, there has been little systematic research into the characteristics of this disorder. An important step in characterizing SWSD is to determine its prevalence and consequences among people who work various types of shifts. The present study aims to determine the prevalence of SWSD in a sample of rotating and permanent night workers drawn from the general population. Furthermore, this study compares the frequency of specific morbidities in shift workers with SWSD and day workers reporting similar sleep-wake complaints. A critical question addressed in the present study is whether SWSD is associated with any unique morbidity beyond that associated with insomnia and excessive sleepiness in a day-work sample. If so, this would provide evidence that SWSD may convey a unique risk for specific negative consequences.

PROCEDURES

Participants

Subjects were drawn from the general population of tricounty metropolitan Detroit using random-digit dialing techniques. Participants completed a 20-minute telephone interview, which included questions related to work status, sleep habits, excessive sleepiness, insomnia, disability, and psychiatric history. Individuals participating in this study were drawn from the population as part of a larger ongoing epidemiologic study investigating the prevalence of excessive sleepiness. For eligibility, the calling address had to be a residence and the participant had to be an adult between the ages of 18 to 65 years. A random probability selection procedure was used to determine the sex of the target adult. If 2 or 3 adults within a target sex were present in a household, a random probability selection procedure (oldest/second, oldest/youngest) was used to determine the target respondent. If 4 or more adults of the target sex were present in the household, the last-birthday method was used to determine the target respondent. In order to maintain an unbiased sample, only individuals who could not answer the questions due to sensory or mental impairment were excluded from the sample. From 4,682 eligible participants, 3,283 interviews were obtained (response rate 70.1%). Subjects were asked to select the category that best described their current work schedule (past 2 weeks). Response choices included: "regular day shifts," "regular night shifts," "regular evening shifts," "rotating shifts," or "not working/retired." Individuals working regular night shifts and individuals working rotating shifts were selected and compared to the day workers from the sample. Individuals identifying themselves as being on regular evening shifts and those who did not work, were retired, or were unemployed were excluded. Evening workers were excluded because recent studies have shown that individuals on evening schedules get significantly more sleep than day workers.[34] The age and sex distribution of each study group and the total sample is shown in Table 1. Subjects were paid $25.00 for their participation. The protocol was approved by the institutional review board of Henry Ford Hospital.

Assessment

Total sleep time was determined by 2 interview questions. Individuals reported their average nightly weekday total sleep time and weekend total sleep time over the past 2 weeks. Similarly, time in bed was determined by asking individuals their bed time and wake time for both weekdays and weekends. Sleep efficiency was calculated as the total sleep time divided by the time in bed multiplied by 100. For weekly means of each variable, a weighted average of weekend and weekday reports was calculated ([5 × weekday total sleep time + 2 × weekend total sleep time] / 7). Weekend work days and weekday non-work days were not differentiated. Sleep-parameter data were not available for the first 121 individuals (< 5%) due to delayed inclusion of specific questions. Data from these individuals were excluded from analyses beyond demographic data (Table 1). The number of caffeinated beverages consumed per day as well as the percentage of obese snorers (body mass index ≥ 30 and reported loud snoring; proxy for possible sleep apnea) were also assessed in each group (Table 1).

Insomnia was assessed using criteria based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for insomnia.[38] Specifically, in order to meet insomnia criteria, individuals must have reported difficulty falling asleep, staying asleep, or nonrestorative sleep for at least 1 month. In addition, this sleep disturbance had to occur at least "sometimes" or "often" over their lifetime and had to meet a self-reported severity criteria of at least 6 out of a possible 10 (10 = most severe) over the past 3 months.

Sleepiness was measured using the Epworth Sleepiness Scale (ESS).[38] This scale has been validated in previous studies[39,40] and has been shown to discriminate between clinical samples of individuals with and without sleep disorders.[41] The ESS has also been shown to predict objectively measured excessive sleepiness in the general population.[42] In order to estimate prevalence rates of excessive sleepiness, a sample-based cutoff score was utilized. Previous studies have used a score of 10 or higher on the ESS to denote excessive sleepiness.[43] However, these studies have generally been performed using clinic samples. Thus, as the present study was done using a population-based sample, a score equal to the total sample mean plus 1 SD was used as the cutoff criteria for excessive sleepiness. To facilitate comparisons with clinical samples, we have also included the prevalence rates of excessive sleepiness using a cutoff of 10 or higher on the ESS.

SWSD Criteria

It is recognized that, in the clinical setting, individuals with SWSD receive a full diagnostic workup, often including an overnight polysomnogram. However, due to the large population-based sample identified, a similar diagnostic assessment was not feasible. Therefore, SWSD was defined based on minimum criteria for SWSD as outlined in the *International Classification of Sleep Disorders–Revised.*[2] Specifically, individuals were required to meet criteria for either excessive sleepiness or insomnia as defined above and had to be working the night shift or a rotating shift over the past 2 weeks. In addition to classifying each of the shift-work groups, we divided day workers into those who met sleepiness and insomnia criteria and those who did not.

Reports of specific medical problems were assessed with 2 questions. The first question asked participants to report if they currently had any form of heart disease. The second question asked participants to report if they currently had a stomach ulcer. These questions were selected due to the known association between shift work and heart disease and gastrointestinal problems.[44,45]

Morbidity related to daily functioning or quality of life was assessed using several questions. Participants were asked to report the total number of days of missed work over the past 3 months due to sleep problems; the total number of days of family or social activities missed over the past 3 months due to sleep problems; the total number of automotive accidents that they had been involved in as the driver over their lifetime; and the number of these accidents that were related to sleepiness. (Non–sleepiness-related accidents were also computed as the total number of accidents minus the number of sleepiness-related accidents.)

Depression was assessed during the phone interview using the Diagnostic Interview Schedule.[46] This measure has been validated in previous studies and corresponds closely to clinical assessments of major depression.[47] Scoring of the Diagnostic Interview Schedule was based on lifetime *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for major depression. A measure of mood/personality was assessed using the short form of the Eysenck Neuroticism Scale.[48]

Analyses

First, sleep-related variables (total sleep time, sleep efficiency, excessive sleepiness, etc.) were compared across each of the 3 work groups (day, night, and rotating) and follow-up posthoc comparisons were performed if a significant main effect of group was present. For continuous variables, 1-factor analysis of covariance (ANCOVA) was used to compare data between groups with age as the covariate. Posthoc comparisons were performed using the least significant difference procedure when significant main effects or interactions were present. χ^2 analyses were performed on categorical variables. The second set of analyses was performed to examine the impact of group and the presence of symptoms on the specific outcome variables. A 2-factor ANCOVA was performed with Work Group (day, night, and rotating) and Insomnia (presence or absence) as factors, and Sleepiness as the dependent measure. We hypothesized that shift workers who reported insomnia would report a greater degree of sleepiness compared to those who did not report insomnia. The presence of *either* symptom (sleepiness or insomnia) was then assessed and both shift-work groups were divided into those who met minimum criteria for SWSD (Symptoms) and those who did not (as outlined above). The χ^2 and ANCOVA were performed on

Table 1—Demographic Characteristics of Each Day/Night Worker Sample

Demographic Characteristics	Day Workers (n = 2036)	Permanent Night Workers (n = 174)	Rotating Workers (n = 360)	Total Sample (N = 2,570)	Tricounty Census Data (N = 4,043,467)
Men, %	52.7	54.6	46.1	51.9	48.5
Women, %	47.3	45.4	53.9	48.1	51.5
Age, years*	41.2 ± 11.6	38.8 ± 12.1	36.0 ± 12.3	40.3 ± 11.9	36.6‡
Caffeine, cups/day	2.7 ± 3.0	3.1 ± 3.2	2.7 ± 2.7	2.7 ± 3.0	-
Obese snorers, %	3.0	5.0	3.1	3.2	-

*Significant difference between groups ($P < .03$ for all) Data are presented as mean ± SD.
‡Age value was taken from total population mean age in 2000 census.
Obese snorers refers to the percentage of individuals with a body mass index ≥ 30 and "loud snoring"
Caffeine includes total cups per day of coffee and other caffeinated beverages.

morbidity measures to determine if shift workers who met SWSD criteria had significantly greater morbidity as compared to shift workers without SWSD. Following these analyses, the third group—day workers—were also divided with regard to symptoms of either insomnia or daytime sleepiness. Logistic regression and 2-factor ANCOVA were performed. These analyses included Work Group (day, night, or rotating) and Symptoms (present or absent) as separate factors. An interaction on these analyses would indicate that insomnia or excessive sleepiness produces differential morbidity in 1 or more of the groups. Finally, for variables where interactions were significant (differential morbidity), a follow-up ANCOVA was performed to determine which particular symptom or combination of symptoms was driving the morbidity identified.

RESULTS

Table 1 shows demographic data for the 3 work groups and corresponding 2000 census values where available. There were small, but statistically significant, age differences between groups. Night workers were significantly younger than the day workers and older than the rotating workers $F_{2,2550} = 32.2$, $P < .05$ for all). Age was used as a covariate in analyses in order to account for these differences. There were no significant differences in sex ($\chi^2 = 5.8$, $P > .05$), caffeine intake ($F_{2,2554} = 1.3$, $P > .05$), or the percentage of obese snorers between groups ($\chi^2 = 1.4$, $P > .05$).

Habitual sleep and related data for each group are shown in Table 2. Group differences were found for several sleep-related parameters, as detailed in the last column of Table 2. The most consistent differences were found between the night-worker and the day-worker samples with decreased total sleep time, decreased sleep efficiency, and an increased prevalence of insomnia and daytime sleepiness in night workers.

A work-group analysis of sleepiness in those experiencing insomnia and those who did not experience insomnia was undertaken. A significant main effect of Work Group was present ($F_{2,2429} = 3.2$, $P = .04$). Both night and rotating workers experienced significantly more sleepiness than day workers ($P < .01$). A main effect of Insomnia was also found ($F_{1,2429} = 37.8$, $P < .001$), as individuals with insomnia reported significantly more daytime sleepiness (10.4 ± 5.5) than those not reporting insomnia (7.8 ± 4.3). Thus, both the effects of insomnia as well as shift work were independent and additive in terms of excessive sleepiness. There was no Group × Insomnia interaction ($P = .46$).

Prevalence of SWSD

Using the minimum criteria for SWSD, 32.1% of night workers and 26.1% of rotating workers met the criteria (Table 2). However, 18% of day workers reported at least 1 symptom (insomnia or excessive sleepiness). When determining prevalence rates for SWSD, it is important to identify the differential prevalence of these symptoms in each shift-worker sample in comparison to the day-worker sample. This value will be more representative of the prevalence of such symptoms uniquely related to shift work. Thus, the "true prevalence" (ie, differential prevalence) of insomnia or excessive sleepiness in the night- and rotating-worker sample was 14.1% and 8.1%, respectively. The corresponding overall "true prevalence" of SWSD was 10.0% of shift workers between the ages of 18 and 65 (Table 2).

Outcome Variables

Within the 2 shift-work groups, those who met SWSD criteria and those who did not were compared on each measure of morbidity (Table 3). No interactions were present for any of the variables ($P > .05$ for all), indicating that experiencing significant morbidity related to SWSD did not depend on the type of shift work in which one engaged. Importantly, for nearly all variables assessed, SWSD was associated with significantly greater mor-

Table 2—Sleep-related Parameters Across Each Shift/Day Worker Sample

Sleep Parameter	Day Workers (n = 1950)	Night Workers (n = 162)	Rotating Workers (n = 337)	Total Sample all Workers (n = 2449)	Post-hoc comparisons
Total sleep time, h	6.8 ± 1.2	6.1 ± 1.5	6.7 ± 1.5	6.7 ± 1.3	N<D
Time in bed, h	7.4 ± 1.1	7.3 ± 2.1	7.6 ± 1.6	7.5 ± 1.3	-
Sleep efficiency, %	91.5 ± 14.4	88.2 ± 28.0	90.5 ± 19.0	91.2 ± 16.3	N<D
WE-WD difference, min	57.2 ± 85.6	60.9 ± 102.6	39.3 ± 102.0	55.0 ± 89.5	R<D
ESS score	8.0 ± 4.5	9.2 ± 5.2	8.6 ± 4.6	8.1 ± 4.5	N>D, R>D
ESS ≥ 10, %	32.7	44.8	35.8	34.0	N>D, N>R
ESS ≥ 13, %	15.5	24.7	20.3	16.8	N>D, R>D
Insomnia, %	8.6	18.5	15.7	10.2	N>D, R>D
Prevalence of insomnia or ES, %	18.0	32.1	26.1	20.1	N>D, R>D
"True Prevalence" of SWSD (%)	0	14.1	8.1	10.0	N>D, R>D

Data are presented as mean ± SD. Omnibus and posthoc comparisons were evaluated at a = .05; total sleep time and time in bed are weighted weekly means.
N refers to night shift; D, day shift; R, rotating shift; WE-WD; weekend total sleep time minus weekday total sleep time; see text for insomnia criteria; sleep efficiency is defined as total sleep time / time in bed × 100; "True prevalence" of shift work sleep disorder (SWSD) is defined as the differential prevalence of insomnia or excessive sleepiness (ES, an ESS [Epworth Sleepiness Scale] score ≥ 13) between each respective shift-work and day-work sample. Data for "true prevalence" in the total sample are 18.0%-(mean of rotating and night samples, 28.1%) = 10.0.

bidity in comparison to individuals without SWSD ($P < .05$). The only exceptions to this pattern were for non–sleepiness-related accidents and heart disease where there were no differences between individuals with or without SWSD ($P > .15$ for both). In terms of risk, the odds ratio for ulcers in night workers with SWSD was 3.82 (95% confidence interval [CI] = 1.18-12.32), and the odds ratio for ulcers in rotating workers with SWSD was 4.30 (95% CI = 1.67-11.09). For the combined group of shift workers with SWSD, the odds ratio for ulcers was 4.18 (95% CI = 2.00-8.72). A main effect of Shift Type (night vs rotating) was present for days of missed work, indicating that rotating workers missed work more frequently than night workers ($P = .04$). There were no other significant main effects of Shift Type.

The next set of analyses was aimed at determining the effects that were unique to shift workers with SWSD. That is, to assess what morbidities related to insomnia or excessive sleepiness are greater in shift workers as compared to day workers. These were important analyses in that, if unique effects were observed, either as independent contributions (2 main effects) or interactive (significant interaction), one could conclude that insomnia or excessive sleepiness does produce morbidity in shift workers beyond that seen in day workers experiencing those same symptoms. Data for the prevalence of ulcers are displayed in Figure 1. The analysis revealed a main effect for Group ($P < .001$), with both night workers (odds ratio = 3.13, 95% CI = 1.62-6.05) and rotating workers (odds ratio = 2.32, 95% CI = 1.32-4.06) having an elevated prevalence rate of ulcers when compared to day workers. There was also a main effect of Symptoms ($P < .001$), indicating that individuals with insomnia or excessive sleepiness had elevated rates of ulcers (odds ratio = 4.55, 95% CI = 2.47-8.37). Thus, both work shift and sleep-wake symptoms independently contribute to the increased prevalence of ulcers seen in shift workers. There was no Group × Symptoms interaction ($P = .97$). For depression, there was only a main effect of Symptoms, indicating that individuals with insomnia or excessive daytime sleepiness had greater rates of depression (odds ratio = 2.57, 95% CI = 2.01-3.27) but no main effect of Group ($P = .12$). Thus, shift work per se is not associated with depression. There was only a main effect of Group for heart disease ($P = .01$), indicating that individuals on night (odds ratio = 2.57, 95% CI = 1.24-5.30) and rotating (odds ratio = 2.01, 95% CI = 1.06-3.83) shifts had greater rates of heart disease compared to day workers, but no main effect of Symptoms was present. Thus, work shift, rather than sleep-wake symptoms, is associated with the increased prevalence of heart disease in shift workers.

In evaluating the continuous outcome measures, the following had a significant main effect of Symptoms: missed work ($F_{1,2421} = 37.09$, $P < .001$), missed family and social activities ($F_{1,2419} = 130.10$, $P < .001$), sleepiness-related accidents ($F_{1,2438} = 15.55$, $P < .001$), and neuroticism ($F_{1,2420} = 140.07$, $P < .001$). In each case, Symptoms were associated with greater impairment. Main effects of Group were present for missed work ($F_{2,2421} = 14.47$, $P < .001$), as well as missed family and social activities ($F_{2,2419} = 25.27$, $P < .001$). Thus, both main effects were present for missed work and missed family and social activities. For the analysis of days of missed work, there was also a significant Group × Symptoms interaction ($F_{2,2421} = 7.19$, $P = .001$). Posthoc comparisons revealed that rotating workers with SWSD missed significantly more days of work in comparison to day workers with symptoms of insomnia or excessive sleepiness ($P = .009$). For missed family or social activities, there was also a Group × Symptom interaction ($F_{2,2419} = 18.84$, $P < .001$). Posthoc comparisons revealed that night workers as well as rotating workers with SWSD missed significantly more family or social activities over the past 3 months in comparison to day workers with insomnia or excessive sleepiness ($P < .05$ for both) (Figure 2). For the additional outcome variables (accidents and neuroticism), no significant interactions were found, nor were there additive effects of both Symptoms and Shift. Only main effects of Symptoms

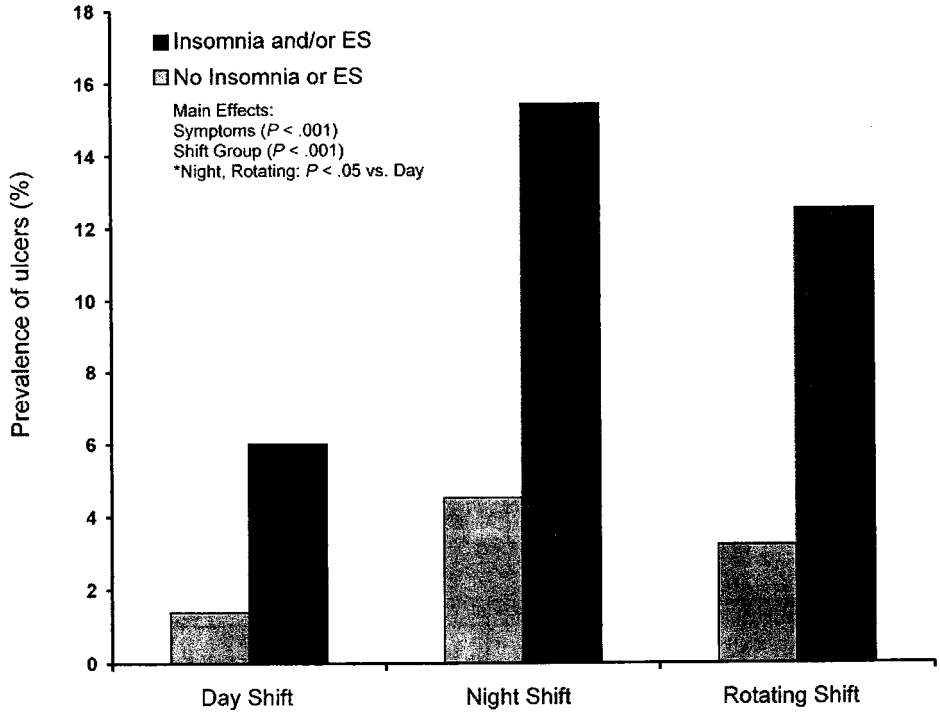

Figure 1—Prevalence of ulcers among day, night, and rotating-shift workers with or without insomnia and/or excessive sleepiness (ES).

were found for sleepiness-related accidents and neuroticism.

The symptom complex (ie, distribution of symptom combinations) was also determined. These final analyses examined the distribution of morbidity among each symptom profile for the analyses, which revealed unique morbidity related to SWSD (ulcers, missed days of work, and missed family/social activities). The distribution of each of the 4 possible symptom profiles within each group is shown in Table 4. In the first analysis, days of missed work was examined. There was a significant Group × Symptom Profile interaction ($F_{6,2415} = 9.48$, $P < .001$) (Figure 3). Posthoc analyses revealed that rotating workers with both insomnia and excessive sleepiness missed work more frequently than day workers with those same symptoms ($P = .03$). Other groups were comparable with regard to the number of days of missed work given their symptom complex. Thus, it appears that for missed work, only the combination of both insomnia and excessive sleepiness conveys any unique morbidity. For missed family and social activities, there was also a significant Group × Symptom Profile interaction ($F_{6,2413} = 12.96$, $P < .001$). Posthoc tests revealed that the presence of insomnia was the only symp-

Table 3—Morbidity and Sleep Measures in Shift Workers Who Met or Did Not Meet Criteria for SWSD and Day Workers with and Without Symptoms of Insomnia or Excessive Sleepiness

	Permanent Night Workers		Rotating Workers		Day Workers	
	No SWSD (n = 110)	SWSD (n = 52)	No SWSD (n = 249)	SWSD (n = 88)	No symptoms (n = 1598)	Symptoms (n = 352)
Ulcers, %	4.5	15.4*	3.2	12.5*	1.4	6.0
Heart disease, %	6.4	7.7	4.4	5.7	3.1	4.0
Missed work, no. days	0.3 ± 0.9	1.0 ± 2.3*	0.6 ± 2.8	3.3 ± 12.8*	.20 ± 1.1	1.2 ± 4.6
Missed family/social activities, no. days	1.5 ± 9.0	8.6 ± 21.7*	1.0 ± 4.2	10.1 ± 22.7*	.60 ± 3.1	3.6 ± 11.6
Depression, %	14.5	32.7*	13.7	31.8*	11.8	25.0
Neuroticism score	2.6 ± 2.8	5.1 ± 2.8*	3.0 ± 2.8	5.2 ± 3.4*	2.5 ± 2.5	4.9 ± 3.5
Sleepiness-related accidents, no.	0.04 ± 0.2	0.1 ± 0.4*	0.1 ± 0.2	0.2 ± 0.5*	.06 ± .27	.17 ± .63
Non–sleepiness-related accidents, no.	1.6 ± 1.8	1.2 ± 1.3	1.6 ± 1.7	1.4 ± 1.6	1.8 ± 1.9	1.7 ± 1.7
Total sleep time, h	6.4 ± 1.4	5.5 ± 1.6*	6.7 ± 1.3	6.5 ± 2.0	6.9 ± 1.1	6.2 ± 1.4
Time in bed, h	7.5 ± 2.0	7.1 ± 2.2	7.5 ± 1.5	7.6 ± 2.0	7.5 ± 1.0	7.3 ± 1.4
Sleep efficiency, %	88.7 ± 22.0	86.3 ± 39.7	91.7 ± 17.5	87.5 ± 23.0	92.4 ± 12.7	86.8 ± 18.8

Data are presented as mean ± SD.

*Significant difference between individuals meeting criteria for shift work sleep disorder (SWSD) and those who did not meet criteria (main effect of SWSD was only tested if the omnibus – F value or χ^2 was significant); Depression was determined using the Diagnostic Interview Schedule based on *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria; For missed work as well as missed family and social activities, the number of days refers to days missed during the past 3 months.

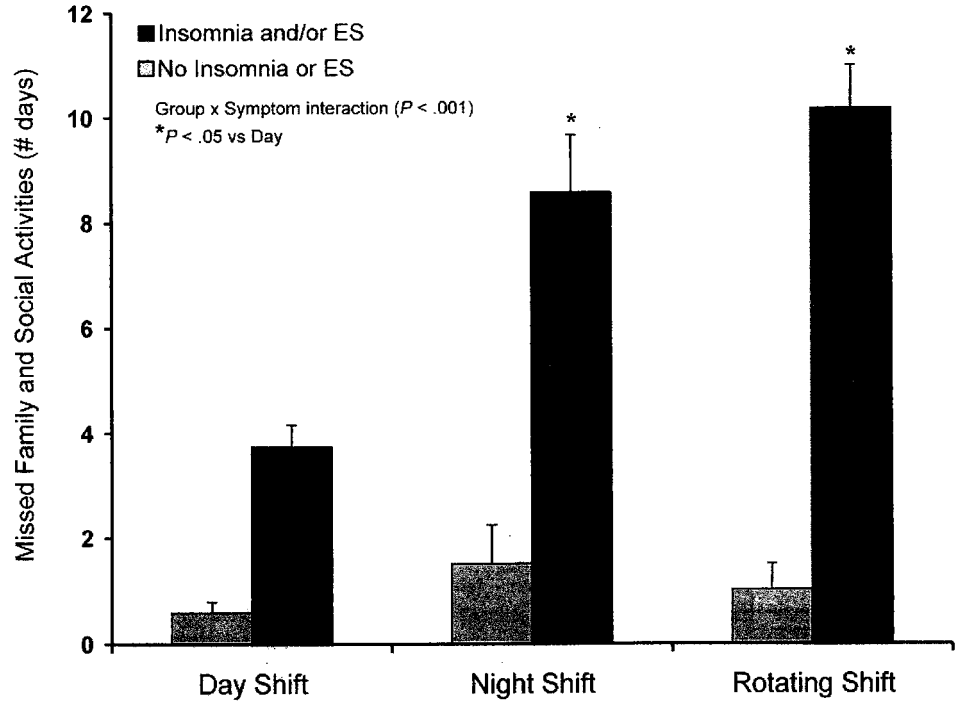

Figure 2—Mean number of days of days of missed family and social activities (± SEM) during the past 3 months in day, night, and rotating-shift workers with or without insomnia and/or excessive sleepiness (ES).

tom that introduced any unique effects beyond that observed in the day-worker sample. Specifically, rotating workers who reported insomnia missed more family and social activities in comparison to day workers with insomnia ($P = .003$). The difference between night workers who reported insomnia and day workers with insomnia approached significance ($P = .07$).

DISCUSSION

Results from the present study suggest that the prevalence of insomnia or excessive sleepiness is 32% and 26% in night and rotating shift workers, respectively. Given that the summed prevalence of these symptoms in the general population is approximately 18%, this amounts to a "true prevalence" of SWSD of approximately 10% of night and rotating workers. Because 6.4% of all workers are night or rotating workers,[1] it is estimated that approximately 1% of the working population would meet the criteria for SWSD. Although no estimates of the population prevalence of SWSD have been published to our knowledge, our results are considerably less than clinical estimates of 2% to 5% of the population.[2] Our data are consistent with 2 recent studies showing that circadian rhythm and other sleep disorders are more prevalent in night-shift workers compared with day workers and that insomnia, excessive sleepiness, and circadian rhythm disorders are associated with significant morbidity (accidents and absenteeism) in shift-work samples.[4,33]

Previous studies have demonstrated copious behavioral, health, and social morbidity associated with shift work.[4,6,45,49-53] However, we are unaware of studies that have examined these outcomes in shift workers meeting criteria for SWSD relative to those who do not. As one might expect, the present study findings support the notion that a large part of the negative sequelae associated with shift work is related to insomnia and daytime sleepiness, at least in terms of risk. Three patterns of morbidity emerged. First, certain morbidity is directly attributable to shift work. This is evident in the shift-work main-effect only findings (see discussion of heart disease below). Second, the presence of *both* main effects (shift work and symptoms) indicates an additive independent relationship where individuals with SWSD have increased morbidity as they carry both risk factors (see discussion of ulcers below). Finally, interactions indicate a *multiplicative* effect, where individuals with SWSD had increased morbidity that is not explained by the additive effects of shift work and symptoms of insomnia or excessive sleepiness (see discussion of missed work below). This pattern of results shows that individuals with SWSD have much higher rates of morbidity crossing several domains in comparison to shift workers without SWSD. In most cases, the elevated morbidity was greater than that seen for day workers with similar symptoms.

It has long been recognized that individuals exposed to shift work are at greater risk for experiencing gastrointestinal symp-

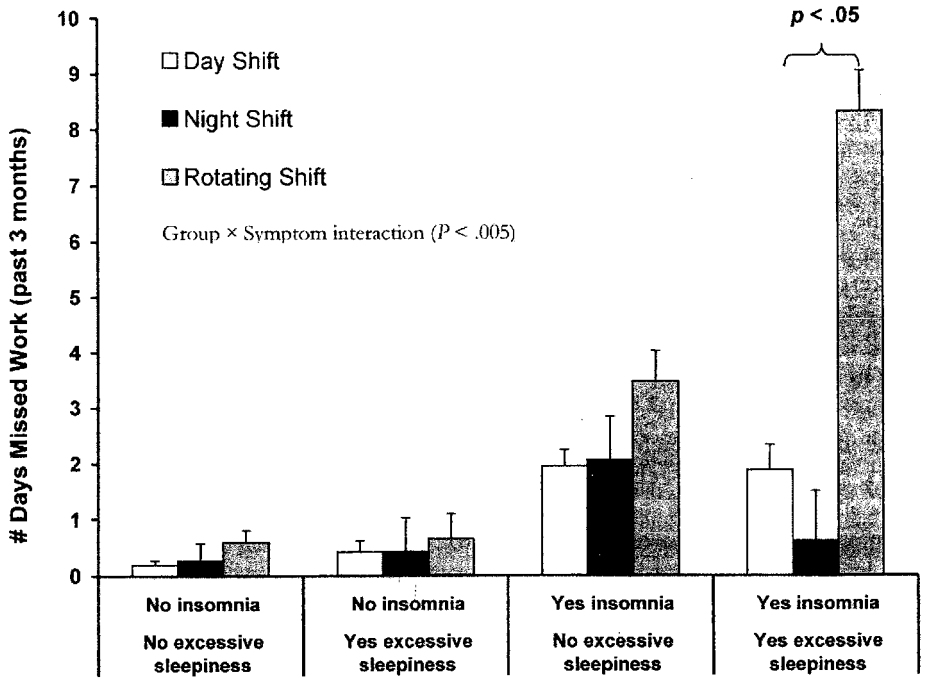

Figure 3—Mean number of days of missed work during the past three months (± SEM) in day, night, and rotating-shift workers grouped by each symptom combination of insomnia and/or excessive sleepiness (ES).

Table 4—Distribution of Symptom Profiles in People Working Days, Nights, and Rotating Shifts

Symptom profile	Day Workers (n = 1950)	Night Workers (n = 162)	Rotating Workers (n = 337)	Total Sample (N = 2,449)
No insomnia or sleepiness, %	78.6	64.2	68.5	76.3
Insomnia without sleepiness, %	6.1	10.5	10.1	6.9
Sleepiness without insomnia, %	12.8	17.3	15.7	13.5
Insomnia and sleepiness, %	2.5	8.0	5.6	3.3

toms and ulcers.[45,53] The present study links a large part of this morbidity to the insomnia and excessive sleepiness found in this population. However, morbidity independently related to shift work was also demonstrated, suggesting that both factors play a role. It has been shown that shift work is associated with increased secretion of gastrin and pepsinogen,[54] and it has been speculated that such increases may mediate the elevated risk for both gastric and duodenal ulcers in shift workers. It is possible that elevations of gastrin and pepsinogen levels also accompany the sleep disturbance and ensuing sleepiness in SWSD. For heart disease, the present findings indicate a risk related to shift work but not specific to insomnia or excessive sleepiness symptoms. This effect remained significant after controlling for additional risk factors (body mass index, smoking status, hypertension, alcohol intake and diabetes, $P < .05$). This finding is consistent with previous research that has shown an increased risk for cardiovascular disease in shift workers compared with day workers.[55-59] Further research is needed to identify what aspects of shift work may convey such increased risk. Although findings in animals suggest that chronic shifts of the circadian system can exacerbate the mortality associated with cardiomyopathic heart disease,[60] it is unclear what, if any, aspects of the circadian system may account for the elevation of heart disease in shift workers. In addition to circadian disruption, night workers in the present study are likely experiencing a chronic sleep debt, as evidenced by reduced sleep efficiency and reduced total sleep time in comparison to day workers. This chronic sleep debt may account for their high levels of excessive sleepiness, as has been demonstrated in recent studies,[61-63] and could potentially contribute to the cardiovascular effects. Specifically, a recent study has demonstrated an elevation in C-reactive protein, an inflammatory marker of cardiovascular morbidity, following 10 days of partial sleep deprivation.[64] However, in a secondary analysis of the present data, total sleep time was not a significant predictor of heart disease ($P = .83$). Other data support the possibility that cardiac morbidity in shift workers may be mediated through the effects of shift work on sleep-related cardiac autonomic activity.[52]

Aspects of morbidity related to quality of life did show multiplicative effects. That is, individuals with SWSD experienced impairments in quality of life beyond that which would be expected given their shift-work status and sleep-related symptoms. The elevated work absenteeism and impaired social aspects of quality of life related to symptoms of insomnia or excessive sleepiness were exacerbated by shift work. Furthermore, it appears that this differential increase in morbidity in shift workers is related to insomnia in the case of social consequences and the combined effects of insomnia and excessive sleepiness in the case of missed work. This pattern of results suggests that both symptoms convey important information and should be considered in clinical management.

There are several limitations of the present study. First, while we chose to leave the epidemiologic nature of the study intact, it will be important for future studies to determine if these relationships are maintained using more clinically based case-control samples of individuals with SWSD. Also, the representative community-based methodology of the present study did not allow us to objectively verify the presence or location of ulcers using radiographic examinations. However, the prevalence rate found for ulcers was consistent with that of other population-based studies and studies involving shift workers.[53] Thus, we believe the present results are likely to provide an accurate reflection of ulcers and their relative prevalence in our subpopulations. Accident rates were also not verified independent of subjective reports. However, it is unclear if other methodologies would produce more reliable results as many minor accidents are not reported and would be missed when using conventional police or department of state databases. Although a 70.1% response rate puts some limits on generalizability, this response is in line with other representative population-based studies[42,6566] and is unlikely to significantly impact the results.[67] Practical limitations also prevented us from assessing physiologic measures of sleepiness using standard techniques such as the Multiple Sleep Latency Test.[68] Although Multiple Sleep Latency Test measurement may have produced more reliable and sensitive assessments of sleepiness, such enhancements of methodology would likely lead to even more robust findings and significance for several of the outcomes that approached significance. Another limitation involves the fact that we did not determine where in the work rotation each of the rotating workers was at the time of interview, though we did know that the worker was on a "rotating" schedule during the past 2 weeks. Previous data suggest that the average duration of a work rotation is a week or less, depending on occupation. Thus, it is likely that most of the rotating workers assessed were currently working a schedule out of sync with their endogenous biologic rhythm.

Another potential limitation was that individuals on an "evening" shift were not included as part of the present paper. This decision was made on the basis of data that suggest that workers on an evening shift obtain significantly more sleep than individuals on day shifts. A recent meta-analysis showed that evening workers average approximately 7.6 hours of sleep per night,[34] considerably greater than the day workers in the present study at 6.8 hours per night. Nonetheless, a separate analysis was performed to compare the evening workers (n = 152) to the day-worker sample on measures of sleep habits and the prevalence of insomnia and excessive sleepiness as potential SWSD symptoms. In terms of sleep habits, evening workers spent significantly **more** time in bed (7.7 hours vs 7.4 hours, $P = .002$), had an equivalent sleep efficiency (92.1% vs 91.5%, $P = .81$) and, thus, reported a significantly **greater** amount of total sleep time (7.0 hours vs 6.8 hours, $P = .03$) in comparison to day workers. The prevalence of insomnia (12.5% vs 8.6%, $P = .11$) as well as excessive sleepiness (17.1% vs 15.5%, $P = .59$) was not significantly different between the evening-and day-worker samples, respectively. Finally, the prevalence of SWSD symptoms as a whole (insomnia or excessive sleepiness) was not significantly different between the evening and day workers (21.5% vs 18.0%, $P = .30$). Thus, evening-shift workers are less likely to have a sleep debt than any of the groups included in our analyses. Moreover, the timing of most evening shifts and the levels of sleep disturbance suggest that significant circadian disruption is unlikely for this group.

The distinction between shift workers meeting criteria for SWSD and those who do not is an important one because previous studies have shown that not all shift workers experience sleep-wake symptoms.[33] Indeed, there appears to be a subgroup of individuals (ie, SWSD) with an elevated vulnerability to certain detrimental effects of shift work. Specifically, the present results suggest that a number of morbidities in shift workers are

related to sleep-wake symptoms (eg, depression), whereas others are related to shift work independent of sleep-wake symptoms (eg, heart disease). The present results also support the view that there are certain negative outcomes for which sleep-wake symptoms and shift work make independent additive or multiplicative contributions (eg, ulcers, missed work). This latter pattern of morbidity would appear to be especially disconcerting from a clinical perspective because individuals with SWSD would appear to be at a substantially high risk for experiencing these negative consequences. Future studies should help to identify the mechanisms that lead to these patterns of morbidity and determine appropriate treatment strategies that may limit such negative outcomes. Indeed, differences in basal circadian amplitude[69,70] and phase[71] have been implicated as components related to shift-work tolerance, including sleep disturbance, sleepiness, and digestive problems. Other investigators have found evidence for hormonal involvement in dissatisfaction with shift work.[72] Clearly, additional studies are needed to determine the mechanisms responsible for individual vulnerability to the negative consequences of shift work. Future work may benefit from the measurement of noncircadian variables as well, such as an elevated vulnerability to sleep disturbance in response to stress.[73]

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A New Method for Measuring Daytime Sleepiness: The Epworth Sleepiness Scale

Murray W. Johns

Sleep Disorders Unit, Epworth Hospital, Melbourne, Victoria, Australia

Summary: The development and use of a new scale, the Epworth sleepiness scale (ESS), is described. This is a simple, self-administered questionnaire which is shown to provide a measurement of the subject's general level of daytime sleepiness. One hundred and eighty adults answered the ESS, including 30 normal men and women as controls and 150 patients with a range of sleep disorders. They rated the chances that they would doze off or fall asleep when in eight different situations commonly encountered in daily life. Total ESS scores significantly distinguished normal subjects from patients in various diagnostic groups including obstructive sleep apnea syndrome, narcolepsy and idiopathic hypersomnia. ESS scores were significantly correlated with sleep latency measured during the multiple sleep latency test and during overnight polysomnography. In patients with obstructive sleep apnea syndrome ESS scores were significantly correlated with the respiratory disturbance index and the minimum SaO_2 recorded overnight. ESS scores of patients who simply snored did not differ from controls. **Key Words:** Sleepiness—Questionnaire—Sleep propensity—Insomnia—Obstructive sleep apnea syndrome.

A large proportion of adult patients who present to sleep disorder centers have disorders associated with excessive daytime sleepiness. These include obstructive sleep apnea syndrome (OSAS), periodic limb movement disorder (PLMD), narcolepsy, idiopathic hypersomnia and other miscellaneous disorders (1). The severity of their chronic daytime sleepiness is an important aspect of each patient's assessment. Thus, there is a great need for a simple standardized test for measuring a patient's general level of sleepiness, which is independent of short-term variations in sleepiness, with the time of day and from day to day.

The multiple sleep latency test (MSLT) is widely used and is generally believed to provide a valid measurement of sleepiness on the particular day of the test (2,3). It is based on the premise that the sleepier the subject, the quicker he will fall asleep when encouraged to do so while lying down in a nonstimulating environment. The MSLT has a reasonably high test–retest reliability over periods of months in normal subjects (4). Assuming the same reliability holds true for patients, the MSLT must be considered the standard method for measuring their chronic daytime sleepiness. However, the MSLT is very cumbersome, time-consuming and expensive to perform. It takes all day, both for the subject and the polysomnographer and is not easy to justify as a routine test for all patients.

Other measures of sleepiness have been devised (5,6). In the maintenance of wakefulness test (MWT) the latency to sleep onset is measured with the subject sitting in a dimly lit, warm, quiet room, trying to stay awake rather than to fall asleep (5). However, all such tests share the disadvantage of the MSLT in being cumbersome and expensive. Similar criticisms can be levelled at tests of sleepiness based on pupillometry (7), or cerebral evoked potentials (8). Other assessments of sleepiness have involved prolonged psychomotor performance tests, the results of which are not related in any simple or consistent way to sleepiness in different subjects (9).

By contrast, the Stanford sleepiness scale (SSS) is a quick and simple test (10). It involves the subject's own reports of symptoms and feelings at a particular time. Visual analogue scales (VAS) of sleepiness/alertness have also been used in this context (11). However, these tests do not attempt to measure the general level of daytime sleepiness, as distinct from feelings of sleepiness at a particular time. Nor, it appears, is the subjective sleepiness that they measure the same as the objective sleepiness measured by the MSLT (3,7). Scores on the SSS or on a VAS of sleepiness are not significantly correlated with sleep latency in the MSLT,

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Address correspondence and reprint requests to Dr. Murray W. Johns, Sleep Disorders Unit, Epworth Hospital, Melbourne, Victoria 3121, Australia.

TABLE 1. *The Epworth sleepiness scale*

THE EPWORTH SLEEPINESS SCALE

Name: _____
Today's date: _____ Your age (years): _____
Your sex (male = M; female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the *most appropriate number* for each situation:

0 = would *never* doze
1 = *slight* chance of dozing
2 = *moderate* change of dozing
3 = *high* chance of dozing

Situation	Chance of dozing
Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theater or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	

Thank you for your cooperation

even when measured at virtually the same time (12). These subjective reports may be related more to tiredness and fatigue than to sleep propensity, as manifested by the tendency to fall asleep.

The present report describes the development and use of a new questionnaire, the Epworth sleepiness scale (ESS), designed to measure sleep propensity in a simple, standardized way. The scale covers the whole range of sleep propensities, from the highest to the lowest.

Development of the ESS

The concept of the ESS was derived from observations about the nature and occurrence of daytime sleep and sleepiness. Some people who suffer from excessive daytime sleepiness keep themselves busy and choose not to lie down nor to sit and relax during the day, thereby purposely avoiding daytime sleep. Others who may be bored, with spare time or who are socially withdrawn but who may not be very sleepy, choose to lie down and sleep during the day. About 50% of ostensibly healthy medical students usually sleep during the day at least once in an average week (13). Among 17–22-year-old recruits entering the French army, 19% reported sleeping during the day, regularly or occasionally. But only 5% complained of daytime sleepiness (14). Thus, knowing how frequently or for how long subjects usually sleep during the day will probably not provide a useful measurement of their sleepiness.

By contrast, sleepy people often describe how they doze off inadvertently while engaged in activities that involve low levels of stimulation, relative immobility and relaxation, such as sitting and watching TV. Earlier questionnaire surveys have indicated which situations, commonly encountered in daily life, are the most soporific (15). A large survey among adults in New Mexico asked about their frequency of falling asleep in five situations (16). The authors derived a score from the three "most sleepy" questions, which referred to falling asleep while "inactive in a public place", "at work", and "in a moving vehicle as passenger or driver". MSLTs on 116 of these subjects showed a statistically significant correlation between their sleep latency (SL) and their answers to those three questions ($r = -0.32$, $p < 0.001$).

The ESS is based on questions referring to eight such situations, some known to be very soporific; others less so. The questionnaire, which is self-administered, is reproduced in Table 1. Subjects are asked to rate on a scale of 0–3 how likely they would be to doze off or fall asleep in the eight situations, based on their usual way of life in recent times. A distinction is made between dozing off and simply feeling tired. If a subject has not been in some of the situations recently, he is asked, nonetheless, to estimate how each might affect him.

The ESS tries to overcome the fact that people have different daily routines, some facilitating and others inhibiting daytime sleep. For example, the ESS does not ask how frequently the subject falls asleep while watching TV. That would depend on how frequently he watched TV as much as on his sleepiness. Instead, the subject rates the chances that he would doze off whenever he watches TV.

One question asks how likely the subject would be to doze off while lying down to rest in the afternoon when circumstances permit. It was felt that normal people probably would, and sleepy people certainly would tend to doze off in that situation. Never to do so would indicate an unusually low level of sleepiness, as described by some insomniacs. Some other situations were included in the questionnaire because it was believed that only the most sleepy people would doze in them—while sitting and talking to someone, and in a car while stopped for a few minutes in traffic. These suppositions proved correct.

The numbers selected for the eight situations in the ESS were added together to give a score for each subject, between 0 and 24. These ESS scores proved capable of distinguishing individuals and diagnostic groups over the whole range of daytime sleepiness.

TABLE 2. *The groups of experimental subjects, their ages and ESS scores*

Subjects/diagnoses	Total number of subjects (M/F)	Age in years (mean ± SD)	ESS scores (mean ± SD)	Range
Normal controls	30 (14/16)	36.4 ± 9.9	5.9 ± 2.2	2–10
Primary snoring	32 (29/3)	45.7 ± 10.7	6.5 ± 3.0	0–11
OSAS	55 (53/2)	48.4 ± 10.7	11.7 ± 4.6	4–23
Narcolepsy	13 (8/5)	46.6 ± 12.0	17.5 ± 3.5	13–23
Idiopathic hypersomnia	14 (8/6)	41.4 ± 14.0	17.9 ± 3.1	12–24
Insomnia	18 (6/12)	40.3 ± 14.6	2.2 ± 2.0	0–6
PLMD	18 (16/2)	52.5 ± 10.3	9.2 ± 4.0	2–16

METHODS

Subjects

A total of 180 adult subjects completed the questionnaire. There were 30 controls who were mainly hospital employees, working during the day, who gave a history of normal sleep habits without snoring. There were 150 patients with various sleep disorders, whose ages, sex and diagnostic categories are shown in Table 2. Every new patient who presented to the Epworth Sleep Disorders Unit answered the ESS at their first consultation. After investigation, all patients with the diagnoses listed in Table 2 were included in the study until there were 150. The ages of patients ranged from 18 to 78 years. The mean age within diagnostic groups varied from 36 to 52 years. Men greatly outnumbered women in the snoring, OSAS and PLMD groups. The sexes were about equal in the other groups, apart from the insomniacs where women outnumbered men.

A total of 138 patients had overnight polysomnography, but another 12 who were clearly suffering from either chronic psychophysiological or idiopathic insomnia did not. The latter diagnoses were made on the basis of each patient's history, using the criteria set out in the International Classification of Sleep Disorders (1). Other insomniacs, with mood disorders or drug effects, were excluded.

Twenty-seven patients had MSLTs after overnight polysomnography. They had four naps, at 1000, 1200, 1400 and 1600 hours. Sleep latency was measured from the time lights were switched off until the onset of stage 1 sleep of at least 1 minute duration, or the onset of either stage 2 or rapid eye movement (REM) sleep. The early onset of REM sleep was indicated by the occurrence of REM sleep within 20 minutes of sleep onset. Of the 27 patients, 11 had narcolepsy diagnosed from the patient's history, particularly of cataplexy, associated with an SL of less than 10 minutes and the early onset of REM sleep in two or more naps (10 patients) or in one nap (1 patient with cataplexy). Fourteen of the 27 patients had idiopathic hypersomnia, diagnosed from their excessive daytime sleepiness in the absence of either cataplexy or the early onset of REM sleep in the MSLT. The remaining two patients had excessive daytime sleepiness due to OSAS. The ESS scores for the 27 patients who had MSLTs ranged from 11 to 24.

All patients with primary snoring had presented initially because of the intensity and persistence of their snoring, on most nights at least. Many had been observed at home to pause in their breathing at night, suggesting that they may have had sleep apnea, but this was found not to be of clinical significance by polysomnography. The respiratory disturbance index (RDI) was calculated as the number of apneas and hypopneas causing a drop of >3% in the arterial oxygen saturation per hour of sleep. The RDI for primary snorers was ≤5. The 55 patients with OSAS were divided into three subcategories according to their RDI, regardless of their complaints about daytime sleepiness or insomnia (Table 3). The RDI for mild OSAS was within the range >5–15; for moderate OSAS the range was >15–30, and for severe OSAS it was >30.

A diagnosis of PLMD was made only if there were at least 90 separate movements in one or both legs per night. The mean periodic movement index for these subjects, calculated as the number of movement events per hour of sleep, was 43.6 ± 30.4 (SD). Patients who had both PLMD and OSAS were excluded from this study. However, 9 of the 18 subjects with PLMD snored during polysomnography without having OSAS.

Statistical methods

The ESS scores of male and female control subjects were compared by a Student's *t* test. Differences in ESS scores between the diagnostic groups were tested by one-way ANOVA and then by posthoc Scheffé tests. A separate ANOVA and posthoc Scheffé tests were

TABLE 3. *ESS scores in mild, moderate and severe OSAS*

	Mean RDI ± SD	Total number of subjects (M/F)	ESS scores (mean ± SD)	Range
Mild OSAS	8.8 ± 2.3	22 (21/1)	9.5 ± 3.3	4–16
Moderate OSAS	21.1 ± 4.0	20 (20/0)	11.5 ± 4.2	5–20
Severe OSAS	49.5 ± 9.6	13 (12/1)	16.0 ± 4.4	8–23

used to test the differences in ESS scores between primary snorers and the three categories of OSAS. The Scheffé test is conservative and is suitable for groups with unequal numbers of subjects (17). The distribution of sleep latencies ,measured in minutes, was highly skewed positively and was normalized by $\log_e$ transformation. The relationships between pairs of continuous variables, such as RDI and sleep latency during overnight polysomnography, were tested by Pearson correlation coefficients and linear regression. Statistical significance was accepted at $p < 0.05$ in two-tailed tests.

RESULTS

The mean ESS score for control subjects was 5.9 ± 2.2 (SD) and their modal score was 6. There was no significant difference in the scores between male and female controls (males = 5.64 ± 2.56; females = 6.06 ± 1.84, $t = 0.520$, $p = 0.607$). Consequently, no distinction was made between the sexes in other groups.

Patients suffering from disorders known to be associated with excessive daytime sleepiness reported the likelihood of dozing under circumstances that were not conducive to sleep in normal subjects. For example, 96% of the patients with either narcolepsy or idiopathic hypersomnia reported some chance, and often a high chance, of dozing while sitting and talking to someone, or in a car while stopped for a few minutes in the traffic. Only 6% of controls reported a slight chance of doing so.

Patients with persistent psychophysiological or idiopathic insomnia reported either a complete inability or only a slight chance of dozing while lying down to rest in the afternoon when circumstances permitted. By contrast, 94% of controls reported some likelihood of dozing then.

One-way ANOVA demonstrated significant differences in ESS scores between the seven diagnostic groups in Table 2 ($F = 50.00$; df = 6,173; $p < 0.0001$). Posthoc tests between paired groups showed that the ESS scores for primary snorers did not differ from controls ($p = 0.998$). Scores for OSAS, narcolepsy and idiopathic hypersomnia were significantly higher than for controls ($p < 0.001$) or primary snorers ($p < 0.001$). The insomniacs had significantly lower scores ($p < 0.01$) than all groups other than controls, for which the difference did not quite reach statistical significance ($p = 0.063$). The ESS scores of patients with PLMD did not differ significantly from controls ($p = 0.149$).

A separate one-way ANOVA for the ESS scores of primary snorers and the three subcategories of OSAS showed significant differences between these groups ($F = 23.11$; df = 3,82; $p < 0.001$). Posthoc tests then showed that ESS scores for each level of OSAS were significantly higher than for primary snorers ($p = 0.035$ for mild OSAS; $p < 0.001$ for moderate and severe OSAS). Scores for severe OSAS were higher than for moderate OSAS ($p < 0.001$), but the difference between mild and moderate OSAS did not reach statistical significance ($p = 0.085$).

Considering all 55 patients with OSAS together, there was a significant correlation, on the one hand, between ESS scores and RDI ($r = 0.550$, $p < 0.001$) and on the other hand, between ESS scores and the minimum SaO_2 recorded during apneas overnight ($r = -0.457$, $p < 0.001$). The RDI and the minimum overnight SaO_2 during apneas were also significantly correlated ($r = -0.687$, $p < 0.001$). The linear regression equations for these three relationships, in the form $Y = a + bx$, were as follows:

$$(\text{RDI}) = -0.674 + 2.006(\text{ESS score})$$
$$(\text{minimum } SaO_2\%) = 86.47 - 1.055(\text{ESS score})$$
$$(\text{minimum } SaO_2\%) = 84.15 - 0.440(\text{RDI})$$

Among the 138 patients who had overnight polysomnography there was a significant correlation between ESS score and (ln) sleep latency at night ($r = -0.379$, $n = 138$, $p < 0.001$). In the smaller group of patients who had MSLTs, the correlation between ln (SL) during the day and ESS score was also statistically significant ($r = -0.514$, $n = 27$, $p < 0.01$. The linear regression equation for this relationship was ln (SL) = 3.353 − 0.091(ESS score).

Individual ESS scores of 16 or more, indicating a high level of daytime sleepiness, were found only in patients with narcolepsy, idiopathic hypersomnia or OSAS of at least moderate severity (i.e. RDI > 15). All patients with either narcolepsy or idiopathic hypersomnia had higher ESS scores than the controls (i.e. ESS > 10) as did 12 of 13 patients with severe OSAS. The remaining patient in the latter category had an ESS score of 8 and was clinically not much affected by his sleep apnea.

Within the group of patients with PLMD, the periodic movement index, which ranged from 16 to 122 movements per hours of sleep, was not significantly correlated with ESS scores ($r = 0.049$, $n = 18$, $p > 0.1$).

DISCUSSION

These results provide evidence that a questionnaire-based scale as brief and as simple as the ESS can give valid measurements of sleep propensity in adults. ESS scores significantly distinguished groups of patients who are known from other investigations to have differences in their levels of sleepiness, as measured by the MSLT (2,18). ESS scores were significantly correlated

with sleep latency measured during the day with MSLTs and at night with polysomnography. This is despite any effect of the first night in the laboratory. Others have found a significant positive correlation between the SL at night and during the day in the same subject (19).

ESS scores greater than 16, indicative of a high level of daytime sleepiness, were encountered only in patients with moderate or severe OSAS (RDI > 15), narcolepsy or idiopathic hypersomnia. These disorders are known to be associated with excessive daytime sleepiness as measured by the MSLT (2,18). Nevertheless, high ESS scores, by themselves, are not diagnostic of a particular sleep disorder, any more than is an SL of 5 minutes in an MSLT.

ESS scores were correlated with both the RDI and the minimum SaO_2 recorded during polysomnography in patients with OSAS of differing severity. In the past, these measures of the severity of OSAS have been found to be related to the SL in MSLTs in some, but not in all investigations (18,20). The finding that ESS scores can distinguish patients who simply snore from those with even mild OSAS is evidence for the sensitivity of the ESS. The questionnaire should be useful in elucidating the epidemiology of snoring and OSAS, and any associated cardiovascular or cerebrovascular risks. Previous investigations of this kind have tended to blur the distinction between primary snoring and OSAS (21).

In the patients with PLMD, the finding of an almost zero correlation between their periodic movement index and ESS scores suggests that whatever level of daytime sleepiness is associated with PLMD, it is not related simply to the frequency of limb movements. It may be more closely related to the frequency of those movements producing arousal rather than those that do not. This distinction was not made here and further investigation is required to clarify this relationship.

The low ESS scores of patients with idiopathic or psychophysiological insomnia are consistent with evidence that such patients have a low sleep propensity, even when they are able to relax (22). It must not be assumed, however, that this is necessarily so for other kinds of insomnia, such as with mood disorders.

The relatively wide range of ESS scores in the control subjects [2–10] is consistent with evidence that some healthy adults, without recognizable sleep disorders, remain sleepier than others during the day (23). Such differences persist in MSLTs, even after extending the hours of nocturnal sleep to overcome possible sleep deprivation (24). The sleep propensity of a subject on a particular day would be influenced by the quality and duration of prior sleep or of sleep deprivation, the time of day, the presence of various sleep disorders, drug effects, the level of interest and motivation induced by the situation at hand, as well as longer-term physiological differences. The ESS does not distinguish the nature of long-term physiological or pathological processes that produce a particular level of sleep propensity. Other investigations, including overnight polysomnography, are required for that.

The ESS assumes that subjects can remember whether or not and under what circumstances they have dozed off during the day as part of their "usual way of life in recent times". The present results suggest that most patients can give meaningful self reports about this aspect of their behavior and that their ESS scores provide a measurement of their general level of daytime sleepiness, from low to very high levels. This has not been achieved previously by any other published questionnaire.

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

An American Academy of Sleep Medicine Report

Timothy I. Morgenthaler, MD[1]; Teofilo Lee-Chiong, MD[2]; Cathy Alessi, MD[3]; Leah Friedman, PhD[4]; R. Nisha Aurora, MD[5]; Brian Boehlecke, MD[6]; Terry Brown, DO[7]; Andrew L. Chesson Jr., MD[8]; Vishesh Kapur, MD, MP[9]; Rama Maganti, MD[10]; Judith Owens, MD[11]; Jeffrey Pancer, DDS[12]; Todd J. Swick, MD[13]; Rochelle Zak, MD[5]; Standards of Practice Committee of the AASM

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

The expanding science of circadian rhythm biology and a growing literature in human clinical research on circadian rhythm sleep disorders (CRSDs) prompted the American Academy of Sleep Medicine (AASM) to convene a task force of experts to write a review of this important topic. Due to the extensive nature of the disorders covered, the review was written in two sections. The first review paper, in addition to providing a general introduction to circadian biology, addresses "exogenous" circadian rhythm sleep disorders, including shift work disorder (SWD) and jet lag disorder (JLD). The second review paper addresses the "endogenous" circadian rhythm sleep disorders, including advanced sleep phase disorder (ASPD), delayed sleep phase disorder (DSPD), irregular sleep-wake rhythm (ISWR), and the non–24-hour sleep-wake syndrome (nonentrained type) or free-running disorder (FRD). These practice parameters were developed by the Standards of Practice Committee and reviewed and approved by the Board of Directors of the AASM to present recommendations for the assessment and treatment of CRSDs based on the two accompanying comprehensive reviews. The main diagnostic tools considered include sleep logs, actigraphy, the Morningness-Eveningness Questionnaire (MEQ), circadian phase markers, and polysomnography. Use of a sleep log or diary is indicated in the assessment of patients with a suspected circadian rhythm sleep disorder (Guideline). Actigraphy is indicated to assist in evaluation of patients suspected of circadian rhythm disorders (strength of recommendation varies from "Option" to "Guideline," depending on the suspected CRSD). Polysomnography is not routinely indicated for the diagnosis of CRSDs, but may be indicated to rule out another primary sleep disorder (Standard). There is insufficient evidence to justify the use of MEQ for the routine clinical evaluation of CRSDs (Option). Circadian phase markers are useful to determine circadian phase and confirm the diagnosis of FRD in sighted and unsighted patients but there is insufficient evidence to recommend their routine use in the diagnosis of SWD, JLD, ASPD, DSPD, or ISWR (Option). Additionally, actigraphy is useful as an outcome measure in evaluating the response to treatment for CRSDs (Guideline). A range of therapeutic interventions were considered including planned sleep schedules, timed light exposure, timed melatonin doses, hypnotics, stimulants, and alerting agents. Planned or prescribed sleep schedules are indicated in SWD (Standard) and in JLD, DSPD, ASPD, ISWR (excluding elderly-demented/nursing home residents), and FRD (Option). Specifically dosed and timed light exposure is indicated for each of the circadian disorders with variable success (Option). Timed melatonin administration is indicated for JLD (Standard); SWD, DSPD, and FRD in unsighted persons (Guideline); and for ASPD, FRD in sighted individuals, and for ISWR in children with moderate to severe psychomotor retardation (Option). Hypnotic medications may be indicated to promote or improve daytime sleep among night shift workers (Guideline) and to treat jet lag-induced insomnia (Option). Stimulants may be indicated to improve alertness in JLD and SWD (Option) but may have risks that must be weighed prior to use. Modafinil may be indicated to improve alertness during the night shift for patients with SWD (Guideline).

Keywords: Circadian, light therapy, melatonin, naps, jet lag, shift work

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

1.0 INTRODUCTION

THIS PRACTICE PARAMETER PAPER IS WRITTEN AS A COMPANION ARTICLE TO THE TWO ACCOMPANYING REVIEW ARTICLES ON CIRCADIAN RHYTHM SLEEP disorders (CRSDs) authored by a task force of experts convened by the American Academy of Sleep Medicine (AASM).[1,2] The companion review papers summarize the peer-reviewed scientific literature published through October 2006. The authors of the review papers evaluated the evidence presented by the reviewed studies according to the Oxford System for Evidence-Based Medicine[3] http://www.cebm.net/index.aspx?o=1025. Using this infor-

Table 1—Levels of Evidence:

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

1. Validating studies test the quality of a specific diagnostic test, based on prior evidence.
2. Reference standards: PSG, sleep logs, actigraphy, phase markers, validated self-reports.
Oxford levels adapted from Sackett[8]

mation and a system described by Eddy[4] (i.e., Standard, Guideline, or Option), the Standards of Practice Committee (SPC) and Board of Directors of the AASM determined levels of treatment recommendation presented in the practice parameters below. The purpose of the present document is to provide evidence-based recommendations for the assessment and treatment of CRSDs.

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

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

2.0 METHODS

The SPC of the AASM commissioned content experts in circadian rhythm sleep disorders in 2005 to review and grade evidence in the peer-reviewed scientific literature regarding the assessment and treatment of circadian rhythm disorders. An extensive review designed to find relevant published evidence retrieved 2084 articles, and is described in detail in the review paper.[1] Abstracts of these articles were reviewed by task force members to determine if they met inclusion criteria. Initial data extraction, preliminary evidence grading in accordance with the standards in Table 1, and initial data entry into evidence tables were performed by professionals contracted by the SPC to expedite the review process. All evidence table entries were reviewed by at least one other task force member. Thus, all evidence grading was performed by independent review of the article by a minimum of two experts–one, a professional experienced in the evidence review process, and the other a content expert. Areas of disagreement were addressed, and if needed, the chair of the task force arbitrated the final decision on evidence level. Final summaries of information from included articles are listed in an evidence table available at http://www.aasmnet.org/.

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

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

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

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

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

Table 2— AASM Levels of Recommendations

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

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

3.0 RESULTS AND RECOMMENDATIONS

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

3.1 General Recommendations for Evaluation of Circadian Rhythm Sleep Disorders

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

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

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

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

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

This recommendation is unchanged from the recently updated practice parameter paper on the use of actigraphy.[6] This prior practice parameter paper and accompanying review provided evidence that changes in actigraphy measures are in agreement with other outcome measures in the assessment of response to intervention in patients with CRSDs.

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

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

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

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

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

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

3.2 Recommendations for Evaluation and Treatments of Circadian Rhythm Sleep Disorders

3.2.1 Shift Work Disorder

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

Table 3— Summary of Recommendations

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

* Mixed modality therapy may be effective in elderly-demented/Nursing Home ISWR patients (Guideline) or those with moderate to severe mental retardation (Option)
#Timed melatonin may be effective in those with moderate to severe mental retardation, but is not recommended at present for elderly-demented/ Nursing Home patients (Option)
Caff = caffeine; Sighted=sighted persons; Unsighted=unsighted persons; - = no recommendation formulated due to lack of evidence.

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

One level 3 study[11] showed that the Morningness-Eveningness Questionnaire (MEQ) score did not reliably predict an individual's adaptability to perform shift work. Another level 3[12] study demonstrated that morning-type individuals may be significantly sleepier than evening-type persons during simulated night shift work. One level 2[13] and two level 3[14,15] studies have utilized timing of melatonin rhythm (urinary aMT6s, DLMO) to evaluate phase shift among night shift workers; results from these studies have varied ranging from an absence of phase shifts to complete adaptation. Using mathematical de-masking algorithms, core body temperature minimum (CBTmin) has been used in several simulated shift work studies to evaluate phase shifting;[16-20] its application in the field appears limited. While these measures have, for the most part, been used in simulated shift work studies, there are no trials evaluating the diagnostic accuracy of these tests in clinical practice.

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

One level 1,[21] two level 2,[22,23] one level 3,[24] and one level 4[25] studies utilizing both shift work laboratory simulation and field investigations have shown that napping, including early pre-shift sleep periods, increased alertness and vigilance, improved reaction times, and decreased accidents during night shift work, without affecting post-shift daytime sleep.

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

One level 2[26], five level 3[11,27-30] and one level 4[31] studies, utilizing different light intensities (2,350 to 12,000 lux) administered in various schedules (20 minutes during breaks; four 20-minute periods throughout the night shift; 30 minute exposures; at least 50% of the shift; during the first half of the shift; or as long as possible during the shift; and with or without restriction of daytime light exposure using goggles) have demonstrated subjective improvements in work time performance tasks, alertness, and mood compared to ordinary light exposure. Some studies, but not others, have also shown shifts in certain phase markers of circadian rhythms (e.g., salivary melatonin, CBTmin), and improvements in daytime sleep.

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

Results from two level 1[32,33] shift work simulation studies, as well as one level 1,[34] three level 2[35-37] and one level 3[38] field studies among night workers were analyzed. Compared to placebo, melatonin administration prior to daytime sleep after night work shift improved daytime sleep quality and duration, caused a shift in circadian phase in some but not all subjects, but failed to enhance alertness at night. Melatonin doses in these studies ranged from 0.5 to 10 mg. From these data, effectiveness did not appear to correlate with dosage strength or form. However, both level 1 simulation studies showed a positive effect on sleep quality and used dosages ranging from 1.8 to 3 mg.

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

This recommendation is based on both night shift simulation experiments (two level 1 studies using triazolam[39,40] and one level 2 study of temazepam[41]) and night shift field investigations (one level 1[42] and one level 2[43] study of zopiclone, and one level 3[44] study of triazolam). These studies have generally demonstrated improvements in the duration and quality of daytime sleep compared to controls but without consistent effects on objective measures of nighttime alertness. Although the evidence for a positive effect on daytime sleep is strong (favoring a "Standard" strength recommendation), the balance of risk and benefit for shift workers is less clear. The clinician should consider that such medications might worsen other coexisting sleep conditions such as sleep related breathing disorders, and take care to individualize therapy and monitor for adverse effects by close follow-up.

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

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

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

3.2.2 Jet Lag Disorder

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

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

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

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

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

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

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

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

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

The accompanying review identified 12 double-blind, placebo-controlled field trials of melatonin. The dose of melatonin ranged from 0.5 to 10 mg, administered at bedtime, for up to 3 days prior to departure and up to 5 days upon arrival at the destination. Two level 1[52,53]and four level 2[54-57] studies demonstrated improvement in JLD symptoms with melatonin administration. Conversely, one level 1[47] study did not demonstrate improvement in JLD symptoms with melatonin, and another level 2[58] study found melatonin was more effective than placebo during the first 3 days post-travel, but after 3 additional days melatonin lost its advantage. Four level 1[52,53,59,60] and one level 2[61] studies found that melatonin administered following travel improves the duration and quality of sleep, based on both subjective and objective measures of sleep. In addition, one level 2 study[62] found that melatonin accelerated entrainment of cortisol rhythms to the new time zone, and another level 2 study[61] found that melatonin accelerated circadian entrainment based on oral temperature rhythms.

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

The most effective dose of melatonin for JLD is unclear. One level 1 study[53] found 5 mg immediate-release melatonin to be more effective at relieving symptoms of JLD compared to a 2 mg slow-release formulation, but it was only marginally more effective than a 0.5 mg immediate-release formulation. These results suggest that immediate-release formulations in doses of 0.5 to 5 mg may be effective at relieving JLD symptoms. Melatonin preparations are not regulated by the Food and Drug Administration. However, the medical literature has not produced evidence of significant risk derived from its use. Thus, the benefits are well supported, and the risks seem low.

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

Three level 1[52,60,63] and six level 2[64-69] studies tested the use of hypnotic agents for JLD-induced insomnia. Four studies involved use of traditional benzodiazepine hypnotics. One level 2 study[69] found that temazepam 10 mg had little effect on JLD symptoms, sleep quality, or circadian entrainment following westward travel. However in another level 2 study,[66] temazepam 20 mg improved subjective sleep quality following eastward travel, but sleep and circadian measures did not improve. One level 2 study[68] involving use of midazolam found improvements in subjective sleep following eastward travel. Finally, one level 2 simulation study[64] designed to mimic westward travel found that triazolam was not different from placebo in sleep efficiency or total sleep time (measured by PSG).

Five studies used one of the newer non-benzodiazepine hypnotics. One large level 1 study[63] found that zolpidem 10 mg administered at bedtime for 3–4 nights following eastward travel across 5–9 time zones improved self-reported total sleep time and sleep quality, and reduced awakenings from sleep; however daytime symptoms of JLD were not addressed. Another level 2 study[65] found that zopiclone 7.5 mg given at bedtime improved sleep duration (measured by actigraphy) for the four post-flight days following a 5-hour westward flight. Daytime activity was also greater, but subjective JLD scores were not improved (compared to placebo).

Two studies compared a non-benzodiazepine hypnotic with melatonin or placebo following eastward travel. One large level 1 study[52] found that zolpidem 10 mg administered during a night flight and for 4 days after arrival following eastward travel across 6–9 time zones was significantly better than melatonin 5 mg (or placebo) in counteracting JLD symptoms, and better at achieving self-reported sleep duration and self-reported sleep quality (but not verified by actigraphy). In this study, a group receiving zolpidem plus melatonin did not report better sleep or better JLD scores than the zolpidem alone group. Another level 1 study[60] found that zopiclone 15 mg (compared to melatonin 2 mg or placebo) administered for one night only after arrival found that zopiclone and melatonin were equally effective at improving both subjective and objective (actigraphy) sleep duration and quality. Other symptoms of JLD were not assessed.

One small level 2 study of simulated eastward 8 hour time shift[67] compared zolpidem 10 mg (versus placebo) given at the new bedtime on the first two nights following the shift with the effects of continuous bright light exposure (versus dim light) upon awakening on the day of the advance and the following day. Total sleep times (by polysomnography) did not differ between treatments, though sleep efficiency improved with zolpidem (on the night of the shift only) or with bright light (on the night after shift only). No other symptoms of JLD were reported.

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

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

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

3.2.3 Advanced Sleep Phase Disorder

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

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

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

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

This is a reiteration of the prior practice parameter paper provided regarding indications for PSG.[10] Regarding ASPD, no studies retrieved for review utilized PSG to make this diagnosis. One level 2 study[72] found the expected advance in the time of sleep onset in ASPD subjects; on the other hand, another level 2 study[74] found fairly standard bedtimes in ICSD-ASPD diagnosed subjects.

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

There were two level 2 studies[71,72] using DLMO as a circadian marker and one level 3 study[73] using urinary 6-sulfatoxy melatonin (MT6) acrophase which found advanced melatonin secretion in presumed ASPD subjects. Three level 2 studies[74-76] and one level 4 study[77] found early core body temperature minima in patients with ASPD, sleep maintenance or terminal insomnia. The review indicated that the available data are limited by heterogeneity of subjects. Additionally, none of the studies evaluated the use of circadian markers as diagnostic aids (no measures of the sensitivity or specificity of the tests). Thus, although the results of such measures are generally consistent with advanced circadian timing, measuring circadian markers can not yet be recommended as diagnostic aids.

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

This recommendation is based on available evidence and committee consensus. One level 4 study[78] achieved sleep advance with sleep scheduling. There have been six studies using scheduled bright light as a treatment. One level 3 study[73] found

evening light exposure no more effective than placebo in shifting circadian phase. A level 2 study[79] succeeded in reducing time in bed after awakening in the morning. Another level 2 study[74] that used ICSD criteria to determine ASPD presence succeeded in improving sleep variables but another level 2 replication of this study[75] did not. One level 4[77] and one level 2 study[76] achieved post-treatment DLMO phase delays and improved sleep quality in patients with complaints of terminal insomnia. Although there is a rationale for using melatonin for ASPD, there is no reported evidence in support of this treatment. Overall, the evidence for efficacy of these interventions is weak or conflicting, but the risks and costs entailed are low. As there are few alternatives, an individualized approach using one or more of these treatments with follow up to ascertain efficacy or side effects may be appropriate.

3.2.4 Delayed Sleep Phase Disorder

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

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

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

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

One level 1[80] and one level 2[81] study demonstrated that properly timed morning light exposure causes a phase advance of sleep onset time and circadian rhythms (CBTmin), and increases objectively determined daytime alertness. In the reviewed studies, 2500 lux for 2-3 hours prior to or at rise time was used. The effects of lower doses, blue light wavelengths, or other timings are not yet known. The treatments were generally well tolerated and of some beneficial effect, but more potent and less difficult to follow treatments are needed.

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

This recommendation for chronotherapy is based only on two level 4 case report studies[82,83] and committee consensus; there are no controlled trials supporting its efficacy or safety. Longer lasting and more practical alternatives are needed given that compliance with the treatment is difficult and lasting benefit has not been demonstrated.

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

This recommendation is supported by one level 1[84] two level 2[85,86] and one level 4[87] studies. Afternoon or evening administration of melatonin shifts circadian rhythms (indicated by dim light melatonin onset [DLMO] and core body temperature minimum, [CBTmin]) to an earlier time. Compared to placebo, melatonin treatment reduced sleep onset latency, but there was no change in total sleep time or subjective daytime alertness. As with other studies involving melatonin, the optimal timing and dosing of melatonin administration are not established. In the reviewed studies, three used 5 mg[84,85,87] while one [86] used two strengths (0.3 mg and 3 mg). Effective times of administration varied between 1.5 and 6 hours prior to the habitual bedtime.

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

This recommendation is based on one level 1[88] multicenter study in which no benefit compared to placebo was noted following administration of vitamin B12 (1 mg) three times a day to 50 subjects for four weeks.

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

This parameter is based on committee consensus. There was only one level 4 report[83] indicating some benefit, but sufficient evidence to support this practice is lacking.

3.2.5 Free-Running Circadian Rhythm Sleep Disorder

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

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

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

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

This parameter is supported by evidence presented in the accompanying review and by committee consensus. There are one level 2[89] and seven level 4 studies[90-96] that have used the melatonin rhythm

as an indicator of phase in sighted individuals. In addition, there are four level 2 studies[97-100] and four level 4 studies[101-104] that have used the timing of melatonin secretion to determine free running rhythms in blind individuals. There is also one level 4 study[105] that used core body temperature measurements to detect free-running rhythms. Multiple measurements of circadian phase over the course of several weeks are suggested for all circadian markers. The ICSD-2 suggests use of sleep logs or actigraphy for more than seven days in order to establish the daily drift of the endogenous rhythm. Since sleep-wake times are influenced by social schedules and requirements, these data may be less compelling than phase markers, which provide a more direct measure of the intrinsic circadian rhythm. This is particularly the case when the diagnosis is suggested by sleep log data or actigraphy, but these data are conflicting or thought unreliable.

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

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

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

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

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

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

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

There are four level 4 case reports[110-113] and five small level 2 studies[98-102] which successfully entrained FRD rhythms in blind individuals using a variety of doses, timing and duration of melatonin treatment. A recent level 4 case report[103] suggests that physiological doses (approximately 0.3 mg) may be more effective than pharmacologic doses (typically >2 mg) for this indication.

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

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

3.2.6 Irregular Sleep-Wake Rhythm

An irregular sleep-wake rhythm (ISWR) is characterized by a relative absence of a circadian pattern to the sleep-wake cycle. Total sleep time is essentially normal, but there are multiple irregular sleep bouts during a 24-hour period. ISWR is commonly associated with neurological impairment, and much of the clinical research in this condition has involved older people with dementia.

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

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

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

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

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

Two studies tested melatonin administration for ISWR in patients with dementia. The first was a large level 1 study[117] which tested administration of 8 weeks of melatonin (10 mg or 2.5 mg,

sustained release formulations) among patients with Alzheimer disease with disturbed sleep patterns that were presumably consistent with an ISWR. The study found no evidence of improvement in sleep (by actigraphy). A second smaller level 1 trial [128] found that slow-release melatonin (6 mg) also had no effect on actigraphically estimated sleep.

Three level 4 studies found some benefit in treating sleep disturbances in severely impaired children with presumed ISWR, including children with severe psychomotor retardation,[129] and neurologically multiply disabled children.[130,131] However, one level 2 study[132] which involved use of melatonin to improve sleep in girls with Rett syndrome and associated mental retardation was negative.

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

Two studies tested mixed modality approaches for sleep disturbance (presumably consistent with ISWR) in older people with dementia. One level 2 study[118] in nursing home residents (the majority with dementia) tested a short (5-day) mixed modality intervention (increased daytime sunlight exposure, increased physical activity, structured bedtime routine, and decreased nighttime noise and light) decreased daytime sleeping. Another level 1 study[116] in community-dwelling dementia patients tested an 8-week mixed modality intervention (combining light exposure, exercise, sleep scheduling, and sleep hygiene) which decreased nighttime awakenings, decreased total wake time, decreased daytime sleepiness and decreased symptoms of depression. A Level 4 study[133] in children with moderate to severe mental retardation who had failed prior medication/behavior treatment for sleep disturbance, combined bright light exposure (for 8 months) with a behavioral program, and found that 5 out of 14 patients responded to treatment with improvement in nocturnal and 24-hour sleep.

4.0 SUMMARY AND FUTURE RESEARCH

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

4.1 Molecular Genetics of CRSD

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

4.2 Jet Lag

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

4.3 Shift Work Disorder

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

4.4 Advanced Sleep Phase Disorder

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

4.5 Delayed Sleep Phase Disorder

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

4.6 Free-Running Disorder

Although appropriately timed bright light exposure and melatonin administration have been shown to be effective, there are few treatment studies of free-running disorder CRSD among sighted individuals because of the rarity of the condition. Appropriately timed melatonin in doses from 0.5 mg to 10 mg have been shown to entrain totally blind people who have FRD. The effective dose may be even less than 0.5 mg (the dose that approximates a physiological plasma concentration). Treatment must be sustained or relapse will occur. Entrainment may not occur for weeks or months after initiating treatment, depending on the phase of the patient's rhythm when treatment is started and the period of the patient's free-running rhythm. There are limited data on the use of hypnotic medications to promote sleep and on stimulant medications to enhance alertness.

4.7 Irregular Sleep-Wake Rhythm Disorder

It is important that future studies of ISWR patients (such as elderly dementia patients) characterize them according to formal sleep diagnostic criteria. This will enable the development of a body of knowledge describing the effectiveness of clinical treatments for patients with specific clinical characteristics. While there have been no studies examining prescribed sleep/wake scheduling per se, some of the mixed modality treatments[116,118] included structuring the sleep/wake schedule as part of their treatment protocols. Although abnormalities in both circadian phase and amplitude may underlie the other CRSDs, diminished circadian amplitude is often hypothesized to be especially important in ISWR. Consequently, numerous studies have attempted to treat inferred ISWR by structuring and reinforcing relevant circadian time cues (*zeitgebers*) in order to increase the amplitude of the circadian cycle. These interventions have included daytime light exposure, melatonin supplementation, and mixed modality treatments, typically combining daytime light exposure with behavioral interventions, such as sleep/wake scheduling and increasing daytime activity. Bright light exposure during the day has had modest effects on the consolidation of sleep and wake in nursing home patients with Alzheimer disease (AD) and associated ISWR. More data are needed to support the effectiveness of this treatment, as well as information regarding the most efficacious timing of light exposure. Current data do not support the use of melatonin for treating ISWR, at least in association with AD. However, the efficacy of smaller doses of melatonin and emerging melatonin receptor agonists has yet to be determined. More research is needed in the area of mixed modality approaches to determine if such treatment approaches might be more efficacious than the use of light alone. There is great need for rigorous, well-controlled clinical trials of hypnotic treatments for sleep disturbance in demented patients to fill a serious and continuing gap in our knowledge. There is also a great need to conduct carefully controlled clinical trials of the efficacy of stimulant medications, such as modafinil in AD patients.

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

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Physical Examination: Mallampati Score as an Independent Predictor of Obstructive Sleep Apnea

Thomas J. Nuckton, MD, MS[1-3]; David V. Glidden, PhD[3]; Warren S. Browner, MD, MPH,[1-3]; David M. Claman, MD[2,4]

[1]The California Pacific Medical Center Research Institute, San Francisco and the [2]Department of Medicine, the [3]Department of Epidemiology and Biostatistics, and the [4]Division of Pulmonary and Critical Medicine and The UCSF Sleep Disorders Center, University of California, San Francisco, CA

Study Objective: To assess the clinical usefulness of the Mallampati score in patients with obstructive sleep apnea. Mallampati scoring of the orophyarynx is a simple noninvasive method used to assess the difficulty of endotracheal intubation, but its clinical usefulness has not been validated in patients with sleep-disordered breathing.

Design: Prospective multivariate assessment of a predictor variable.

Setting: The UCSF Sleep Disorders Center.

Patients or Participants: One hundred thirty-seven adult patients who were evaluated for possible obstructive sleep apnea.

Interventions: Prospective determination of the Mallampati score, assessment of other variables for multivariate analysis, and subsequent overnight polysomnography.

Measurements and Results: The Mallampati score was an independent predictor of both the presence and severity of obstructive sleep apnea. On average, for every 1-point increase in the Mallampati score, the odds of having obstructive sleep apnea (apnea-hypopnea index ≥ 5) increased more than 2-fold (odds ratio [per 1-point increase] = 2.5; 95% confidence interval: 1.2-5.0; p = .01), and the apnea-hypopnea index increased by more than 5 events per hour (coefficient = 5.2; 95% confidence interval: 0.2-10; p = .04). These results were independent of more than 30 variables that reflected airway anatomy, body habitus, symptoms, and medical history.

Conclusions: Our results indicate that Mallampati scoring is a useful part of the physical examination of patients prior to polysomnography. The independent association between Mallampati score and presence and severity of obstructive sleep apnea suggests that this scoring system will have practical value in clinical settings and prospective studies of sleep-disordered breathing.

Keywords: Obstructive sleep apnea, physical diagnosis, performance

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INTRODUCTION

OBSTRUCTIVE SLEEP APNEA (OSA) MAY AFFECT AS MANY AS 1 IN 5 ADULTS AND HAS THE POTENTIAL FOR CAUSING SERIOUS LONG-TERM HEALTH consequences, including cardiovascular disease, hypertension, and stroke and a reduced quality of life.[1-6] Despite years of research into the causes and consequences of OSA, the early identification of patients who are most at risk remains challenging. Airway variables that are associated with OSA have been incorporated into complex models involving detailed physical or radiographic measurements of the face, jaw, and oral cavity[7-10] that are difficult to apply in clinical settings. Terms used to describe the physical examination of the airway, such as "crowded," "narrow," or "low-lying," are frequently imprecise or subject to interpretation. Additionally, most airway characteristics have not been subjected to a multivariate analysis with extensive adjustments for possible confounding variables, a crucial validation process needed prior to widespread clinical utilization.

The Mallampati score, derived from a simple airway-classification system, has been used to identify patients at risk for difficult tracheal intubation for more than 20 years.[11-15] The system is noninvasive and simple to learn, and it requires no special equipment. Prior studies have reported the unadjusted associations between a standard Mallampati score and OSA[16-18] or the associations after controlling for specific variables such as ethnicity, neck circumference, and body mass index.[19] The usefulness of this system, however, has not been validated by a rigorous multivariate analysis, with extensive adjustments for body habitus, symptoms, and medical history. Therefore, in this prospective study, we sought to validate the clinical usefulness of the Mallampati score by examining the association between Mallampati score and OSA, after adjustments for a large number of potentially confounding variables.

METHODS

Patients

Patients of at least 18 years of age referred to the University of California, San Francisco Sleep Disorders Center and evaluated for possible OSA were eligible for the study. These patients represented a convenience sample studied over a 6-month period. Patients who had prior otolarnygologic surgery or radiofrequency procedures, who were consistently using continuous positive airway or bilevel pressure or who required oxygen during polysomnography were excluded.

All measurements, including the Mallampati score, were made prior to polysomnography as part of a routine clinical assessment. Chart review was utilized to obtain the results of polysomnography and to confirm variables. Approval for the study, which included the use of information and the review of clinical notes and medical records, was obtained from the UCSF institutional review board.

Disclosure Statement

This was not an industry supported study. Drs. Nuckton, Glidden, Browner, and Claman have indicated no financial conflicts of interest.

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Address correspondence to: Thomas J. Nuckton, MD, MS, CPMC Research Institute, 2200 Webster Street, Room 518, San Francisco, CA 94115-1821; Tel: (415) 600-1468; Fax: (415) 600-1753; E-mail: nuckton@cpmcri.org

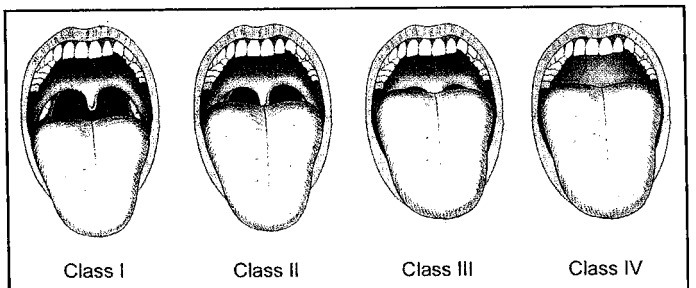

Figure 1—Mallampati Airway Classification (I-IV Scale). During assessment, the patient is instructed to open his or her mouth as wide as possible, while protruding the tongue as far as possible. Patients are instructed to not emit sounds during the assessment. Class I: soft palate and entire uvula visible; Class II: soft palate and portion of uvula visible; Class III: soft palate visible (may include base of uvula); Class IV: soft palate not visible

Measurements

The Mallampati score was obtained during the physical examination of each patient. For all patients, the assessment of scores was done or directly supervised by the same physician. The score was assessed by asking the patient to open his or her mouth as wide as possible, while protruding the tongue as far as possible. The patient was instructed to not emit sounds during the assessment. A standard I to IV grading system was used (Figure 1).[13-15] A modified Mallampati score, obtained without protruding the tongue[20,21] but that is otherwise identical to standard scoring, was also assessed. All patients subsequently underwent either inpatient (SensorMedics; Yorba Linda, CA) or home (Nellcor Puritan Bennett (Edentrace without electroencephalogram; Ottawa, ON) polysomnography. In both types of studies, thermistors were used to quantify airflow. The polysomnogram results were assessed and scored by an experienced sleep polysomnographic technician who was unaware of the study hypothesis.

We also ascertained characteristics similar to those measured in other studies of OSA, as well as others with potential clinical importance.[1-6,9,10,18,20-27] Historical variables included a history of snoring (none, mild, moderate, severe), witnessed apnea (none, some nights, most nights, all nights), gasping episodes or sudden awakening (none, some nights, most nights, all nights), number of daily unintentional dozing episodes (number per day), morning headache (none, some nights, most nights, all nights), and family history of OSA. The Epworth Sleepiness Scale was used to assess subjective sleepiness.[28,29] This score is based on a questionnaire in which patients are asked to rate how likely they are to fall asleep during several situations. Scores range from 0 to 24, and higher scores indicate a higher propensity toward daytime sleepiness.

Medical history variables included medically treated hypertension, diabetes, hypothyroidism, gastroesophageal reflux, sinusitis or rhinitis, cerebrovascular accident, dementia, Parkinson disease, obstructive lung disease, coronary artery disease, congestive heart failure, dysrhythmia, depression, antidepressant use, HIV status, tobacco use (current use and total pack-years), alcohol consumption (drinks per day), and prior alcohol abuse. Other measurements included neck circumference (cm), body mass index (kg/m^2), tonsil size (0-IV),[20,21] and degree of overjet (mm).

The primary outcome variables were OSA and the apnea-hypopnea index (AHI), as determined by polysomnography. OSA was defined as an AHI of 5 or greater.[1,30] The AHI refers to the total number of episodes of either cessation (apnea) or decrease in airflow (hypopnea) per hour.[30] Apnea was determined by a cessation of airflow for 10 or more seconds; hypopnea was determined by a decrease in airflow combined with a 4% or greater decrease in oxygen saturation.

Statistical Analysis

Multiple logistic regression was used to identify the variables that were independently associated with the presence of OSA. Each variable with a significant association ($p < .05$) by bivariate regression was included in a multiple-variable regression model. The area under a receiver- operator curve was calculated for each significant bivariate logistic regression variable, and likelihood ratios were calculated for each Mallampati score.

Only 1 patient had Parkinson disease, and only 1 patient had dementia; neither had OSA, and these variables were not included in the final analysis. The goodness of fit of the logistic regression model was assessed with the Hosmer-Lemeshow test[31] and a receiver-operator curve for the multivariable model was generated. Multiple linear regression was used to identify the variables that were independently associated with the AHI on a continuous scale. Pearson product-moment and Spearman rank correlations, and χ^2 tests were used to examine the relationships between variables. Because Mallampati scoring was done or supervised by the same physician for all patients, interrater reliability was not assessed.

Several alternative analyses were done. The modified version of the Mallampati score, (without protrusion of the tongue) and a version of the Mallampati system that was scored on a scale of I to III instead of I to IV (categories III and IV combined into a single category) were substituted for the standard Mallampati score in multivariate logistic-regression models. Finally, we modeled the associations of both Mallampati score and neck circumference, with alternate definitions of OSA (AHI $\geq$ 10, $\geq$ 15, and $\geq$ 20). STATA computer software (Version 9.1; College Station, TX) was used for the analyses.

RESULTS

We studied 137 patients with suspected OSA and who had been referred to the University of California Sleep Disorders Center (Table 1). Overall, 80 (58%) of 137 patients had OSA as defined by an AHI of 5 or greater. The AHI for all patients ranged from 0 to 126, with a mean ± SD of 18.1 ± 24.6.

Several variables were associated with an increased risk of OSA (Table 2). The proportion of patients with OSA, the likelihood ratios for OSA, and the AHI as measured on a continuous scale, all increased with greater Mallampati scores (Figure 2). OSA was present in 4 of 12 patients with Mallampati Class I (likelihood ratio = 0.4), 24 of 50 patients with Mallampati Class II (likelihood ratio = 0.7), 45 of 65 patients with Mallampati Class III (likelihood ratio = 1.6), and 7 of 10 patients with Mallampati Class IV (likelihood ratio = 1.7).

In a multivariate model, Mallampati score was independently associated with an increased risk of OSA (Table 3). For every 1-point increase in the Mallampati score, the odds of having OSA increased by more than 2-fold (odds ratio [per 1-point increase] = 2.5; 95% confidence interval: 1.2, 5.0; $p = .01$). The Hosmer-Lemeshow test indicated that the fit of the multiple logistic regression model was good ($p = .34$), and the area under the receiver-operator curve for the model was 0.86. Neck circumference,

Table 1—Clinical Characteristics of 137 Patients Assessed for Possible Obstructive Sleep Apnea[a]

Characteristic	Results
Age, y	46 ± 12
Men, %	99 (72)
Mallampati score[b]	
Mean	2.5 ± 0.8
Class I	12 (9)
Class II	50 (36)
Class III	65 (47)
Class IV	10 (7)
Body mass index, kg/m^2	31.3 ± 6.9
Neck circumference, cm	40.9 ± 3.6
Overjet, mm	3.6 ± 2.3
ESS score (0-24)[c]	10.4 ± 5.2
History of snoring	129 (94)
History of witnessed apnea	85 (63)
History of gasping/sudden awakening	55 (40)
History of unintentional dozing	42 (31)
Medical history	
Hypertension	29 (21)
Sinusitis/Rhinitis	25 (18)
Depression	35 (26)
Hypothyroidism	12 (9)
Gastroesophageal reflux	10 (7)
Diabetes mellitus	10 (7)
Cerebrovascular accident	4 (3)
Cardiac disease[d]	11 (8)
Obstructive lung disease	22 (16)
Parkinson disease	1 (<1)
Dementia	1 (<1)
HIV positive	7 (5)

[a]Data are presented as mean ± SD or number (percentage); data are missing for neck circumference in 3 patients, for Epworth Sleepiness Scale (ESS) score in 1 patient, and for witnessed apnea in 1 patient. Ninety-four patients (69%) were assessed by inpatient polysomnography; the others were assessed by home polysomnography.
[b]Standard Mallampati score assessed with tongue protruded. A modified Mallampati score (assessed without tongue protruded) was also obtained (Class I: n = 7 [5%]; Class II: n = 32 [23%]; Class III: n = 84 [61%]; Class IV: n = 14 [10%]).
[c]The ESS score is based on a questionnaire in which patients are asked to rate how likely they are to fall asleep during several situations. Scores range from 0-24; higher scores indicate a greater propensity toward daytime sleepiness.
[d]Cardiac disease includes coronary artery disease, heart failure, and dysrhythmia.

witnessed apnea, and hypertension were the only other variables that were independently associated with an increased risk of OSA (Table 3).

The substitution of a modified Mallampati score, in which the tongue was not protruded, yielded similar results (odds ratio [per 1-point increase] = 2.1; 95% confidence interval: 1.0, 4.3; p = .04). The Mallampati scale of I to III was also independently predictive (odds ratio [per 1-point increase] = 2.8; 95% confidence interval: 1.3, 6.0; p = .01). Finally, in models that also included neck circumference, Mallampati score was predictive of OSA defined by an AHI ≥ 10 (odds ratio [per 1-point increase] = 1.8; 95% confidence interval: 1.0, 3.1; p = .04), an AHI ≥ 15 (odds ratio [per 1-point increase] =1.8; 95% confidence interval: 1.0, 3.1; p = .04), and an AHI ≥ 20 (odds ratio [per 1-point increase] =2.1; 95% confidence interval: 1.1, 3.8; p = .02) (Table 4).

Table 2—Variables Associated with an Increased Risk of Obstructive Sleep Apnea[a]

Variable (95% CI)	Odds Ratio	p value	Area under ROC curve
Mallampati Score (I-IV), per 1-point increase	2.0 (1.2, 3.2)	< .01	0.63
Age, per 10-y increase	1.5 (1.1, 2.0)	.01	0.65
Male Sex	2.2 (1.0, 4.6)	.05	0.58
Body mass index, per 5-kg/m^2 increase	1.5 (1.1, 1.9)	.01	0.65
Neck circumference, per 2.5-cm increase	2.0 (1.4, 2.7)	< .01	0.73
ESS score, per 5-point increase	1.4 (1.0, 2.0)	.04	0.60
Dozing episodes, per episode/day increase	1.9 (1.1, 3.4)	.02	0.61
Witnessed apnea[b] episode/day increase	1.8 (1.3, 2.6)	< .01	0.67
Gasping/sudden awakening[b]	1.6 (1.0, 2.5)	.04	0.60
Hypertension	3.4 (1.3, 9.1)	.01	0.59

[a]Unadjusted (bivariate) associations. Having obstructive sleep apnea was defined as having an apnea-hypopnea index ≥5. CI refers to confidence interval; ROC, receiver-operator curve; ESS, The Epworth Sleepiness Scale score, based on a questionnaire in which patients are asked to rate how likely they are to fall asleep during several situations (scores range from 0-24; higher scores indicate a greater propensity toward daytime sleepiness).
[b]Categories included none, some nights, most nights, all nights.

The Mallampati score was also associated with the AHI on a continuous scale (Table 5). For every 1-point increase in Mallampati score, the AHI increased by more than 9 events per hour in the bivariate analysis and by more than 5 events per hour in the multivariate analysis. Age, neck circumference, and severity of witnessed apnea were also independently associated with the AHI (Table 5).

There were no significant associations between Mallampati score and either body mass index (p = .2), tonsil size (p = .3), use of home polysomnography (p = .7), or patient age (p = .9); there were significant but modest associations between Mallampati score and neck circumference (r = 0 .19; p = .03) and Mallampati score and degree of overjet (r = 0 .21; p = .01).

DISCUSSION

We were able to validate the clinical usefulness of the Mallampati score in patients with OSA. This scoring system, which is noninvasive and can be rapidly mastered and assessed in seconds, was associated with both the presence and severity of OSA. On average, for every 1-point increase in Mallampati score, the odds of having OSA increased more than 2-fold and the AHI increased by more than 5 events per hour. Moreover, these associations were independent of all other variables that we measured, including history of snoring, overjet, tonsil size, neck circumference, and body mass index.

The Mallampati score is used by anesthesiologists to assess the difficulty of endotracheal intubation. Presumably, the angle between the base of the tongue and larynx determines, at least par-

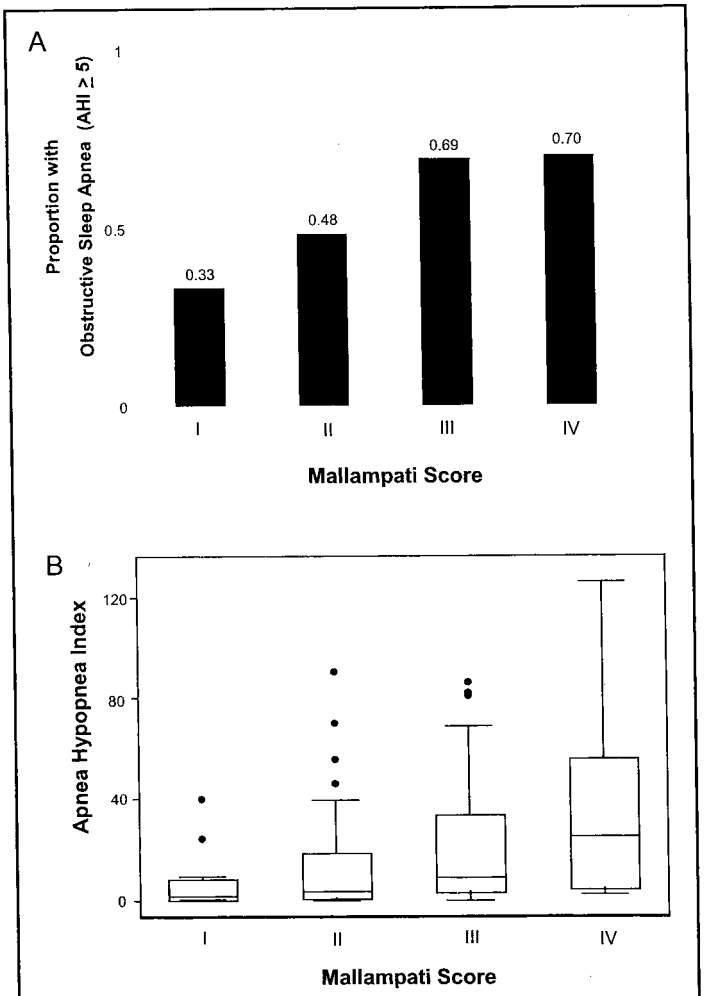

Figure 2—Relationship Between Mallampati Score (I-IV Scale) and Obstructive Sleep Apnea. A. The Mallampati Score (I-IV Scale) vs the proportion of patients with obstructive sleep apnea (OSA) (apnea hypopnea index [AHI] ≥ 5). OSA present in 4 of 12 patients with Class I (likelihood ratio =0.4), 24 of 50 patients with Class II (likelihood ratio =0.7), 45 of 65 patients with Class III (likelihood ratio =1.6), and 7 of 10 patients with Class IV (likelihood ratio =1.7). B. The Mallampati Score (I-IV Scale) vs AHI on a continuous scale. AHI values ranged from 0-126. Standard box plot for each Mallampati score, in which the line in the middle of the box represents the median, the box extends from the 25th percentile to the 75th percentile (interquartile range), the whiskers extend to the upper and lower adjacent values (defined by a maximum of 1.5 × the interquartile range), and points represent outliers.

tially, the accessibility of the larynx; by inference, when the base of the tongue is disproportionately large, or the oropharyngeal cavity is disproportionately small, the tongue masks the visibility of the faucial pillars and uvula.[11,12] These factors could also apply to the risk of OSA. Indeed, an association between difficulty of tracheal intubation and OSA has been reported.[16] Other variables, including neck circumference, witnessed apnea, and medically treated hypertension, were also associated with OSA, consistent with prior reports.[2,6,23,26]

The original Mallampati score was based on a scale of I to III,[11,12] but, over time, has evolved into the I to IV scoring system[13-15] used commonly by anesthesiologists today. In our study, the proportions of patients with OSA were similar in those with a Mallampati score of III or IV. However, the average AHI was higher in patients with a Mallampati score of IV, and, in our regression models, both the AHI and the odds of having OSA increased as Mallampati score increased. The Mallampati score can also be assessed without protrusion of the tongue. Two studies have reported unadjusted associations between OSA and this modified version of the score,[20,21] which is perhaps more reflective of obstruction caused by the tongue during sleep.Regardless, all of these versions were independently predictive of the presence of OSA in our study.

Table 3—Variables Independently Associated With an Increased Risk of Obstructive Sleep Apnea[a]

Variable	Odds Ratio (95% CI)	p value
Mallampati score, (I-IV) (per 1-point increase)	2.5 (1.2, 5.0)	.01
Neck circumference, (per 2.5-cm increase)	1.9 (1.0, 3.5)	.04
Witnessed apnea[b]	1.9 (1.2, 3.1)	< .01
Hypertension	4.9 (1.2, 20)	.03

[a]Results from multivariable analysis (all variables from Table 2 included). Having obstructive sleep apnea was defined as having an apnea-hypopnea index ≥5. CI refers to confidence interval; ROC, receiver-operator curve.
[b]Categories included none, some nights, most nights, all nights.

Table 4—Associations Between Mallampati Score[a], per 1-Point Increase, and Alternate Apnea-Hypopnea Index Cutoffs

AHI	Odds Ratio (95% CI)	p value
≥ 10	1.8 (1.0, 3.1)	.04
≥ 15	1.8 (1.0, 3.1)	.04
≥ 20	2.1 (1.1, 3.8)	.02

[a]Results from limited multivariable analysis (Mallampati score [I-IV], neck circumference, and each apnea-hypopnea index [AHI] cutoff). CI refers to confidence interval.

All patients in our study had been referred for evaluation. Thus, clinicians presumably had some suspicion of having OSA or sleep-disordered breathing prior to referral. Mallampati scoring may not be as useful among patients with a lower probability of having OSA. Because Mallampati scoring was done or supervised by a single physician, interrater reliability was not assessed. We did not assess ethnicity in our study, although a previous study has suggested that Mallampati score may have utility in Asian patients.[19] Odds ratios in our study were not equivalent to risk ratios because the outcome was common, and the likelihood ratios for each Mallampati score were modest, as occurs with the physical examination techniques for a variety of medical problems.[32-36] For these reasons, we remain cautious about the use of the Mallampati score as a simple diagnostic test.

However, given the great simplicity of Mallampati scoring, and the independent nature of the relationship between the Mallampati score and OSA, this score has potential value for facilitating and standardizing communication among clinicians who care for patients with OSA. Mallampati scoring could also be used to prioritize patients for polysomnography, an important consideration given the large backlog of patients awaiting assessment for OSA.[37-40]

Mallampati scoring may have value when used in clinical trials because surgical or other treatment benefits could vary by Mallampati score. Such scoring may facilitate more consistent

Table 5—Variables Associated with the Apnea-Hypopnea Index (Continuous Scale)

Variable	Bivariate		Mulitvariate	
	Coefficient[a] (95%CI†)	P value	Coefficient[a] (95%CI†)	P value
Mallampati score	9.3 (4.0, 15)	< .01	5.2 (0.2, 10)	.04
Age, y	0.4 (0.0, 0.7)	.03	0.3 (0.04, 0.6)	.03
Body mass index, kg/m^2	1.1 (0.5, 1.7)	< .01	0.3(-0.3, 0.9)	.4
Neck circumference, cm	3.0 (1.9, 4.1)	< .01	1.9 (0.7, 3.1)	< .01
Dozing episodes, no./day	6.2 (1.1, 11)	.02	3.6 (-1.0, 8.3)	.1
Witnessed apnea[b]	7.9 (4.4, 11)	<.01	4.2 (0.6, 7.8)	.02
Gasping/ sudden awakening[b]	8.1 (3.4, 13)	<.01	3.2 (-1.4, 7.9)	.2
Snoring[c]	7.0 (2.4, 12)	<.01	3.5 (-1.0, 8.0)	.1

[a]For every 1-point increase in each variable (units designated in parentheses), the apnea-hypopnea index (events/h) increases by the amount of the coefficient. CI refers to confidence interval.
[b]Categories included none, some nights, most nights, all nights.
[c]Categories included none, mild, moderate, severe.

applications of treatments and improve stratification during the analysis of trial outcomes, with little or no increase in trial cost or complexity.

In summary, our results indicate that the Mallampati score, while having limitations as a diagnostic test, is a useful part of the physical examination of patients prior to polysomnography. The independent association between Mallampati score and the presence and severity of OSA suggests that this scoring system will have practical value in clinical settings and in prospective studies of sleep-disordered breathing.

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A Compromise Circadian Phase Position for Permanent Night Work Improves Mood, Fatigue, and Performance

Mark R. Smith, PhD, RPSGT; Louis F. Fogg, PhD; Charmane I. Eastman, PhD

Biological Rhythms Research Laboratory, Department of Behavioral Science, Rush University Medical Center, Chicago, IL

Study Objective: To assess night shift improvements in mood, fatigue, and performance when the misalignment between circadian rhythms and a night shift, day sleep schedule is reduced.

Design: Blocks of simulated night shifts alternated with days off. Experimental subjects had interventions to delay their circadian clocks to partially align with a night shift schedule. Control subjects had no interventions. Subjects were categorized according to the degree of circadian realignment independent of whether they were in the experimental or control groups. Twelve subjects were categorized as not re-entrained, 21 as partially re-entrained, and 6 as completely re-entrained.

Setting: Home sleep and laboratory night shifts.

Participants: Young healthy adults.

Interventions: Experimental subjects had intermittent bright light pulses during night shifts, wore dark sunglasses outside, and had scheduled sleep episodes in darkness.

Measurements and Results: A computerized test battery was administered every 2 hours during day and night shifts. After about one week on the night shift schedule, which included a weekend off, the partially and completely re-entrained groups had markedly improved mood, fatigue, and performance compared to the group that was not re-entrained. The completely and partially re-entrained groups were similar to each other and had levels of mood, fatigue, and performance that were close to daytime levels.

Conclusions: Partial re-entrainment to a permanent night shift schedule, which can be produced by feasible, inexpensive interventions, is associated with greatly reduced impairments during night shifts.

Keywords: Shift work, performance, alertness, mood, human, circadian rhythms, bright light, melatonin

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ALERTNESS AND PERFORMANCE DURING NIGHT WORK CAN BE SERIOUSLY IMPAIRED.[1,2] THIS OCCURS BECAUSE THE MASTER CIRCADIAN CLOCK OF MOST night workers, which controls the body's circadian rhythms (e.g., alertness, temperature, melatonin), does not shift to realign with a night work, day sleep schedule.[3] A sharp increase in sleepiness and decrease in performance occurs around the minimum of the circadian rhythm of body temperature (Tmin), which is usually during the night shift.[4,5] Even with adequate daytime sleep, night shift decrements remain if the circadian clock is not shifted (e.g., Sharkey et al.[6]). Consequently, night work is associated with safety risks for both the individual worker as well as society.[1,2]

Alertness and performance during night shifts can be improved by stimulants such as caffeine[7] and modafinil.[8,9] Bright light exposure during night shifts can also improve alertness via its direct alerting effect.[10] Short naps may also be useful for reducing the decrements in night shift alertness.[7] However, none of these interventions can overcome the nadir in the circadian rhythm of alertness.[7,11] These countermeasures do not address the underlying cause of the problem, which is misalignment between circadian rhythms and the sleep and work schedule.

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Address correspondence to: Charmane I. Eastman, PhD, Biological Rhythms Research Laboratory, 1645 W. Jackson Blvd, Suite 425, Chicago, IL 60612; E-mail: ceastman@rush.edu

Laboratory and field studies of night work have shown that scheduled exposure to bright light and darkness (sleep) can be used to shift the circadian clock to completely align with a night work, day sleep schedule.[12-16] Complete re-entrainment greatly improves alertness and performance during night shifts.[12,17] Despite the appeal of complete re-entrainment from an alertness and safety perspective, few night workers are likely to adopt it because the slowness with which the circadian clock adjusts precludes shifting back to a diurnal schedule on days off. We have thus assessed the feasibility of a compromise sleep schedule combined with interventions to delay the circadian clock to only partially entrain to the night work, day sleep schedule. The goal of partial re-entrainment is to delay the sleepiest circadian time out of the night work period, into the first portion of the daytime sleep episodes after work, as well as to maintain it near the end of late nighttime sleep episodes on days off. When a compromise phase position is maintained throughout alternations between night shifts and days off, it is conducive of afternoon and evening alertness on days off, as well as alertness during night shifts.

In a series of 4 studies with alternating blocks of night shifts and days off,[18-21] we defined the target compromise circadian phase position as a dim light melatonin onset (DLMO) of 3:00. At this phase, the Tmin, an estimate of the sleepiest circadian time, which occurs about 7 h after the DLMO,[22-24] will fall at ~10:00. The sleepiest circadian time would thus be early in the daytime sleep episodes after night work (daytime sleep started at 8:30) and late in the sleep episodes on days off (sleep started at 3:00). The last 2 studies of this series showed that scheduled exposure to bright light and darkness (sleep) delayed the circa-

Table 1—Subject Demographics

	n	M:F	Age (Mean ± SD)	M/E[a] (Mean ± SD)
Not Re-Entrained	12	5:7	28.1 ± 1.7	53.3 ± 5.1
Partially Re-Entrained	21	9:12	24.0 ± 1.1	54.5 ± 1.6
Completely Re-Entrained	6	2:4	25.2 ± 2.7	54.7 ± 4.5

[a]Morningness-Eveningness score[25]

dian rhythms of most of the subjects to a point near the compromise phase position after two blocks of night shifts separated by an intervening weekend off.[20,21] Here we present mood, fatigue, and performance data from these 2 studies. Our primary objective was to compare mood, fatigue, and performance for subjects who were completely, partially, or not re-entrained to the night work, day sleep schedule. We hypothesized that subjects who achieved partial re-entrainment (circadian phase close to the target compromise phase position) would show improvements during the night shifts relative to subjects that were not re-entrained, and would be similar to those who achieved complete re-entrainment to the night work, day sleep schedule. A secondary objective was to compare mood, fatigue, and performance measured during night shifts to daytime levels. We hypothesized that subjects achieving either partial or complete re-entrainment would rate themselves and perform at close to daytime levels, while not re-entrained subjects would show more night shift impairment, relative to daytime levels.

METHODS & DESIGN

The last 2 studies in this series were named #3[20] and #4[21] in their titles. For clarity, here we refer to them as studies A[20] and B,[21] respectively. Each was a between-subjects design with a control and experimental group. In all groups there were large individual differences in the final circadian phase position at the end of the series of night shifts and days off. The present analyses pool data from these 2 studies and are based on final circadian phase position independent of group assignment (experimental or control) or study. Subjects were divided into 3 groups (not re-entrained, partially re-entrained, completely re-entrained), as explained below.

Subjects

Twenty-four subjects completed study A, and 19 subjects completed study B. Four subjects completed both studies, and the data for these subjects' participation was included only once, leaving 39 subjects in the analyses. The decision of which data to include for these 4 subjects was made by the corresponding author before data analyses began on the basis of the final DLMO for each subject, in an attempt to make the sample sizes of the 3 groups more similar. The age, sex, and morningness-eveningness score[25] for the 3 groups were similar (Table 1). Subjects had a BMI < 30 kg/m^2, were nonsmokers, habitually drank < 300 mg caffeine/day, and did not take prescription medication, except for 9 female subjects who used hormonal contraceptives. A urine toxicology screen when beginning the study verified that subjects did not use recreational drugs. In the month preceding the study, subjects had not worked night shifts or crossed more than 3 time zones. These studies were approved by the Rush University Medical Center Institutional Review Board. All subjects provided written informed consent.

Baseline Sleep and Morning Light Schedule

During a 15 day baseline period, all subjects maintained a regular sleep/wake schedule. Subjects remained in bed from 23:00-7:00 on weeknights, while on weekends bedtime was between 23:00-00:00, with wake time between 7:00-8:00. Subjects were required to go outside for ≥ 15 minutes of light exposure every day between 8:00-9:00. A baseline circadian phase assessment (described below) was conducted on days 15-16. After this phase assessment subjects returned to the baseline schedule of sleep/wake and light exposure for an additional 6 days before coming to the lab for the first night shift.

STUDY INTERVENTIONS

Beginning on study day 23, subjects came to the lab for a series of night shifts (23:00 to 07:00). Subjects in study A underwent 3 night shifts, 2 days off, and 4 more night shifts (Figure 1). Subjects in study B underwent 3 night shifts, 2 days off, 5 more night shifts, and 2 more days off. On each night shift the experimental subjects were exposed to 15-min intermittent bright light pulses from light boxes containing fluorescent lamps (5095K, Sun Ray, Sun Box Company, Inc), timed to delay circadian rhythms. In study A, the experimental group received 5 light pulses. The first pulse began at 00:45 and the last pulse ended at 5:00. In study B, the experimental group received 4 light pulses. The first pulse began at 00:45 and the last pulse ended at 4:00. The light pulse from 4:45 to 5:00 during each night shift in study B was omitted because the final phase assessment in study A showed that some experimental subjects delayed slightly more than desired, into the complete re-entrainment category. At a typical distance and angle of gaze, the illuminance of the bright light pulses was ~ 4100 lux, the irradiance was ~ 1200 μW/cm^2, and the photon density was ~ 3.1 x 10^{15} photons/cm^2/second. Light pulses were separated by 45 minutes of room light (< 50 Lux, 4100K). Subjects in the control groups remained in this room light throughout the night shifts.

Experimental subjects were required to remain in bed during scheduled times after night shifts and on weekends off (black bars in top panel of Figure 1). Scheduled sleep was from 8:30 to 15:30 on days 23-24 and 28-31, from 8:30-13:30 after the last night shift before a weekend off (days 25 and 32), and from 3:00-12:00 on days off (days 26, 27, 33, 34). Experimental subjects were required to go outside for ≥ 15 minutes of light exposure within the first 2 h after awakening starting on day 23. The purpose of this "light brake" was to keep their circadian clocks from delaying past the target compromise phase position. Sleep and light exposure for control subjects were unrestricted.

Subjects wore sunglasses at all times when outside during daylight hours. Control subjects wore light sunglasses (ranging from 0% transmission at 400 nm to about 55% at 650 nm). Experimental subjects wore darker sunglasses (ranging from 0% at 400 nm to about 25% at 650 nm) that more strongly attenuated short wavelength light. The spectral transmission of both lenses have been published.[18] The primary purpose of the sunglasses was to attenuate phase-advancing outdoor light exposure during the travel home time after night shifts for the experimental groups.

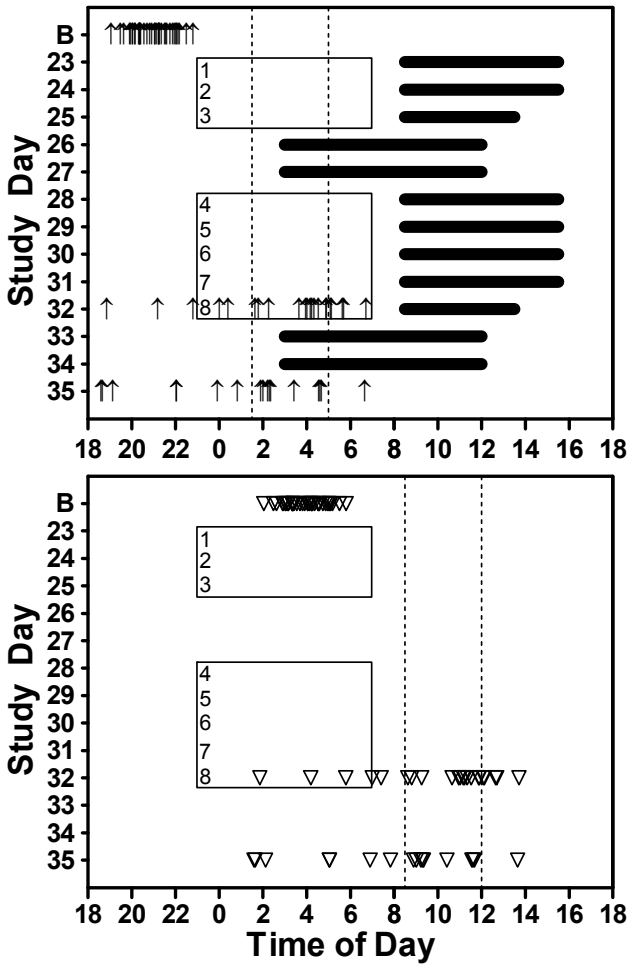

Figure 1—Night shifts from 23:00-7:00 (rectangles) are numbered (1-8). Dark horizontal lines in the top panel indicate scheduled sleep episodes for the experimental groups. Sleep episodes for the control groups were self-selected. Arrows show the times of the dim light melatonin onset (DLMO, top panel) and triangles show the estimated sleepiest circadian times (DLMO + 7 h, bottom panel) for individual subjects during the baseline phase assessment (B) and during the final phase assessment for study A (day 32) and study B (day 35). Subjects were assigned to one of 3 re-entrainment categories based on the time of their final DLMO, and was independent of whether they were in an experimental or control group. Dashed vertical lines in the top panel indicate the criteria used to define the 3 re-entrainment groups, while in the bottom panel 7 h was added to these DLMO criteria to facilitate visualization of the sleepiest circadian time. Subjects with a final DLMO earlier than 1:30 were classified as not re-entrained, with a final DLMO between 1:30 and 5:00 as partially re-entrained, and with a final DLMO later than 5:00 as completely re-entrained. Note that the triangles falling in the left-most category (not re-entrained) correspond to the time of the night shifts or commute home. The triangles falling in between the 2 vertical lines (the partially re-entrained category) correspond to times of sleep for experimental subjects on both work days and on days off.

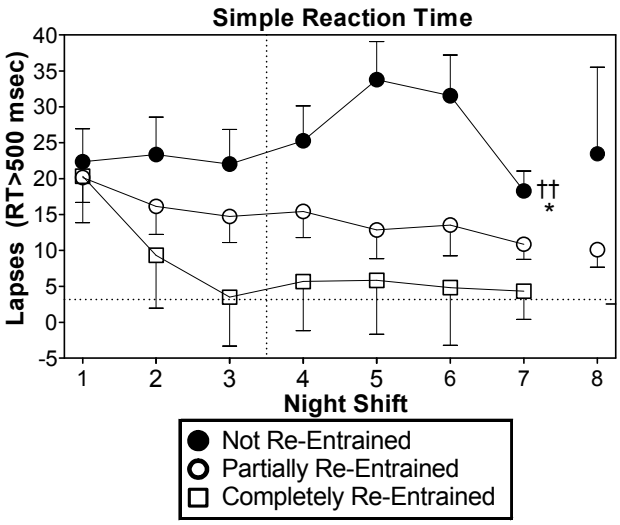

Figure 2—Lapses (reaction time > 500 milliseconds) during the 6:30 test bout of the simple reaction time task. The vertical line between night shifts 3 and 4 indicates that these shifts were separated by 2 days off. Scores are difference-from-baseline. The dotted horizontal lines indicate the baseline mean for all subjects. Symbols denoting statistical significance next to night shift 7 indicate a main effect of group during night shifts 1-7. †† indicates a difference ($P < 0.01$) between the not re-entrained and completely re-entrained groups. * indicates a difference ($P < 0.05$) between the not re-entrained and partially re-entrained groups. The tick mark on the right y-axis indicates average baseline scores during the last test bout at the end of the day shifts (16:30). Error bars show SEM. The other ANAM tasks showed a similar progression across night shifts.

Circadian Phase Assessments

Detailed procedures for the phase assessments have been previously described.[18] For both studies, the baseline phase assessment lasted from 15:30 on day 15 until 12:00 on day 16. In study A, a final 24-h phase assessment began at 18:00 on day 32. In study B, the final phase assessment began after the second weekend off, at 18:00 on day 35. During phase assessments saliva was sampled every 30 min under dim light (< 5 lux) using a salivette (Sarstedt, Newton, NC, USA). Samples were frozen and shipped on dry ice to Pharmasan Labs (Osceola, WI), where they were radioimmunoassayed for melatonin. The sensitivity of the assay was 0.7 pg/mL. The intra-assay variability was 12.1%, and the inter-assay variability was 13.2%.

Mood, Fatigue, and Performance Testing

A test battery was administered on desktop computers 4 times during three day shifts (days 17, 18, and 21) and each night shift. During day shifts, the test battery was administered beginning at 10:05, 12:05, 14:05, and 16:05. During night shifts, it was administered beginning at 00:05, 2:05, 4:05, and 6:05 [see Figure 2 in Smith et al.[19]]. In our results we report data at 00:30, 2:30, 4:30, and 6:30 because the test battery lasted ~ 25 minutes. As part of each test battery, subjects completed the Profile of Mood States (POMS),[26] three 10-point scales assessing tiredness and mental and physical exhaustion, and the Automated Neuropsychological Assessment Metrics (ANAM).[27] For the POMS, data for the fatigue-inertia subscale and total mood disturbance were analyzed. Endpoints of the scales assessing tiredness and exhaustion were (1) "fresh as a daisy" versus "tired to death," (2) "physically exhausted" versus "energetic," and (3) "mentally exhausted" versus "sharp."

The ANAM tasks included simple reaction time, procedural reaction time, mathematical processing, delayed matching to sample, code substitution, and the Stanford Sleepiness

Scale.[28] The simple reaction time task is similar to the psychomotor vigilance task (PVT).[29] In the ANAM version, an asterisk appeared in the middle of the computer screen at variable intervals, and the subjects pressed the left mouse button which recorded reaction time (RT). Lapses were defined as RT > 500 msec. The procedural reaction time task assessed processing efficiency and reaction time when following a defined set of mapping rules. The basic block version of this test was administered. In it a single digit number between 2 and 5 was displayed within a box on the screen. Subjects indicated whether the number was 2 or 3 (left mouse click), or 4 or 5 (right mouse click). The mathematical processing task measured computational skills and working memory. This task entailed adding and subtracting 3 digits between 1 and 9, and indicating whether the answer was greater than 5 (right mouse click) or less than 5 (left mouse click). The delayed matching to sample task measured visuospatial working memory and spatial processing. Subjects viewed a sample pattern produced by a 4 × 4 grid of light and dark squares. After a 5-sec delay in which the screen was blank, 2 comparison grids were displayed side by side on the screen, and the subject indicated which of the 2 grids matched the previously shown grid (left or right mouse click). The code substitution task measured sustained attention and visual search capacity and is similar to the Digit Symbol Substitution Test (DSST).[30] Subjects viewed a "key" across the top of the screen pairing 9 digits with 9 symbols. A single digit-symbol pair was presented at the bottom of the screen and the subject indicated whether the pair matched (left mouse click) or didn't match (right mouse click) the pair in the key above. Subjects received immediate feedback after each response for incorrect responses on the code substitution task. Further details on these tests,[31] including their use in clinical[32] and non-clinical populations,[33] as well their construct validation,[34] have been published.

For the last 4 ANAM tests described above, the percent correct, median reaction time (RT), and the number of slow responses for correct answers were analyzed. Slow responses are akin to lapses, but were defined as responses which exceeded the 90th percentile of the cumulative distribution of each subject's daytime responses. The threshold for slow responses is thus based on each individual's baseline performance, rather than applying an arbitrary threshold to define a lapse in all subjects on tasks for which a commonly accepted lapse threshold has not been established. This method has been used in previous simulated night shift studies.[35,36]

Technical difficulties with data retrieval rendered the Stanford Sleepiness Scale data unavailable.

Additional Procedures

Subjects completed daily event logs to record consumption of caffeine, alcohol, and over-the-counter medication. During the baseline portion of the study ≤ 2 alcoholic drinks per day were allowed. Alcohol was prohibited the day before a night shift and in the 24 h prior to and during each phase assessment. Caffeine (≤ 300mg) was permitted before 17:00 on baseline days, but was prohibited during both day and night shifts and in the 6 h before and during both phase assessments. On daily sleep logs subjects recorded bedtime, sleep onset, wake time, and nighttime awakenings > 5 min.

Data Analysis

Circadian Phase

A locally weighted least squares (LOWESS) curve was fit to each melatonin profile (GraphPad Prism). To determine the DLMO, a threshold was calculated by taking the average of the 5 lowest consecutive raw data points plus 15% of the average of the 5 highest consecutive raw data points.[20,21] The DLMO was the time the fitted curve exceeded and remained above the threshold.

Subjects were divided into 3 groups according to their DLMO at the time of the final phase assessments (Figure 1). The classification for these groups was the same as in our previous study,[17] and was based on where the sleepiest circadian time would occur relative to the night work periods and the day sleep episodes. We estimate the sleepiest circadian time as being near the Tmin, which occurs ~ 7 h after the DLMO.[22-24] Subjects that had a final DLMO earlier than 1:30 were classified as not re-entrained (n = 12; 2 experimental and 10 control subjects). This means their sleepiest circadian time (DLMO + 7 h) was earlier than 8:30, and likely occurred either during the night work period or the commute home. Subjects that had a final DLMO between 1:30–5:00 were classified as partially re-entrained (n = 21; 12 experimental and 9 control subjects). For experimental subjects this put the estimated sleepiest circadian time in the first half of daytime sleep and into the end of the sleep episode on days off. Subjects that had a final DLMO later than 5:00 were classified as completely re-entrained (n = 6; all experimental subjects). For experimental subjects, this put the sleepiest circadian time in the second half of the daytime sleep episodes after night shifts.

Mood, Fatigue, and Performance Testing

To account for large individual differences during day shifts (baseline), all data were transformed into difference-from-baseline scores. The data from the first day shift was excluded as practice. Scores on the second and third day shifts were averaged to form a baseline value. This baseline value was subtracted from scores on each night shift test bout to obtain difference-from-baseline scores.

Improvements in mood, fatigue, and performance were expected to occur when subjects' circadian clocks had delayed far enough so that the sleepiest circadian time moved out of the night work period and commute time home (i.e. partial or complete re-entrainment). Based on the final DLMOs from the entire series of studies,[18-21] we estimate that for most experimental subjects this occurred in the middle of the second block of night shifts (see Figure 1). We thus focused our analyses on night shifts 5–8. All subjects participated in night shifts 5–7, and the scores for these night shifts were averaged for each of the 4 test bouts. Group sizes for the night 5–7 analyses are shown in Table 1. Only subjects in study B participated in night shift 8, so the results for this night are presented separately. There were 17 subjects in study B, and only 1 fell into the completely re-entrained group, so this group was not included, leaving 2 groups and 16 subjects (9 partially re-entrained, 7 not re-entrained) for night 8 analyses.

A repeated measures ANOVA was used to analyze each dependent variable. For the average of nights 5–7, the between subjects factor of group had 3 levels (not re-entrained, par-

tially re-entrained, completely re-entrained), and the within subjects factor of time-of-night had 4 levels (00:30, 2:30, 4:60, and 6:30 test bouts). For night 8, the between subjects factor had only 2 levels (not re-entrained and partially re-entrained). Significant main effects of group were followed by least significant difference post hoc tests, and significant group × time-of-night interactions were elucidated with simple main effects.[37]

Where the data was skewed, statistics were performed on data that was transformed using the formula $(x+c)^{y}$, where c was a constant added to all difference-from-baseline scores so that they were positive numbers, and y was a decimal that normalized the distribution. However, all figures depict the untransformed data to facilitate its interpretation.

Data for one dependent variable had an outlier that was excluded. For one subject, data on the mathematical processing task on nights 5–7 was excluded because this subject's median RT during the 6:30 test bout was 5 SDs above the group mean.

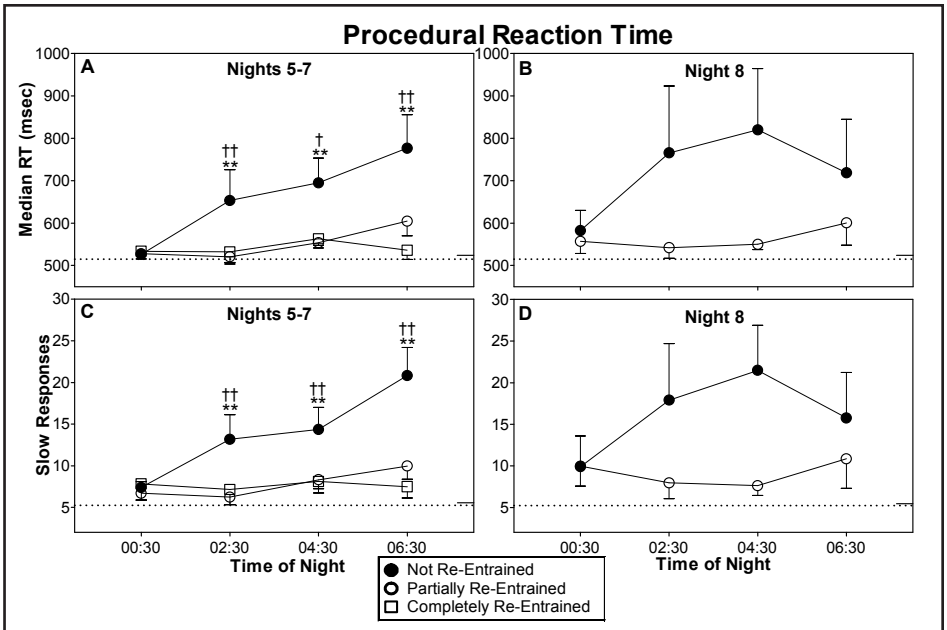

Figure 3—Median reaction time (top) and slow responses (bottom) on the procedural reaction time task. Remaining aspects of figure as for Fig 2. Statistical symbols in panels A and C denote the time points at which the groups differed, following a significant group x time-of-night interaction. †(P < 0.05) and ††(P < 0.01) indicate differences between the not re-entrained and completely re-entrained groups. **indicates a difference (P < 0.01) between the not re-entrained and partially re-entrained group.

Many of the dependent variables that were analyzed with ANOVAs showed the expected significant main effects of time-of-night, such as a gradual deterioration in performance as each night shift progressed. These changes can be seen clearly in the figures that will be presented. However, because we are most interested in how circadian phase affected this change across a night shift, and for brevity, here we only report statistics for main effects of group or group × time-of-night interactions.

To facilitate interpretation of these data, we also present total sleep time (TST) during the days before night shifts 5–8. TST was determined from sleep logs, and was calculated by taking the difference between the sleep onset and waking time, minus awakenings > 5 min. For control subjects, who could sleep whenever they chose, TST was all the sleep that occurred after the end of one night shift and the start of the next night shift. Because there was not homogeneity of variance, TST for the 3 re-entrainment groups on each of days before night shifts 5–8 was compared with Kruskal-Wallis tests.

Summary statistics for all data are means and standard deviations unless otherwise indicated. A 2-tailed significance level of 0.05 was used.

RESULTS

The percent correct for several of the ANAM tasks showed a similar pattern to the median RT and slow responses, but for brevity, here we only report the latter 2. Similarly, the 2 mood measurements and the 3 fatigue measurements showed a very similar pattern. Because of the large amount of data they produced with similar results, here we only report results from the total mood disturbance and mental fatigue scales.

Performance

Simple Reaction Time

Figure 2 shows the progression of lapses across all 8 night shifts. Data from the last test bout (6:30) is shown because the worst performance of a night was typically during this test. Although this figure depicts lapses on the simple reaction time task, data from the other ANAM tasks showed a very similar progression. During the first night shift, subjects in all groups had more lapses than during baseline. The partially re-entrained group showed a reduction in the number of lapses across successive night shifts. The completely re-entrained group had lapses near baseline levels starting at night shift 3. In contrast, the not re-entrained group continued to have an elevated number of lapses during all the night shifts. Across night shifts 1–7, there was a main effect of group [$F_{2,36} = 4.70$, P = 0.02]. Post hoc tests indicated that the not re-entrained group had significantly more lapses than the partially and completely re-entrained groups. More detailed analyses of the simple reaction time task has been previously reported.[20,21]

Procedural Reaction Time Task

The not re-entrained group had slower reaction times (Figure 3, top row). Median RT showed a significant group × time-of-night interaction for night shifts 5–7 [$F_{6,108} = 3.45$, P < 0.01]. The group that was not re-entrained had significantly longer reaction times than either the partially or completely re-entrained groups during the 2:30, 4:30, and 6:30 tests (panel A in Figure 3). On night shift 8, the main effect of group and the group × time-of-night interaction did not reach statistical significance (panel B in Figure 3).

The number of slow responses was also greater for the group that was not re-entrained (Figure 3, bottom row). There was a

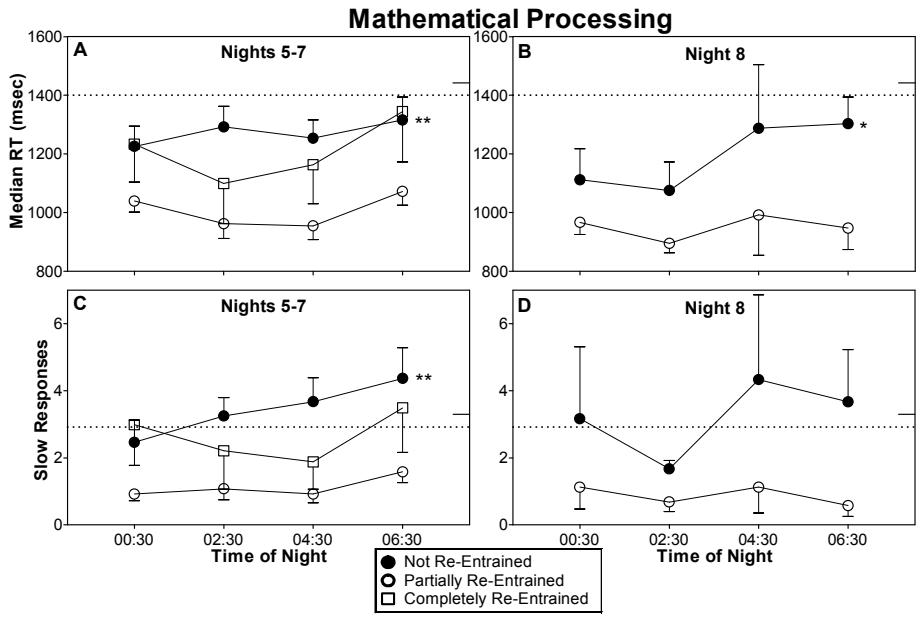

Figure 4—Median reaction time (top) and slow responses (bottom) on the mathematical processing task. Remaining aspects of figure as for Fig 2. Statistical symbols in panels A, B, and C denote a significant main effect of group. *(P < 0.05) and **(P < 0.01) indicate differences between the not re-entrained and partially re-entrained groups.

significant group × time-of-night interaction during night shifts 5–7 [$F_{6,108}$ = 2.87, P = 0.02]. Simple main effects indicated that the not re-entrained group had significantly more slow responses than both the partially or completely re-entrained groups during the 2:30, 4:30, and 6:30 test bouts (panel C in Figure 3). There were no significant differences between the groups on night shift 8 (panel D in Figure 3).

Mathematical Processing Task

Performance was better than during baseline for all 3 groups, but the partially and completely re-entrained group performed better than the not re-entrained group. Median RT was slower in the not re-entrained group (Figure 4, top row). There was a significant main effect of group during nights 5–7 [$F_{2,34}$ = 5.65, P < 0.01]. Post hoc tests indicated that the not re-entrained group had significantly slower median RT than the partially re-entrained group (panel A in Figure 4). On night shift 8 there was also a significant main effect of group [$F_{1,12}$ = 7.79, P = 0.02], indicating that the group that was not re-entrained had significantly slower reaction times than the partially re-entrained group (panel B in Figure 4).

The number of slow responses was greater for subjects that did not achieve re-entrainment (Figure 4, bottom row). On nights 5–7 there was a significant main effect of group [$F_{2,35}$ = 8.25, P < 0.01]. The not re-entrained group had significantly more slow responses than the partially re-entrained group (panel C in Figure 4). Slow responses on night shift 8 showed a similar pattern, but the main effect of group did not achieve statistical significance [$F_{1,13}$ = 3.92, P = 0.07] (panel D in Figure 4).

Matching to Sample Task

Median RT was close to baseline levels throughout the night shifts, and there were no significant differences among the groups (data not shown). For the number of slow responses there was a significant main effect of group on night shifts 5–7 [$F_{2,35}$ = 4.14, P = 0.02]. The group that was not re-entrained had significantly more slow responses than the group that was partially re-entrained, but the difference between the not-entrained and completely re-entrained groups did not reach statistical significance (P = 0.06) (panel A in Figure 5). There was a significant group × time-of-night interaction for the number of slow responses on night shift 8 [$F_{3,39}$ = 3.48, P = 0.04]. Simple main effects showed that the source of this interaction was significantly more slow responses for the not re-entrained group compared to the partially re-entrained group during the 4:30 test bout (panel B in Figure 5).

Code Substitution Task

There were no group differences in median RT (data not shown). However, the group that was not re-entrained had more slow responses (Figure 5, bottom row). There was a significant group × time-of-night interaction on nights 5–7 [$F_{6,108}$ = 2.78, P = 0.02]. The not re-entrained group had significantly more slow responses than both the partially re-entrained and completely re-entrained groups during the 2:30, 4:30, and 6:30 test bouts (panel C in Figure 5). There were no significant group differences in the number of slow responses on night shift 8 (panel D in Figure 5).

Mental Fatigue and Mood Disturbance

All the groups began the night shifts with ratings of mental fatigue and total mood disturbance that were relatively close to their baseline levels (00:30 time points in Figure 6). During night shifts 5–7 (Figure 6, left panels), mental fatigue and total mood disturbance increased for all groups later in the night shifts, but the partially and completely re-entrained groups remained closer to their baseline ratings late in the nights, while the group that was not re-entrained became more fatigued and had greater mood disturbance. On night shift 8 (Figure 6, right panels), ratings for the partially re-entrained group remained very close to baseline levels, while the not re-entrained group demonstrated increased mental fatigue and mood disturbance, especially later in the night shift.

On the mental fatigue scale for nights 5–7, there was a significant main effect of group [$F_{2,36}$ = 5.48, P < 0.01]. Post hoc tests indicated that the not re-entrained group was significantly more mentally fatigued than the partially and completely re-entrained groups (panel A in Figure 6). During night shift 8 there was a main effect of group [$F_{1,14}$ = 4.84, P = 0.045], indicating that the group that was not re-entrained was more mentally fatigued than the group that achieved partial re-entrainment (panel B in Figure 6).

Total mood disturbance was also higher for the group that was not re-entrained (Figure 6, bottom row). On night shifts 5–7, there was a significant main effect of group [$F_{2,36}$ = 4.12,

P = 0.02], with the group that was not re-entrained having significantly greater mood disturbance than the groups that were partially and completely re-entrained (panel C in Fig, 6). For night shift 8 there was a significant main effect of group [$F_{1,14}$ = 4.64, P = 0.049], indicating that the group that was not re-entrained had greater mood disturbance than the group that was partially re-entrained (panel D in Figure 6).

Sleep Duration

There was a significant difference in TST on day 28 (occurring before night shift 5) [$\chi(2) = 9.12$, P = 0.01]. TST on day 28 for the not re-entrained group (6.0 ± 1.1 h) was shorter than the partially re-entrained group (6.9 ± 0.5), while the completely re-entrained group was intermediate (6.4 ± 0.4). There were no significant differences in sleep duration on days 29, 30, and 31 among the three groups (mean TST ranged from 5.7 to 6.9 h). More complete analyses of sleep have been previously reported.[20,21]

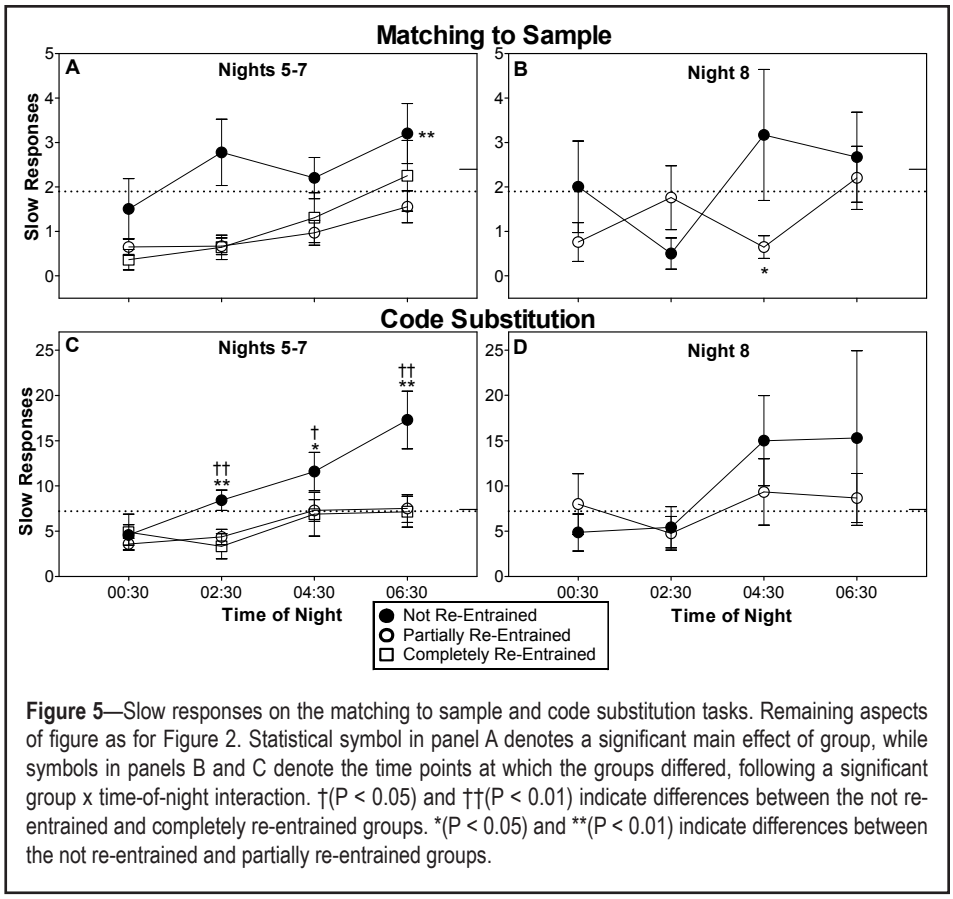

Figure 5—Slow responses on the matching to sample and code substitution tasks. Remaining aspects of figure as for Figure 2. Statistical symbol in panel A denotes a significant main effect of group, while symbols in panels B and C denote the time points at which the groups differed, following a significant group x time-of-night interaction. †(P < 0.05) and ††(P < 0.01) indicate differences between the not re-entrained and completely re-entrained groups. *(P < 0.05) and **(P < 0.01) indicate differences between the not re-entrained and partially re-entrained groups.

DISCUSSION

Reducing circadian misalignment during night shift work markedly reduced ratings of mental fatigue and mood disturbance, while improving measures of performance. On most measurements, the group that achieved partial re-entrainment to the night work, day sleep schedule was better than the group that was not re-entrained, and was comparable to the group that was completely entrained.

These findings are similar to our previous study in which both partial and complete re-entrainment improved mood, alertness, and performance during simulated night shifts.[17] However, in the previous study there were no daytime measurements so we could not assess how subjects felt and performed during night shifts relative to their normal daytime functioning. The present study included testing during daytime work hours, and demonstrated that mood, fatigue, and performance during night shifts were at or close to daytime levels for subjects that achieved partial or complete re-entrainment. It is notable that daytime measurements of mood, fatigue, and performance were not obtained from early morning day shifts, but rather from 9 to 5 work days, when self-ratings and performance would be optimal. This degree of night shift improvement in studies that have baseline measures has rarely been demonstrated, and has been shown only in subjects that were completely re-entrained.[12] It is notable that the subjects in our studies were not permitted to drink caffeine during the night shifts, a practice that might have completely normalized those measurements that were still slightly above baseline values.

A few control subjects achieved partial re-entrainment even though they did not receive bright light pulses during night shifts and only wore lightly tinted sunglasses outside. Thus, night shift bright light and dark sunglasses are not necessary to produce partial re-entrainment and the accompanying benefits to performance, fatigue and mood. However, all the control subjects who achieved partial re-entrainment slept late on days off, and in many cases sleep was even later than the 3:00-noon schedule required of experimental subjects (e.g., see Figure 3, panels G-J in ref[21]). Thus if workers adopt a late enough sleep schedule on days off, then the other manipulations of light exposure may not be necessary. However, since we have shown in Studies A[20] and B[21] that the experimental interventions almost always produced partial or complete re-entrainment in our experimental subjects, the use of these interventions will reduce circadian misalignment while permitting a more socially acceptable sleep schedule.

In lieu of reducing circadian misalignment by shifting the sleepiest circadian time out of the night shift, alternative approaches for improving night shift alertness include symptomatic relief: caffeine consumption, prophylactic napping and the stimulant modafinil. Caffeine improves night shift alertness and performance in laboratory[38,39] and field studies[40] of night work, but does not overcome the strong circadian nadir in alertness late in the night shifts that is present when the circadian clock does not shift. An evening nap has also been shown to improve night shift performance.[38] The combination of caffeine consumption and an evening nap substantially improve night shift performance and enhance the ability to remain awake,[7] and could possibly be one of the best countermeasures for night shift alertness decrements when the circadian clock is not shifted. Modafinil has been shown to improve night shift alertness and performance in healthy volunteers.[8] Modafinil also produces improvements in alertness in patients with shiftwork sleep

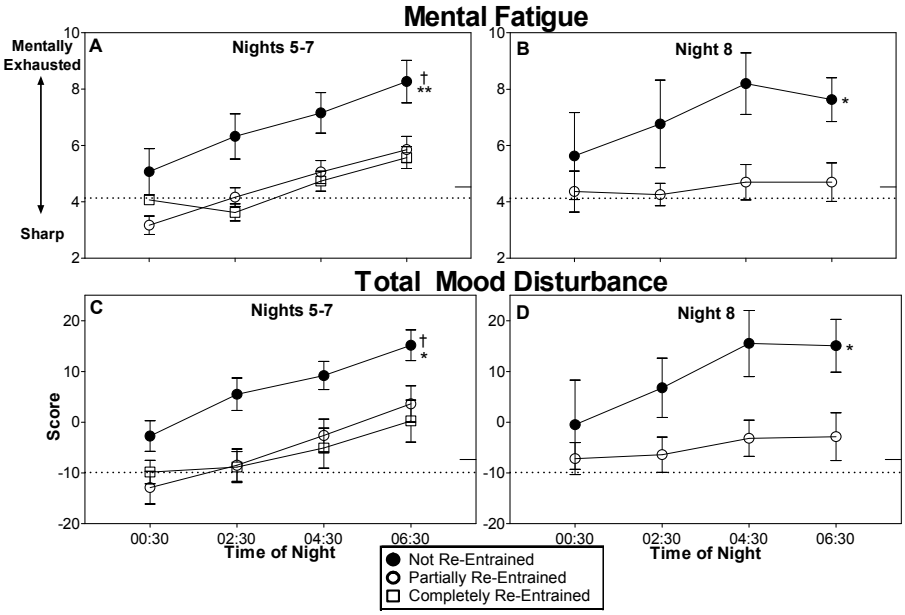

Figure 6—Mental fatigue (top) and total mood disturbance from the Profile of Mood States (POMS) (bottom) during night shifts. Higher mood disturbance scores indicate greater levels of mood disturbance. Remaining aspects of figure as for Fig 2. Statistical symbols denote significant main effects of group. † indicates a difference ($P < 0.05$) between the not re-entrained and completely re-entrained groups. *($P < 0.05$) and **($P < 0.01$) indicate differences between the not re-entrained and partially re-entrained groups.

disorder, but in this population of shiftworkers (who experience the most severe sequelae associated with night work) nighttime alertness is still seriously impaired.[9] This is a population that could benefit greatly from circadian re-alignment, but whether partial re-entrainment (i.e., the attainment of a compromise circadian phase position) would improve night shift alertness and performance in these patients has not been tested.

The performance and alertness decrements during night of work are not only due to circadian misalignment, but are also due to increased homeostatic sleep pressure. This increase in sleep debt could arise when workers are awake for the entire day before working their first night shift, or may result from the chronic partial sleep deprivation that often accompanies night work. Reducing homeostatic sleep pressure during night shifts by scheduling the sleep episodes to occur before rather than after the night shifts (and advancing rather than delaying the circadian clock)[41] can improve alertness and performance during night shifts.[36] However, this strategy may be unappealing to most real shift workers, because afternoon/evening sleep episodes would then occur during the hours when most people enjoy leisure and social activities. Regardless of the direction that the circadian clock is shifted, substantial misalignment will still be present during the first few night shifts because the circadian clock adjusts slowly, and so enhancing alertness with caffeine or modafinil during these night shifts may be an option.

A possible criticism of the partial re-entrainment, compromise circadian phase position, approach is that many workers have rapidly rotating shifts rather than permanent night shifts, and thus realigning their circadian clocks with the work/sleep schedule is impossible. However, it may be possible to reduce circadian misalignment with the appropriate control of light and dark if the shifts rotate slowly.[42] Furthermore, a United States population survey conducted in 2004 indicates that there are more permanent night workers (3.8 million) than rotating shift workers (3.3 million).[43] From a safety perspective, rapidly rotating night shifts, which attempt to attenuate the severity of nighttime alertness impairments by minimizing the sleep deprivation that accompanies night work, do not address a primary cause of those alertness impairments, which is circadian misalignment (i.e. being awake at the sleepiest circadian time). Consequently, a permanent or very slowly rotating shift system that is compatible with partial circadian re-entrainment would be a more reliable way to improve night shift alertness. Studies are needed to test schedules to reduce circadian misalignment within a slowly rotating shift schedule.

One limitation of this study is that we did not know exactly where each subjects' circadian phase was during each night shift. We used circadian phase measurements from the final phase assessment that occurred the day after night shifts 5–7 (study A) or 3 days after night shift 8 (study B). Thus, actual circadian phase during the night shifts could have been different from what we measured during the phase assessment. This could have resulted in subjects at the edges of the not, partial, and complete re-entrainment groups to be placed in the "wrong" category.

Other limitations of these studies provide opportunities for future research. We did not assess mood, fatigue, or performance on days off. Night workers would likely need to feel reasonably well on their days off in order to be satisfied with partial re-entrainment to a compromise circadian phase position. Also, our studies were a hybrid between field and laboratory studies, with night shifts conducted in the laboratory and sleep occurring at home. Subjects were not real shift workers, but rather were young volunteers. This system for producing a compromise circadian phase position should be tested in real night shift workers.

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Sleep Disorders

Treatment of Shift Work Disorder and Jet Lag

Phyllis C. Zee, MD, PhD
Cathy A. Goldstein, MD[*]

Address
*710 North Lake Shore Drive, 5th Floor, Chicago, IL 60611, USA
Email: c-goldstein@md.northwestern.edu

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Opinion statement

With the growth of the 24-hour global marketplace, a substantial proportion of workers are engaged in nontraditional work schedules and frequent jet travel across multiple time zones. Thus, shift work disorder and jet lag are prevalent in our 24/7 society and have been associated with significant health and safety repercussions. In both disorders, treatment strategies are based on promoting good sleep hygiene, improving circadian alignment, and targeting specific symptoms.

Treatment of shift work must be tailored to the type of shift. For a night worker, circadian alignment can be achieved with bright light exposure during the shift and avoidance of bright light (with dark or amber sunglasses) toward the latter portion of the work period and during the morning commute home. If insomnia and/or excessive sleepiness are prominent complaints despite behavioral approaches and adequate opportunity for sleep, melatonin may be administered prior to the day sleep period to improve sleep, and alertness during work can be augmented by caffeine and wake-promoting agents.

For jet lag, circadian adaptation is suggested only for travel greater than 48 h, with travel east more challenging than travel west. Although advancing sleep and wake times and circadian timing for eastward travel with evening melatonin and morning bright light several days prior to departure can help avoid jet lag at the new destination, this approach may be impractical for many people, Therefore, strategies for treatment at the destination, such as avoidance of early morning light and exposure to late-morning and afternoon light alone or in conjunction with bedtime melatonin, can accelerate re-entrainment following eastward travel. For westward travel, a circadian delay can be achieved after arrival with afternoon and early-evening light with bedtime melatonin.

Good sleep hygiene practices, together with the application of circadian principles, can improve sleep quality, alertness, performance, and safety in shift workers and jet travelers. However, definitive multicenter randomized controlled clinical trials are still needed, using traditional efficacy outcomes such as sleep and performance as well as novel biomarkers of health.

Introduction

Humans have an endogenous circadian rhythm slightly longer than 24 h. The International Classification of Sleep Disorders describes nine circadian rhythm disorders defined by a persistent or recurrent pattern of sleep disturbance resulting from either alterations of the circadian timekeeping system or misalignment between the endogenous circadian rhythm and exogenous factors that affect the timing and duration of sleep [1]. Shift work disorder and jet lag are two circadian rhythm disorders that occur due to the alteration of the external environment relative to the internal circadian timing system [2].

Shift work disorder

As of 1991, 20% of the United States workforce participated in some type of shift work [3]. Of these, more than 30% of night workers and 25% of rotating shift workers meet criteria for shift work sleep disorder [3]. In Europe, only 24% of the workforce keeps conventional working hours, and 18.8% have a work schedule that involves night shift work [4]. Shift work disorder is characterized by both insomnia and excessive sleepiness associated with the work period occurring during the usual time for sleep [1]. The diagnosis requires that symptoms are of at least 1 month's duration and circadian misalignment must be demonstrated with a sleep diary or actigraphy [1]. Insomnia and excessive sleepiness are thought to be primarily due to a misalignment between the scheduled sleep/wake cycle and the circadian propensity for sleep and alertness. Typically, the patient is attempting to sleep when the circadian signal for alertness is high and working at a time when the circadian alertness levels are low [1]. In addition to circadian factors, sleep is often shortened in shift workers because of problems with the environment for sleep and because domestic and social responsibilities encroach on the worker's nonconventional sleep time [2]. Therefore, sleep loss, in addition to circadian misalignment, contributes to decreased alertness during night work [5]. Sleepiness in shift workers can be profound: one third of night workers admit to nodding off once a week during work, and one half report falling asleep while commuting [6]. In addition to sleepiness, circadian misalignments in performance have also contributed to serious accidents, including the incidents at Three Mile Island and Chernobyl and the Exxon Valdez disaster [5]. Shift workers with shift work disorder are at higher risk for cardiovascular disease, ulcers, depression, and absenteeism than shift workers without shift work disorder [5]. Because of both public safety concerns and consequences to the patient, treatment of shift work disorder is imperative.

Jet lag disorder

Jet lag disorder is defined as *symptoms* of insomnia and/or excessive daytime sleepiness resulting from travel across at least two time zones [1]. It is also associated with compromised daytime function, general malaise, or somatic complaints (eg, gastrointestinal symptoms) occurring within 1 to 2 days of travel [1]. Unlike travel fatigue, jet lag symptoms do not resolve with an adequate sleep period upon arrival and may occur even when unfavorable air travel conditions (cramped space, etc.) are minimized [7]. Because the intrinsic clock cannot adjust to the change in time zones as rapidly as we can traverse them with jet travel, there is a resultant discord between the timing of sleep as generated by the endogenous circadian rhythm and the sleep/wake times necessary in the new time zone [8••]. Eastward travel often results in sleep-onset insomnia as the endogenous circadian rhythm (as set by the location of origin) is not conducive to sleep at the new, earlier time at the destination; the circadian rhythm must advance. In westward travel, difficulties in remaining asleep are a more prominent problem, as the circadian alerting signal occurs during the desired sleep period at the new destination; the circadian rhythm must delay [7]. In either case, sleepiness results from both circadian misalignment and truncated sleep duration. In jet travel, it has been demonstrated that the endogenous circadian rhythm resets approximately 92 min later each day after a flight westward and approximately 57 min earlier each day after a flight eastward. Therefore it is more difficult to align the intrinsic rhythm with the external clock in eastward travel [9]. Alignment may occur in the opposite direction (referred to as *antidromic reentrainment*) when traveling across more than eight time zones [10]. In addition to the direction of travel

and sleep loss, other factors that may influence the severity of jet lag include the number of time zones crossed, exposure to and the magnitude of local circadian time cues (eg, alteration of light during various times of the year), and individual variance [11]. Thirty million US citizens traveled overseas in 2009, but the exact incidence of jet lag is unknown [12]. Although jet lag is usually benign and transient, it may become recurrent and problematic in those who travel frequently and may result in occupational hazard.

Therapeutic strategies

To understand the therapeutic strategies used in treating shift work disorder and jet lag, one must appreciate how circadian and homeostatic processes interact to regulate sleep and wakefulness. The master clock regulating the endogenous circadian rhythm is located in the suprachiasmatic nucleus (SCN) located in the anterior hypothalamus [5]. The cycle of sleep and wake is the most prominent circadian rhythm, with the highest propensity for sleep occurring near the nadir of core body temperature (occurring approximately 2 to 3 h before the usual wake time) [2].

This circadian process interacts closely with the homeostatic drive for sleep. SCN neurons are active during the subjective day and are stimulated by light. As the homeostatic drive for sleep accumulates with wakefulness, SCN activity increases to maintain alertness and then decreases in the evening, prior to sleep time [5], facilitating sleep. Interestingly, pineal melatonin begins to rise about 2 h before sleep onset [5]. As the homeostatic drive dissipates during sleep, SCN activity remains low. It has been postulated that melatonin helps to maintain sleep by its ability to inhibit the firing rate of the SCN neurons [5].

Light is the strongest cue synchronizing the circadian clock to the external environment [5]. After light is received by melanopsin-containing retinal ganglion cells, photic information is transmitted via the retinohypothalamic tract to the suprachiasmatic nucleus [2]. Light in the evening (before the core body temperature minimum is reached) delays the circadian rhythm, and light given in the morning (after the core body temperature minimum is reached) advances the circadian rhythm. The phase-response curve to light demonstrates that the magnitude of phase shift is greatest when light would usually be absent (during the night).

Melatonin is a hormone regulated by the SCN and secreted by the pineal gland. Melatonin levels begin to rise 1 to 3 h before the habitual sleep time and peak just prior to the core body temperature nadir [5]. In contrast to light, melatonin given in the evening shifts the circadian rhythm to an earlier time, and melatonin given in the morning shifts it to a later time. The phase-response curve to melatonin shows the largest magnitude of change occurring at the time when endogenous secretion is the lowest (during the day).

Treatment

- The treatment of shift work disorder and jet lag is multifaceted and includes strategies to achieve and maintain some degree of circadian alignment (Fig. 1), improve sleep (using hypnotics, melatonin, and behavioral approaches), and facilitate alertness (using light, wake-promoting agents and sleep scheduling) (Table 1). In addition, good general sleep hygiene is an integral part of managing both disorders. Measures include: regular sleep and wake times, routine exercise (but not within three hours of bedtime), abstaining from caffeine, nicotine, heavy meals, alcohol, and stressful or stimulating activities near bedtime, and creating an environment conducive for sleep [5].

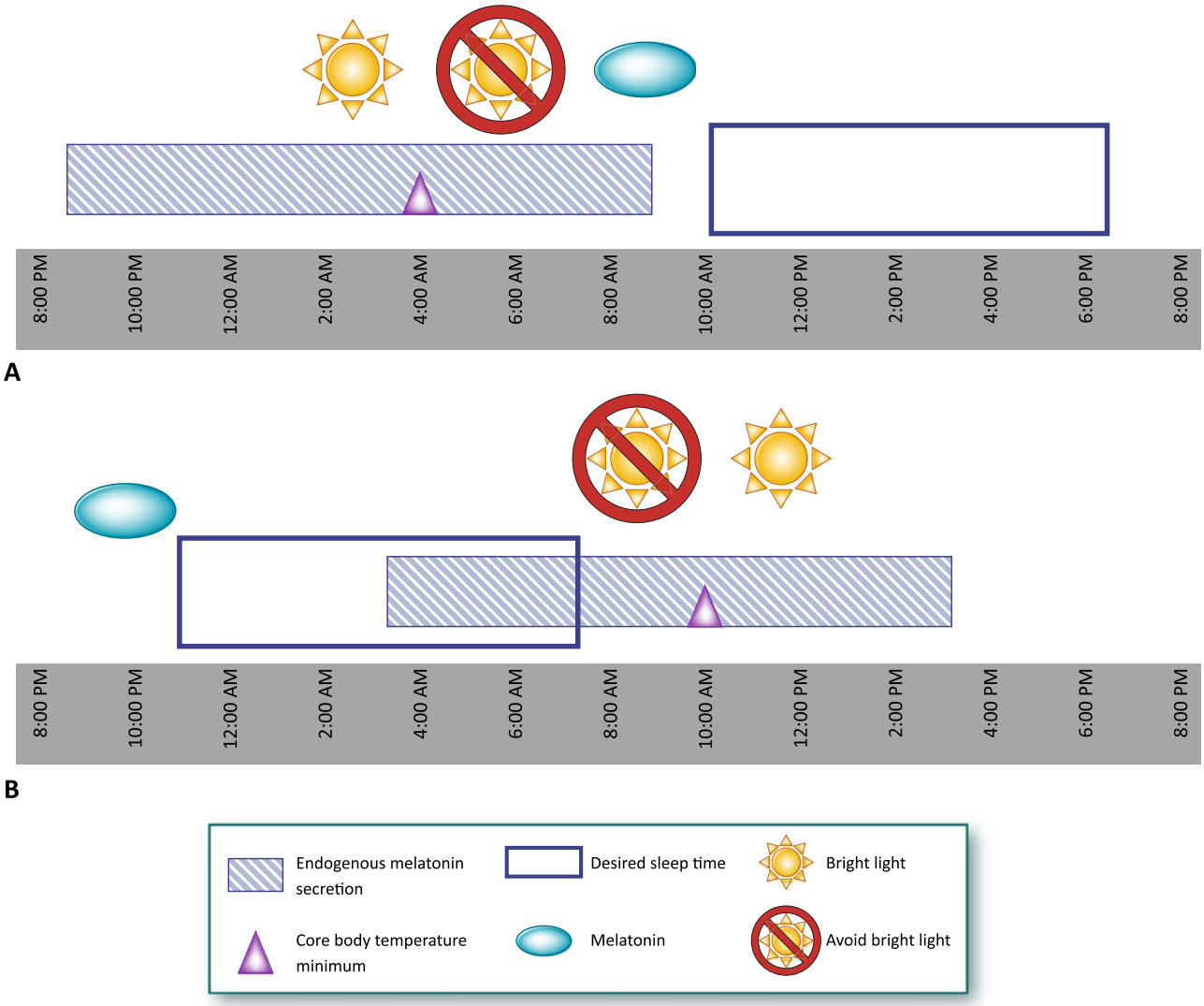

Figure 1. In an individual with normal circadian phase, dim-light melatonin onset occurs 7 h prior to core body temperature minimum, which is about 2 to 3 h before the usual wake time. The timing of the peak of melatonin secretion and core body temperature minimum are associated with a high circadian propensity for sleep and occur within the sleep period during normal conditions. A, In a night-work/day-sleep cycle, circadian sleep-promoting factors occur before the sleep period, so the goal is a phase delay to align the endogenous clock with the external environment with appropriately timed light, avoidance of light, and melatonin. B, With jet travel over six time zones east, the circadian propensity for sleep (as set by the origin of travel) falls after the desired sleep period at the local time in the destination. A phase advance with appropriately timed light and/or melatonin can accelerate circadian alignment. (*Adapted from* Kwon and Zee [5]).

Treating shift work disorder

Diet and lifestyle

Scheduled sleep times

By dissipating the homeostatic drive for sleep, napping is an effective strategy to counteract sleepiness in shift workers. Napping prior to night

Table 1. Treatment of shift work disorder

Treatment modality	Strength of recommendation
Planned napping	Standard[a]
Timed light exposure	Guideline[b]
Administration of melatonin prior to day sleep	Guideline[b]
Hypnotic medication to promote day sleep	Guideline[b]
Modafinil to enhance alertness	Guideline[b]
Caffeine to enhance alertness	Option[c]

[a]Standard—Generally accepted patient care strategy reflecting a high degree of clinical certainty.
[b]Guideline—Patient care strategy reflecting a moderate degree of certainty.
[c]Option—Uncertain clinical use.
(*Adapted from* Morgenthaler et al. [11].)

shift work has been associated with decreased accidents and improved alertness and performance. Beneficial effects of napping before night work were further augmented with caffeine administration [13, Class III; 14, Class I].

Naps of 20 to 50 min duration during shift work have produced improvements in reaction time and have restored performance to that seen at the beginning of the shift. In addition, napping early in the night shift improves objective measures of alertness [15, 16; Class II]. If the nap duration is greater than 30 min, some degree of sleep inertia may occur [15, Class II].

No disruption of the main sleep period occurred secondary to the nap [16, Class II; 17, Class IV]. Planned napping is considered a standard of care in the treatment of shift work disorder by the American Academy of Sleep Medicine (AASM) [11].

Melatonin

The AASM recommends melatonin prior to day sleep as a treatment guideline for shift work disorder [11]. Exogenous melatonin has effects of both resetting the circadian clock and acting as a direct hypnotic [10].

In a randomized, controlled trial of 32 individuals undergoing simulated night work with attempted sleep occurring in the afternoon and evening, melatonin at doses of 3 mg or 0.5 mg or a placebo was given prior to the nonconventional sleep period. Both doses of melatonin resulted in a significant phase advancement (3 h for 0.5 mg and 3.9 h for 3 mg), compared with placebo [18, Class I]. In addition to shift work simulation, the clock resetting effects of melatonin have also been demonstrated in some night workers during field studies [19, Class I].

The addition of melatonin did not augment circadian adaptation in the setting of a treatment strategy using bright light therapy during the night shift and light avoidance in the morning [20, Class II].

Melatonin (1.8–6 mg), given prior to day sleep, has been shown to improve total sleep duration in both simulated night shifts and studies of night workers [21, Class I; 22, Class III; 23, Class II].

No improvements in nighttime alertness have been seen with the use of melatonin [21, Class I; 24, 25, Class II].

No field studies or simulated studies of early morning shift work using melatonin are currently available. However due to the known efficacy of exogenous evening melatonin in advancing circadian rhythms, melatonin may be a rational treatment option for shift work requiring an early rise time. Further studies are needed.

Caffeine

The AASM suggests caffeine as a treatment option to enhance alertness during night work [11].

It is well known that caffeine can be an effective countermeasure for sleepiness during experimentally induced sleep deprivation, making it a feasible option for treatment in shift work disorder and jet lag [8••].

In a double-blind, randomized, placebo-controlled trial of 15 individuals performing simulated night work, coffee (2 mg/kg dose of caffeine) was given immediately prior to and during the first portion of the night shift. There was significant improvement in sleepiness as measured by the multiple sleep latency test, and participants rated themselves as 25% more alert. There was no residual effect on daytime sleep as measured by polysomnography [26, Class I].

A recent meta-analysis found that caffeine (compared with placebo) improved shift workers' performance in multiple domains of neuropsychiatric testing, including memory and attention [27].

Pharmacologic treatment

Benzodiazepines and benzodiazepine receptor agonists

Hypnotic medications have been evaluated for shift work disorder, specifically for the treatment of insomnia occurring as a result of attempting sleep during the period of high circadian alerting signal.

Triazolam (0.25–0.5 mg) and temazepam (20 mg) have been shown to be effective in increasing daytime sleep duration with both subjective and objective measures. No improvements in nighttime alertness (by self report or by mean sleep latency testing) have been demonstrated with either medication, however [28, 29, Class I; 30, Class III; 31, Class II].

Two field studies of shift workers using zopiclone also showed subjective improvements in sleep quality and duration, but there was no evidence of improvement in work performance [32, Class I; 33, Class II].

In a study of seven individuals undergoing simulated rotating shifts, those receiving zolpidem had improved subjective sleep quality, but their mood was worsened during the following work period, compared with placebo [34].

In the AASM practice parameters, the use of hypnotic medication is a treatment guideline to facilitate day sleep in night workers. These agents should be administered with great caution when used for insomnia during the nonconventional sleep period, however, because of the potential for unfavorable effects on nighttime performance and alertness [11]. Further studies are needed to determine the efficacy

of benzodiazepines and benzodiazepine receptor agonists in shift work disorder.

Standard dosage Benzodiazepine and benzodiazepine receptor agonist medications are not approved by the US Food and Drug Administration (FDA) for the specific purposes of treating shift work disorder or jet lag. However, for short-term insomnia, temazepam (7.5–30 mg) or zolpidem (5–10 mg) may be used at bedtime [35, 36]. Zopiclone is not available in the United States.

Contraindications Temazepam and zolpidem should be used with care in elderly and debilitated patients, and alcohol should not be used with either. With temazepam, slow tapering of the medication should be performed prior to discontinuation because of a risk of seizure with abrupt cessation. Zolpidem is a pregnancy category C medication. Pregnancy is an absolute contraindication to temazepam use because of its class X designation [35, 36].

Main drug interactions Central nervous system depressants may have an additive effect with temazepam and zolpidem. Oral contraceptive pills may increase the clearance of temazepam, and probenecid may decrease its clearance [35, 36].

Main side effects The most frequently reported adverse effects of zolpidem are daytime drowsiness, headache, and dizziness. Amnesia may occur with benzodiazepine and benzodiazepine receptor agonist medications, and non–rapid eye movement (NREM) parasomnias such as sleep walking or sleep eating also may occur. The most common adverse effects of temazepam are headache, drowsiness, ataxia, dizziness, confusion, depression, syncope, fatigue, vertigo, and tremor. Patients should be monitored for physiologic dependence on temazepam [35, 36].

Cost/Cost-effectiveness Both zolpidem and temazepam are less than $20 for a 30-day supply, making them cost-effective treatment options.

Wake-promoting medications

Because night shift work occurs during a time of high propensity for sleep, wake-promoting medications have been investigated to improve alertness in shift workers.

In one study, methamphetamine improved mood and performance during the night shift in simulated laboratory workers [37, Class II]. However, because of the minimal evidence supporting its use and its potential for abuse, this medication is not indicated in the treatment of shift work disorder [11].

In a randomized double-blind controlled trial, modafinil (200 mg) was given 30 to 60 min before the start of night shift work, resulting in objective improvement in sleepiness and improved performance on psychomotor vigilance testing. In addition, there were 25% fewer accidents and near-accidents in the modafinil group than in the placebo group ($P<0.001$). Despite these functional improvements and the attenuation of sleepiness, a pathologic level of sleepiness similar to that of narcolepsy (mean sleep latency, 3.8 min) persisted in night shift workers [38, Class I].

Armodafinil is the R isomer of modafinil and has a longer half life (15 h) than the S isomer of modafinil (3–4 h). In a 12-week randomized controlled trial of 254 night shift and rotating shift workers with shift work disorder, 150 mg of armodafinil was given 30 to 60 min prior to beginning the night shift. Armodafinil resulted in a significant increase in

mean sleep latency compared with placebo (3 min vs 0.4 min respectively). By self-report, armodafinil reduced sleepiness during work and on the morning commute. Significant improvement in performance on standardized memory and attention testing was also demonstrated. No worsening in daytime sleep parameters occurred with armodafinil [39•, Class I].

Modafinil and armodafinil are effective in promoting alertness during night shift work and are FDA-approved for the treatment of shift work disorder.

Standard dosage Modafinil (200 mg) or armodafinil (150 mg) taken approximately 1 h prior to shift work.

Contraindications Patients with cardiac signs or symptoms occurring in the setting of stimulant medication should not take modafinil or armodafinil. Caution should be exercised in prescribing these medications for patients with a known history of psychosis, unstable angina, or recent myocardial infarction, and those with seizures. Both drugs are FDA pregnancy category C [40, 41].

Main drug interactions Modafinil and armodafinil may decrease the effectiveness of oral contraceptive pills and other drugs metabolized by the CYP3A4 isoenzyme, and drugs inducing the CYP3A4 enzyme may increase the metabolism of modafinil and armodafinil [40, 41].

Main side effects Rare but life-threatening rashes have occurred with modafinil therapy [40]. Headache, nausea/vomiting, anxiety, nervousness, and insomnia were the most common adverse reactions occurring in clinical trials of modafinil [40]. Headache, nausea/vomiting, dizziness, and insomnia were the most common adverse reactions occurring in clinical trials of armodafinil [41]. Some individuals taking armodafinil had a small elevation in blood pressure [41].

Cost The retail price for a 30-day supply is $475.95 for modafinil (Provigil; Cephalon, Frazer, PA) and $304.97 for armodafinil (Nuvigil; Cephalon, Frazer, PA).

Other treatments

Timed bright light exposure

Timed light exposure can be employed for its circadian phase shifting effects as well as its beneficial effects on alertness and cognitive performance [42]. The AASM suggests the use of timed light during the work period and restriction of morning light in night shift workers as a treatment guideline [11].

In field studies of shift workers, light regimens of 2350 to 12,000 lux for durations of 20 minutes (with multiple exposures) to 6 h have shown improvements in psychomotor performance, subjective alertness, and self-rated mood [43, 44, 45, Class III].

Bright light exposure and the avoidance of light have been used to promote circadian shifts to move the core body temperature nadir from the work period to the sleep period. Studies using this treatment strategy have been performed in both night work simulation and in field testing of actual night workers [5]. Bright light of 6000 to 12,000 lux during at least half of a 12-hour night shift resulted in a significant phase shift in 50% of shift workers receiving the treatment, compared with controls

receiving ambient light [44, Class III]. The largest phase shifts and improvements in subjective sleep quality have occurred in groups using both interventions: bright light during the night shift combined with light avoidance (using dark sunglasses or goggles) the following morning [23, 46; Class II].

Despite the benefits in performance and alertness produced by aligning the circadian rhythm to night work, many patients may be reluctant to do so, as they want to realign their phase to a conventional diurnal waking schedule on days off. One group has proposed the idea of partial alignment using a goal "compromise position" with the core body temperature nadir near 10:00, which puts the highest circadian propensity for sleep early but within the sleep period on work days and late but within the sleep period appropriate for days off. This compromise position was achieved with bright light, light avoidance, and scheduled sleep times (08:30 to 15:30 on work days and 03:00 to 12:00 on days off). Sleep after the last night shift was truncated to 08:30 to 13:30 in anticipation of an earlier bedtime on the days off. The subjects aligning to the "compromise position" had mood, fatigue, and performance ratings that were markedly superior to controls and were similar to those of subjects completely entrained to a night-wake, day-sleep schedule. This partial entrainment strategy may be an effective strategy for permanent night workers to improve function on both work days and days off [47•, Class II].

Standard procedure Although no standard protocol for bright light therapy exists, studies have been performed with both intermittent and sustained exposures of 2350 to 12,000 lux. Ultraviolet wavelength light should be filtered [48]. Light therapy treatment is not regulated by the FDA.

Contraindications Patients with retinopathies should not receive treatment with bright light therapy. Great care should be taken in those using medications causing photosensitization and patients with bipolar disorder [48].

Complications Hypomania, irritability, nausea, headache, blurred vision, eye strain, photophobia, and sleep disturbances are the most frequently reported adverse reactions. Side effects are uncommon, may depend on dose and timing, and may resolve over time [48].

Cost/Cost-effectiveness Light boxes range in price from about $200 to $500. As a one-time investment, this may be a cost-effective option.

Treating jet lag

Diet and lifestyle

Scheduled sleep times

In jet lag, sleep scheduling is used as an adjunct to light in shifting the circadian rhythm.

For travel of greater than 48 h, travelers could attempt to shift their circadian rhythm prior to departure. In a study to determine how much bedtimes could be shifted (while using bright light therapy) in preparation for eastward travel, subjects advancing bedtimes by 2 h per day experienced greater sleep-onset insomnia than those advancing by 1 h per day. Jet lag scores were similar between both groups on most days of

treatment. Therefore, advancing bedtime by 1 h per day in combination with light therapy may be a useful intervention in the anticipation of eastward travel [49, Class II]. This sleep schedule advance prior to travel east is recommended as a treatment option by the AASM [11].

However, for travel less than 48 h, those maintaining the sleep/wake times of the location of origin reported decreased sleepiness and better global jet lag ratings than those adopting the sleep/wake times of the destination location during a study of travel over nine time zones [50, Class II]. The AASM suggests keeping home sleep and wake times during travel of 2 days or less as a treatment option [11].

Exposure to and avoidance of natural light

Bright light therapy has demonstrated significant augmentation of phase shifts in simulated studies of eastward travel. (See the discussion of timed light exposure below.) However, although this phase shift may attenuate circadian misalignment, bright light therapy may be inconvenient during travel, making the exposure to and avoidance of natural light (using dark sunglasses) a more feasible treatment for jet lag.

During westward travel, the goal is to delay the circadian rhythm, so light exposure should be sought during what would be evening in the location of departure and avoided during what would be morning in the location of departure. For eastward travel, to initiate a phase advance, light should be avoided during what would be evening in the location of departure, and light exposure should occur during what would be morning [51].

This strategy is best illustrated by example. If a traveler lives in Chicago and usually sleeps from 11 PM to 7 AM, his core body temperature minimum (assuming normal circadian phase) would likely be close to 4 AM (11 PM Hawaii time). If he departs from Chicago at 0900 and lands in Hawaii at 1600 (local time), he needs to get plenty of afternoon and evening light and avoid bright light in the morning. Conversely, if he travels from Chicago to Paris (where his core body temperature minimum would be at 11 AM), departing at 1800 and arriving at 1100 (local time), he should seek plenty of afternoon light and avoid morning light prior to 11 AM. This example also demonstrates that some degree of phase shifting prior to eastward travel may be beneficial to move the core body temperature minimum to the dark period, preventing light exposure during the wrong portion of the phase-response curve [52].

Melatonin

In multiple studies for jet lag, melatonin has shown benefits likely due to both its phase shifting and sedating effects.

Of nine double-blind, placebo-controlled field studies evaluating the effects of melatonin on subjective measures of jet lag, seven studies showed more favorable ratings of symptoms with melatonin than with placebo. These studies used 0.5 mg to 8 mg (most commonly 5 mg) of melatonin for travel of up to 12 time zones [8••].

Objectively, melatonin has demonstrated increased total sleep time and decreased waking after sleep onset (as measured by actigraphy), compared with placebo [53, Class I].

Melatonin has also shown acceleration of phase shift during travel, as measured by cortisol and melatonin rhythms [54, 55, 56].

Appropriately timed melatonin use, to improve both sleep and waking symptoms, is considered a standard treatment for jet lag by the AASM [8••].

Caffeine

Caffeine has been evaluated in jet lag in two studies, both with 27 subjects traveling eastward over seven time zones. Slow-release caffeine (300 mg) given at 0800 the first 5 days after arrival improved objective measures of daytime sleepiness and accelerated circadian entrainment, as measured by cortisol rhythms. Caffeine did result in greater subjective and objective sleep disruption than placebo [54, 57; Class II].

The AASM suggests caffeine as a treatment option for daytime sleepiness related to jet lag [11].

Pharmacologic treatment

Benzodiazepine and benzodiazepine receptor agonists

The benzodiazepines temazepam, midazolam, and triazolam have been evaluated for the treatment of jet lag in four studies. In eastward travel, temazepam and midazolam showed improvement in subjective sleep quality and objective sleep measures by actigraphy, but no benefits were noted in westward travel [8••].

Zolpidem (10 mg) has demonstrated improved sleep quality and duration, as well as improvement in jet lag symptoms, after eastward travel, but adverse effects (including nausea, vomiting, amnesia, and somnambulism) were greater with zolpidem than with melatonin or placebo [58, 59; Class I].

Zopiclone has also shown increased sleep duration (as measured by actigraphy) in one study of eastward flight and one study of westward flight, compared with placebo, but no improvement in sleep measures was shown in comparison with melatonin, and there is no evidence that this hypnotic improves symptoms of jet lag [53, Class I; 60, Class II].

The AASM does suggest benzodiazepine receptor agonist hypnotic therapy as a treatment option for short-term insomnia resulting from jet lag. However, more research is needed regarding the effect of these agents on waking jet lag symptoms, and patients must be educated about potential side effects [11].

Other treatments

Timed light exposure

In jet lag, light therapy has been used with the goal of shifting circadian rhythms prior to departure. For example, in a study using either intermittent or continuous bright light therapy in the first 3.5 h after awakening (combined with advancing sleep schedules), subjects in the bright light group reset their clock 1.5 to 2 h earlier after 3 days of treatment, versus 0.6 h in the

control group. In addition, those receiving continuous light did not have a worsening in their jet lag score with advancing bedtimes, as did those receiving intermittent or no bright light [61, Class II].

In a field study of westward travel (Zurich to New York), light was used to delay the circadian rhythm after arrival. Although a greater phase delay occurred with bright light therapy, there was no difference in jet lag scale, psychomotor performance, or mood [62, Class II].

Morning bright light therapy (in combination with advancement of the sleep schedule) before travel east is recommended as a treatment option by the AASM.

Emerging therapies for shift work disorder and jet lag

Transdermal melatonin

The homeostatic drive for sleep is dissipated by sleep occurring during the initial portion of the sleep period. During the night, this is counteracted by the circadian propensity for sleep, partly due to the inhibitory effects of melatonin on the SCN [5]. Because night workers are sleeping during the "wrong" circadian time, they lack this mechanism for sleep maintenance.

When 2.1 mg of melatonin (compared with placebo) was given transdermally 1 h before an 8-hour daytime sleep opportunity, waking after sleep onset and in the latter third of the sleep period decreased, sleep efficiency increased, and total sleep time increased. Although melatonin levels remained elevated after the sleep period, subjective alertness and visual attention were not affected, as measured by the Karolinska Sleepiness Scale and psychomotor vigilance testing [63].

A sustained-release method of delivering melatonin may be an effective option for sleep-maintenance insomnia in those with a nonconventional day sleep schedule, but more studies are needed.

Melatonin receptor agonists

Melatonin has produced marked improvement in jet lag symptoms and mixed effects in the treatment of shift work disorder. Because melatonin varies in potency and quality and is not regulated by the FDA, a melatonin receptor agonist may be a promising treatment for shift work disorder and jet lag.

Ramelteon is an MT_1 and MT_2 receptor agonist. In a study to determine the ability of ramelteon to realign the circadian rhythm after an imposed 5-hour advance of sleep-wake times in 75 healthy adults, ramelteon was given 30 min prior to the new bedtime. A significant circadian shift to an earlier time occurred in patients receiving 1 mg, 2 mg, or 4 mg of ramelteon, compared with placebo. Headache and nausea were the most commonly experienced adverse reactions and were mild in severity [64, Class I].

In a recent randomized, double-blind, placebo-controlled trial, 109 individuals with a history of jet lag were given 1 mg, 4 mg, or 8 mg of ramelteon or placebo at their usual bedtime after arrival following eastward travel of five time zones. On all nights following travel, with a 1-mg dose of ramelteon, there was a significant reduction of latency to

persistent sleep (-10.6 min, $P=0.03$) as compared with placebo. When further examining two subsets of the study (those exposed to natural light and those kept in dim light conditions), the group exposed to natural bright light and taking a placebo experienced sleep-promoting effects similar to the effects on those in dim light who received 1 mg of ramelteon. Therefore, ramelteon could be a treatment option during travel when bright light is less accessible (eg, during the winter). There were no significant differences between the ramelteon group the placebo group in sleepiness scales during waking hours. At the 4-mg dose, significant improvements in subjective daytime function, alertness, concentration, sleep quality, and ease of awakening were seen. Adverse effects were similar across all groups [65•, Class I].

Tasimelteon is another MT_1 and MT_2 receptor agonist. In a phase 3, double-blind, randomized placebo-controlled trial, 411 individuals underwent a 5-hour advance of sleep-wake times and received tasimelteon at the new bedtime. Compared with placebo, all doses of tasimelteon were followed by decreased latency to persistent sleep onset, decreased waking after sleep onset, increased total sleep time, and increased sleep efficiency. Results of neurocognitive testing the day after treatment were no different with tasimelteon or placebo [66, Class I].

Agomelatine (also an MT_1 and MT_2 receptor agonist, as well as a serotonin agonist) has been shown in a double-blind, placebo-controlled trial to significantly phase-advance body temperature profiles [67].

The clock-advancing properties of melatonin agonists may be effective in treating shift work disorder resulting from early morning shifts as well as jet lag resulting from eastward travel.

Wake-promoting agents

Although approved for shift work disorder, armodafinil does not currently have an indication in jet lag.

In a recent double-blind, randomized, placebo-controlled study to determine the efficacy of armodafinil in jet lag, 427 individuals traveled eastward over six time zones and were given armodafinil (50 mg or 150 mg) or placebo daily at 7 AM local time after arrival. Those receiving 150 mg of armodafinil had significant improvements in objective measures of sleepiness (mean sleep latency on the Multiple Sleep Latency Test of 11.7 min vs 4.8 min with placebo, $P<0.001$) and less severe symptoms of jet lag [68•, Class I].

Armodafinil may be an effective agent for combating daytime sleepiness associated with jet lag.

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