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Master Class for Neuroscience Professional Development

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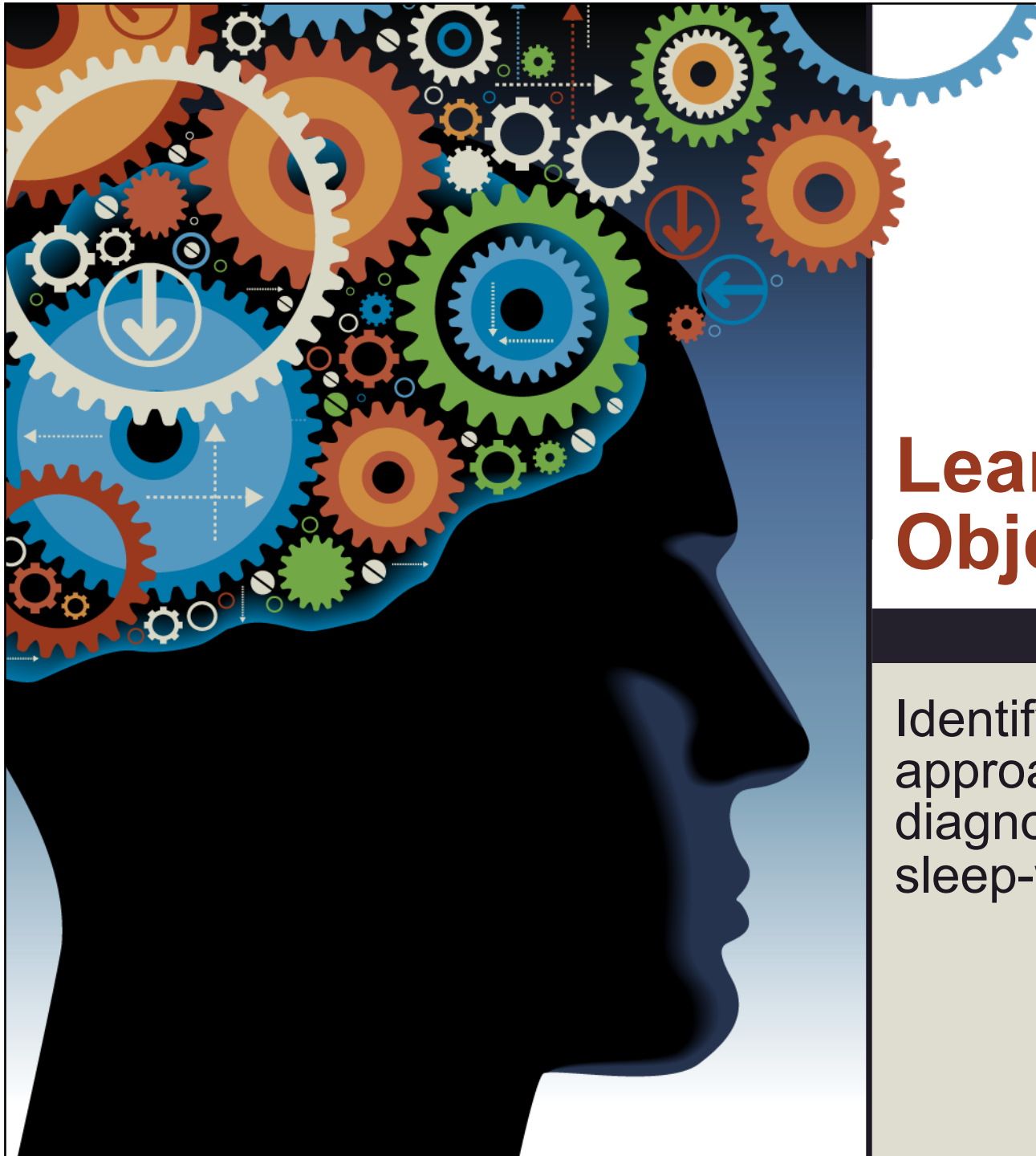
# Insights Into Non-24-Hour Disorder

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Ann Arbor, MI

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## *Disclosures*

- **Grants:** Apnex Medical, Inc.; Merck & Co.;
- **Consultant:** Abbott Laboratories; AstraZeneca Pharmaceutical, Inc.; Intec Pharma, Ltd.; Jazz Pharmaceuticals, PLC; Merck & Co., Inc.; Neurocrine Biosciences, Inc.; Proctor and Gamble; Pfizer, Inc; Purdue Pharma, L.P.; Sepracor, Inc.; Shire Pharmaceuticals, Inc.; Somaxon Pharmaceuticals, Inc.; Somnus Therapeutics, Inc; Steady Sleep Rx Co.; Transcept Pharmaceuticals, Inc.



## Learning Objective

Identify evidence-based approaches to the diagnosis of non-24-hour sleep-wake disorder

# Case Vignette

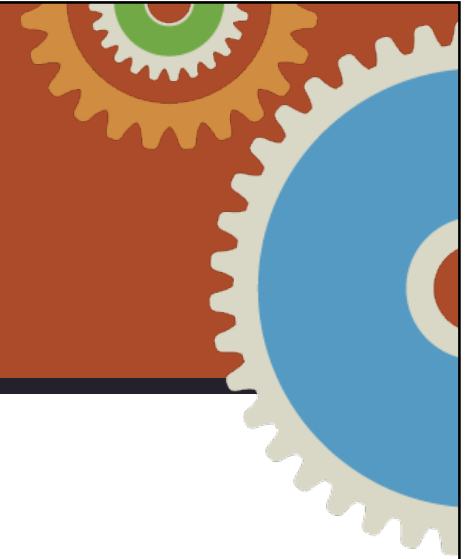


- Ms. Walker is a 52-year-old woman who has been losing her vision over the past 20 years and is now totally blind. Over the past two years, she has had increasing problems with sleep, including cyclical both difficulty falling asleep and staying asleep at night and fatigue during the day.

# Question 1

The circadian rhythm disorder that affects 50% of totally blind people is

- A. Delayed sleep phase syndrome
- B. Advanced sleep phase syndrome
- C. Non-24-hour sleep-wake disorder
- D. Shift work disorder



# Audience Response



With a potential diagnosis of non-24-hour sleep-wake disorder in mind, which of the following tests would be clinically indicated?

- A. Overnight polysomnography, multiple sleep latency test, and maintenance of wakefulness test
- B. Two-week actigraphy and/or sleep diary
- C. Core body temperature, two-week actigraphy, and multiple sleep latency test
- D. Urinary 24-hour 6-sulphatoxymelatonin, overnight polysomnography, and maintenance of wakefulness test

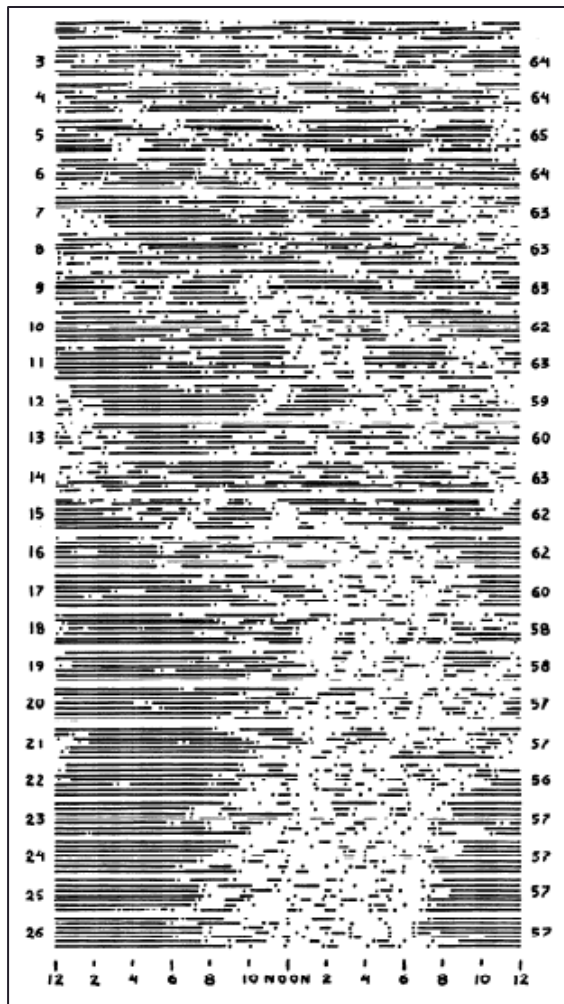
# Circadian Rhythm



- A self-sustained biological rhythm that, within the organism's natural environment, is normally synchronized to a 24-hour period
- Circadian: frequency  $\sim$  1 per day
  - Circa dies (about a day)
- Circadian rhythms can be assessed by evaluating the timing of biological events



# The Incidence of Sleep and Feeding in an Infant



- The incidence of sleep and feeding in infant 4F, from the 11<sup>th</sup> to the 182<sup>nd</sup> day of life.
  - Each line represents a 24-hr. calendar day
  - At bottom: Time, in 2-hourly intervals
  - At left: Numbered weeks
  - At right: Percentage of time spent in sleep during the successive weeks
  - Dark bands: sleep periods, measured to the nearest 5 minutes
  - Breaks between the lines: wakefulness; Dots: feedings
  - Each group of 7 lines is separated from the adjacent groups by a double space

From: Kleitman N, et al. *J Appl Physiol.* 1953;6(5):269-282. PMID: 13108823. For Educational Purposes Only

# Components of the Circadian System



**INPUT = LIGHT**



**TRANSDUCER = RETINAL GANGLION CELLS**



**RHT**

**PACEMAKER**  **= SCN**



**REGULATED SYSTEM**

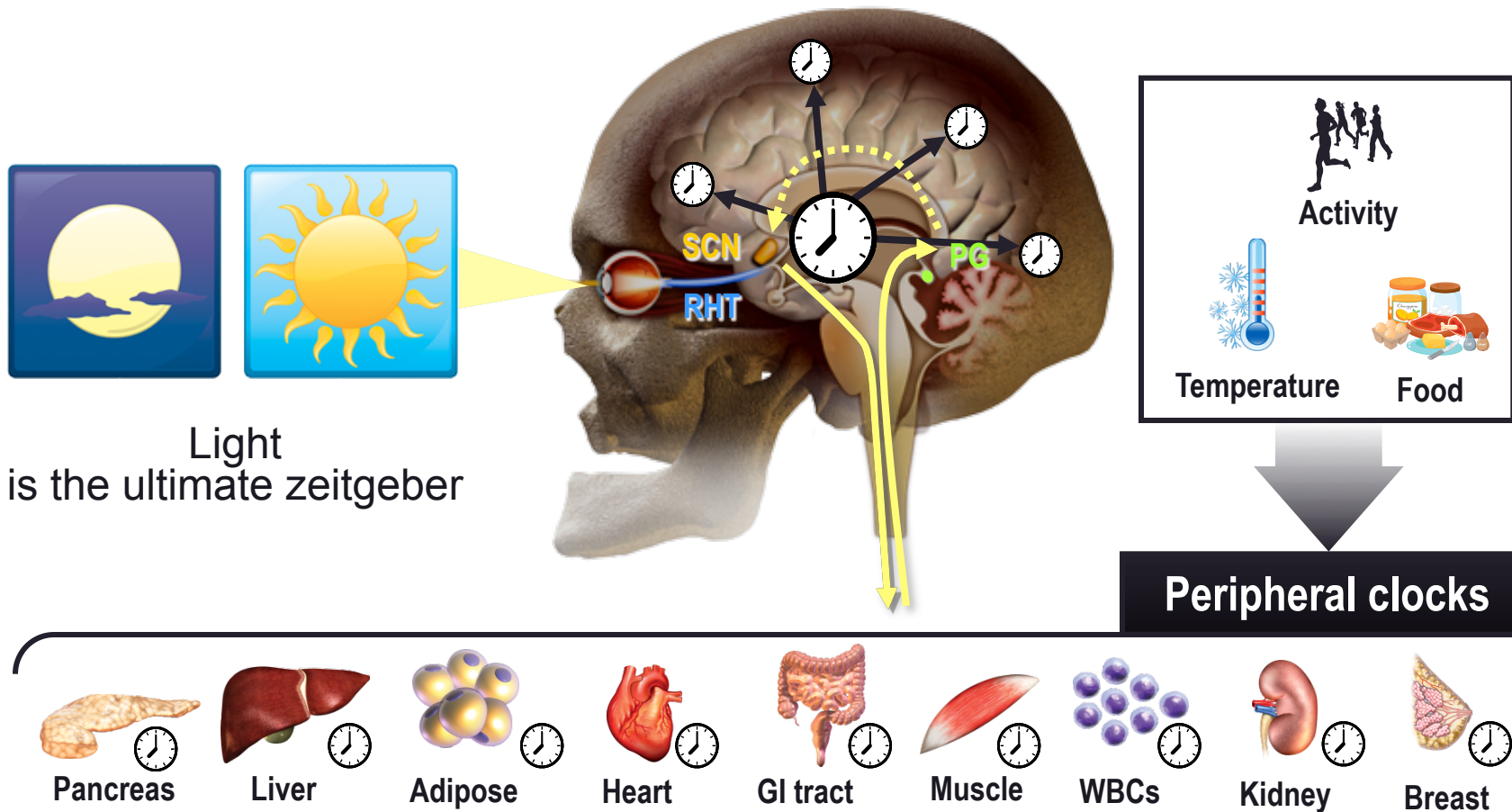


**OUTPUT RHYTHM**

(e.g., running wheel, melatonin, sleep-wake)

RHT = retinohypothalamic tract.  
SCN = suprachiasmatic nucleus.

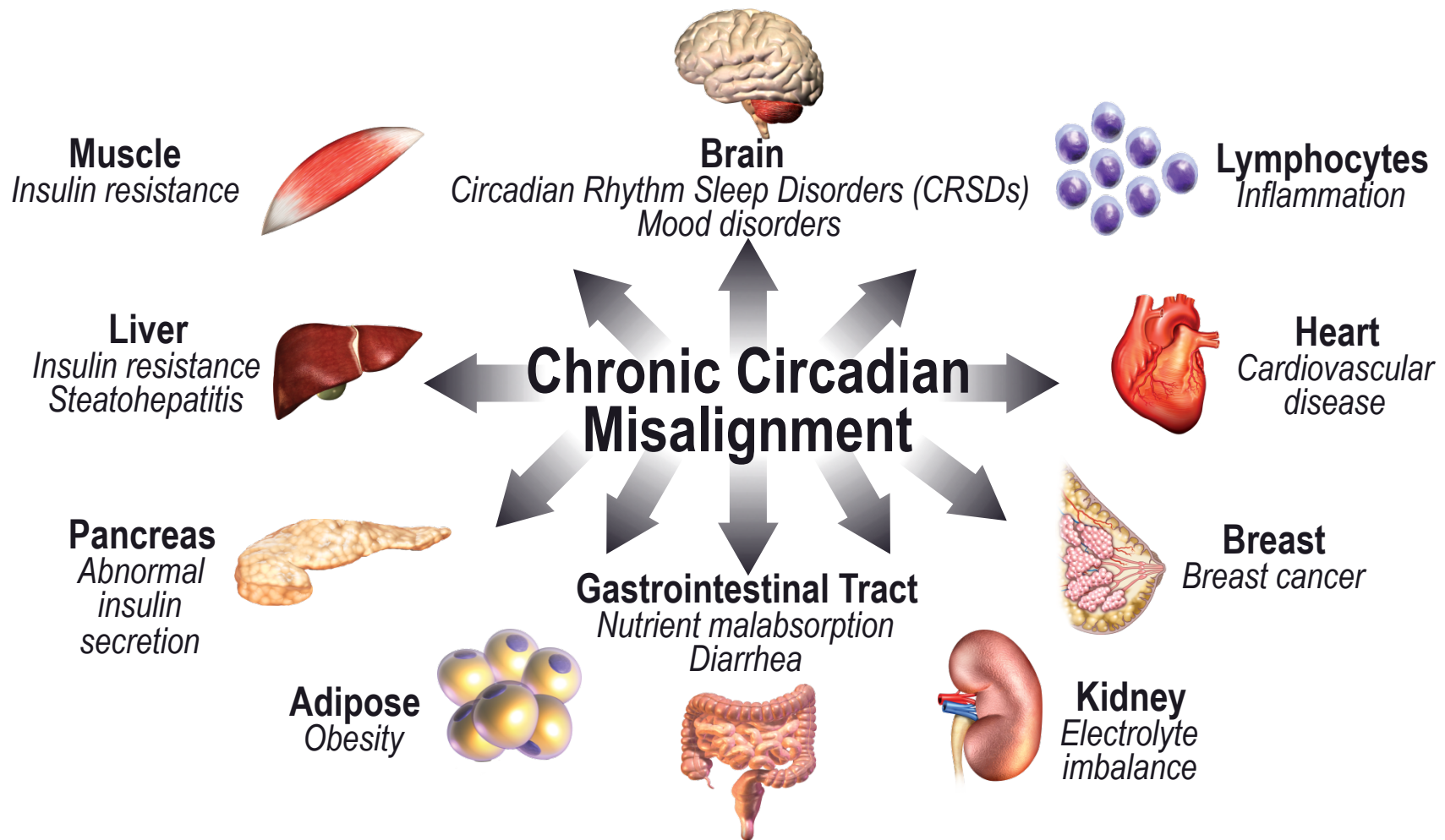
# Entrainment of the Suprachiasmatic Nucleus (SCN) and Peripheral Clocks



RHT = retinohypothalamic tract; PG = pineal gland.

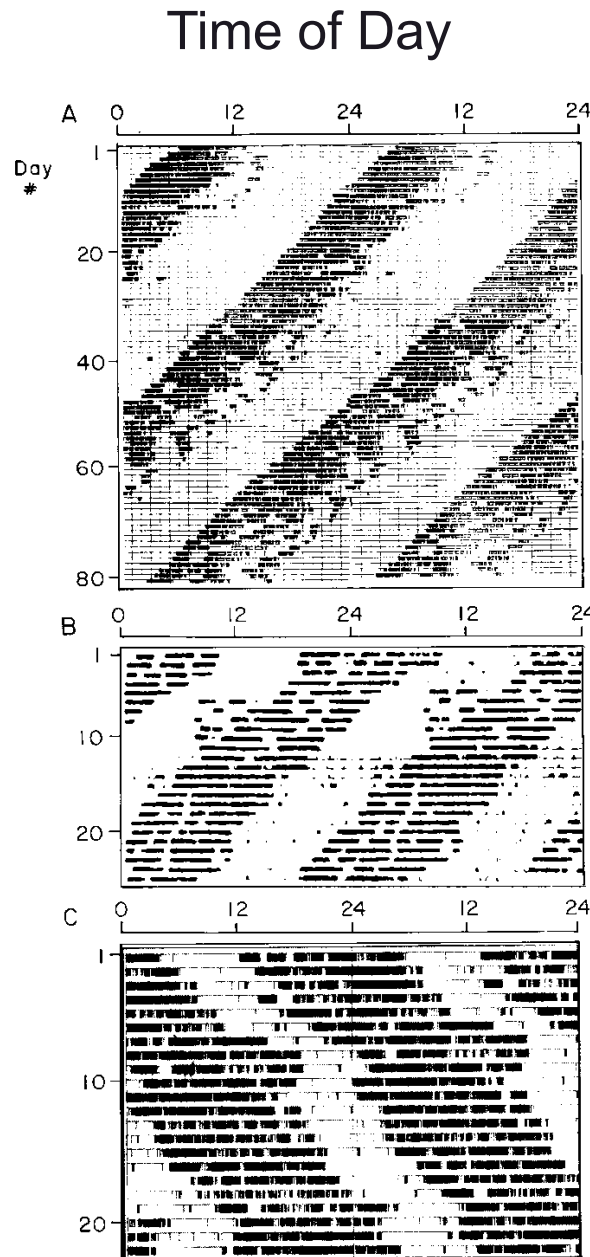
Schibler U, Sassone-Corsi P. *Cell*. 2002;111(7):919-922. PMID: 12507418.

# Circadian Misalignment: Dyssynchrony and Morbidity



Klerman EB. *J Biol Rhythms*. 2005;20(4):375-386. PMID: 16077156.  
Young ME, Bray MS. *Sleep Med*. 2007;8(6):656-667. PMID: 17387040.

# No Zeitgebers: Free-Running Activity and Sleep Rhythms



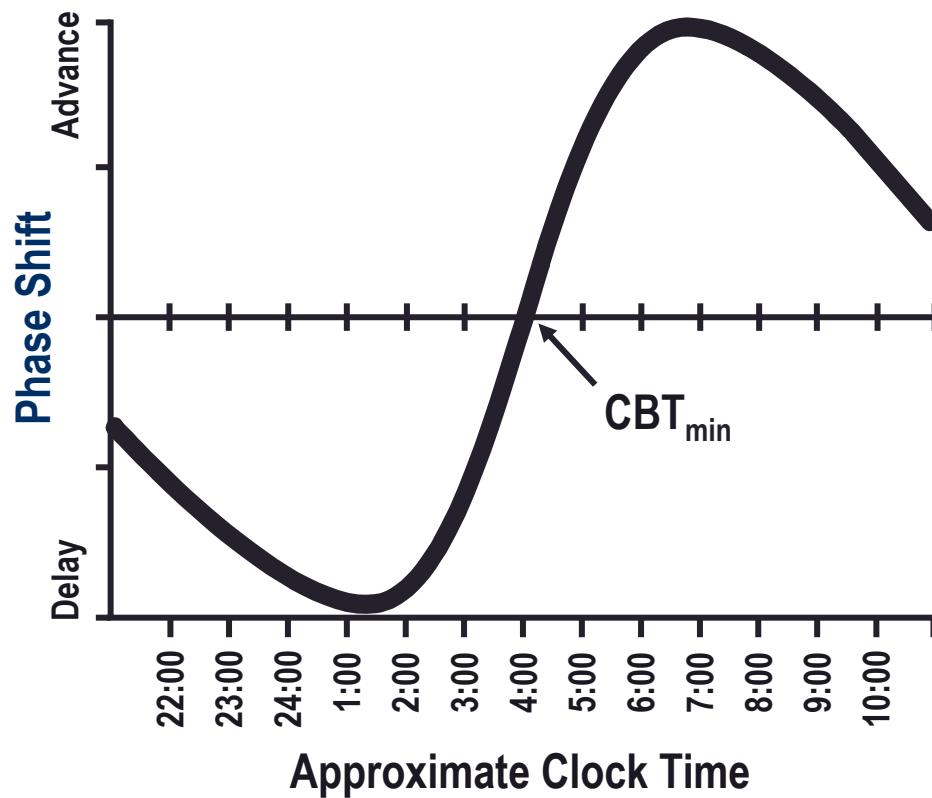
Mouse

Pigtailed  
Monkey

Human

Slide courtesy of Phyllis Zee, MD.  
Used with permission.

# Appropriately Timed Light Phase Shifts Circadian Rhythms

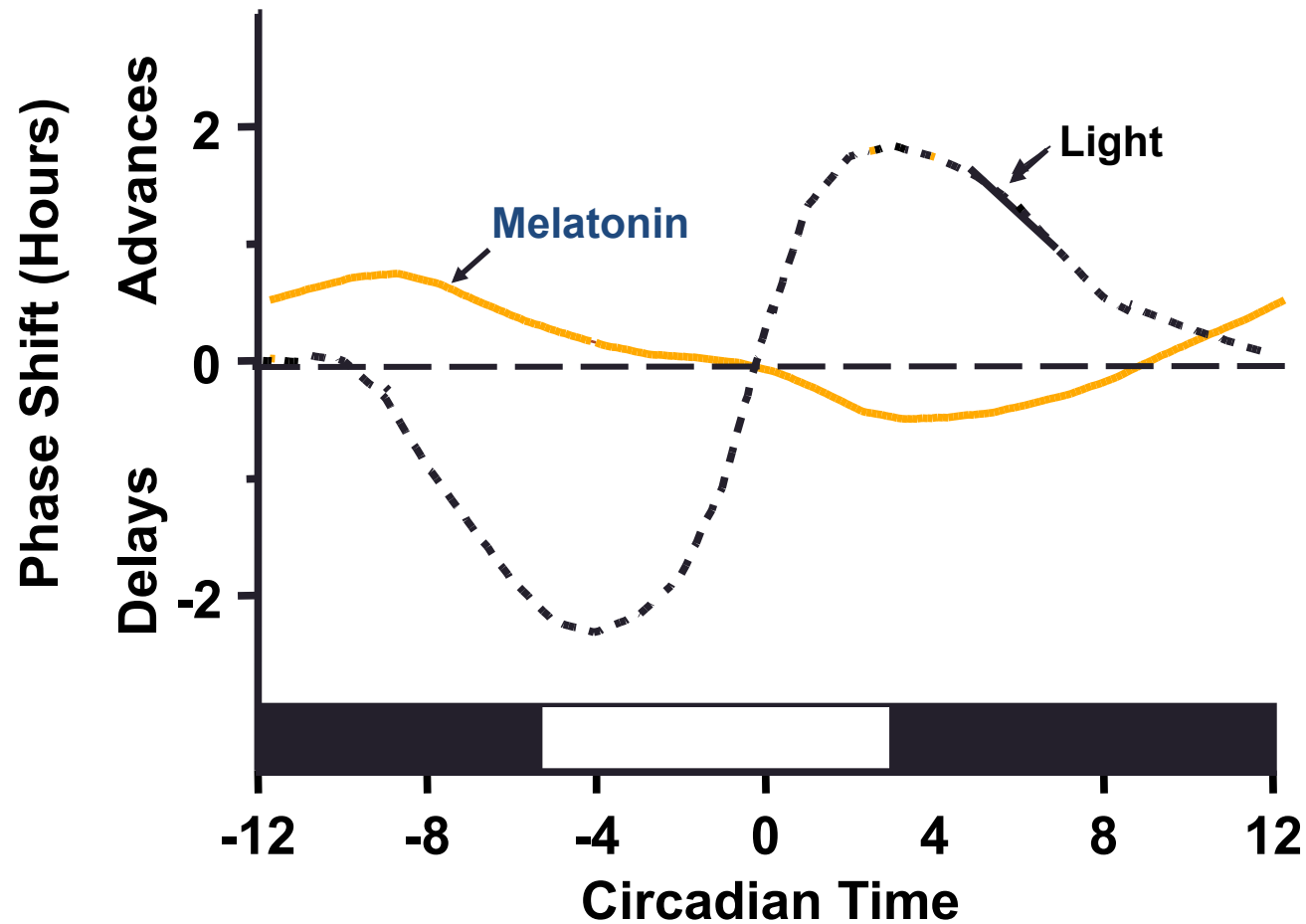


CBT = core body temperature.

Fahey CD, Zee PC. *Psychiatr Clin North Am.* 2006;29(4):989-1007. PMID: 17118278.

Lu BS, Zee PC. *Chest.* 2006;130(6):1915-1923. PMID: 17167016.

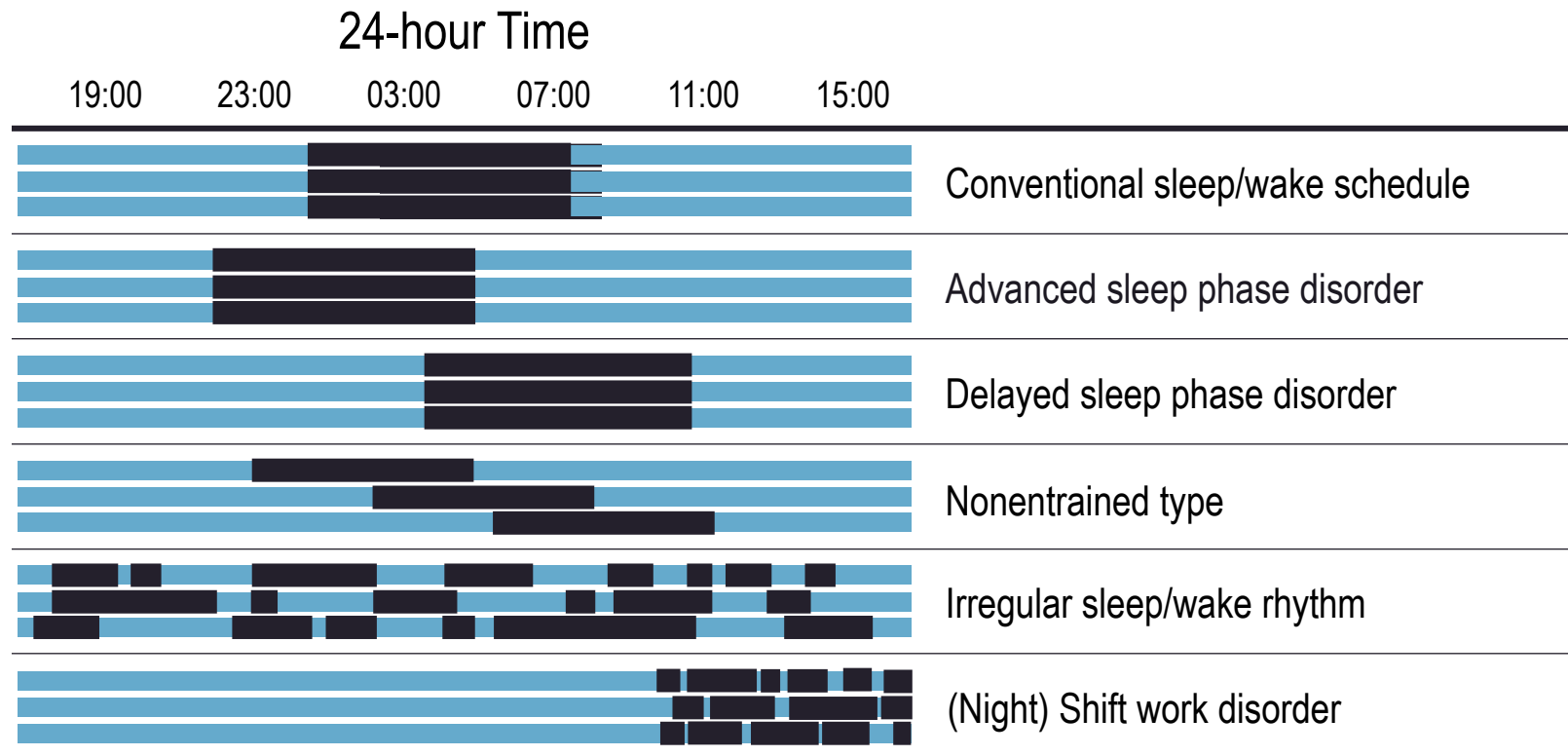
# Phase-Response Curves to Light and to Melatonin



Lewy AJ, et al. *Chronobiol Int*. 1998;15(1):71-83. PMID: 9493716.  
Czeisler CA, et al. *Science*. 1986;233(4764):667-671. PMID: 3726555.  
For Educational Purposes Only



# Circadian Rhythm Sleep Disorders



Enforced “conventional” sleep/wake times may result in insomnia symptoms, chronically insufficient sleep, and associated excessive sleepiness.

Sack RL, et al. *Sleep*. 2007;30(11):1460-1483. PMID: 18041480.

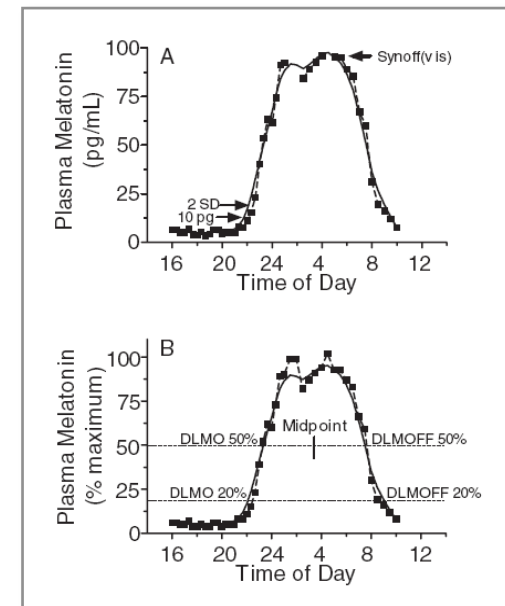
Sack RL, et al. *Sleep*. 2007;30(11):1484-1501. PMID: 18041481.



# Measures of Circadian Timing



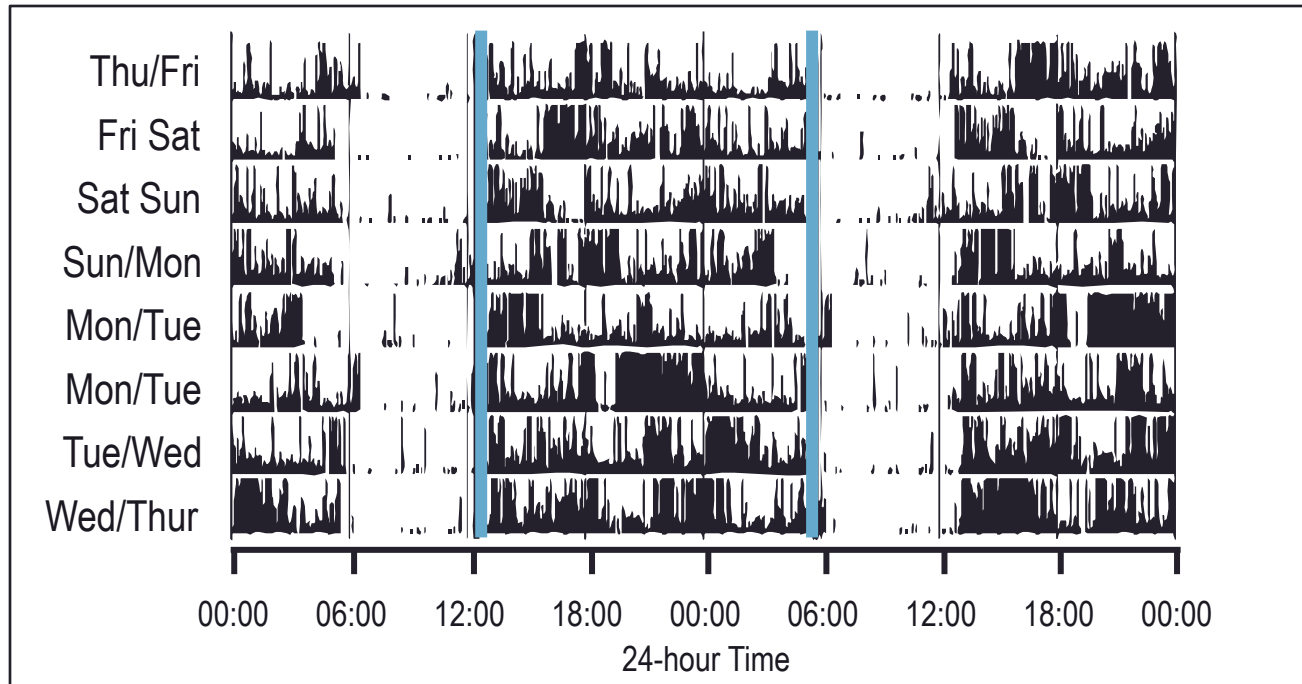
- *Morningness-Eveningness Questionnaire (MEQ)*
  - Horne-Ostberg<sup>1</sup>
  - Munich Chronotype<sup>2</sup>
- Sleep diary (preferably 14 days)
- Actigraphy
- Melatonin (dim-light melatonin onset [DLMO])
  - Salivary (3 pg/ml), serum (10 pg/ml)
  - Urinary 24-hour 6-sulphatoxymelatonin
- Core body temperature
  - Not in *International Classification of Sleep Disorders*, 3rd edition



# Actigraphy



- Records rest/activity cycles (and sometimes light exposure) across time
- Provides estimation of sleep-wake and circadian timing



Morgenthaler T, et al. *Sleep*. 2007;30(4):519-529. PMID: 17520797.

Russo MB, et al. *Aviat Space Environ Med*. 2005;76(7 Suppl):C64-C74. PMID: 16018332.

# Health Consequences of Circadian Disorders

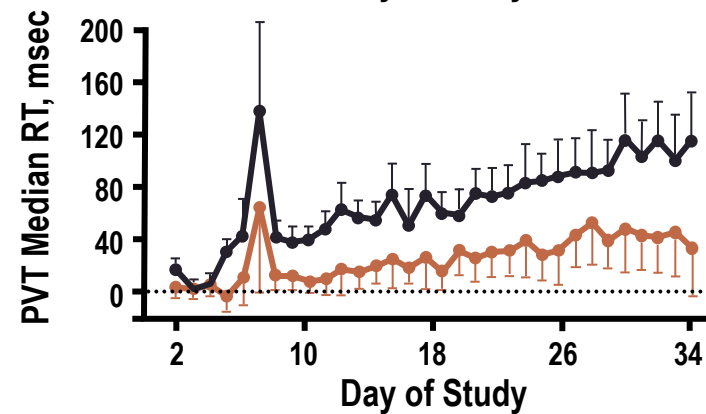
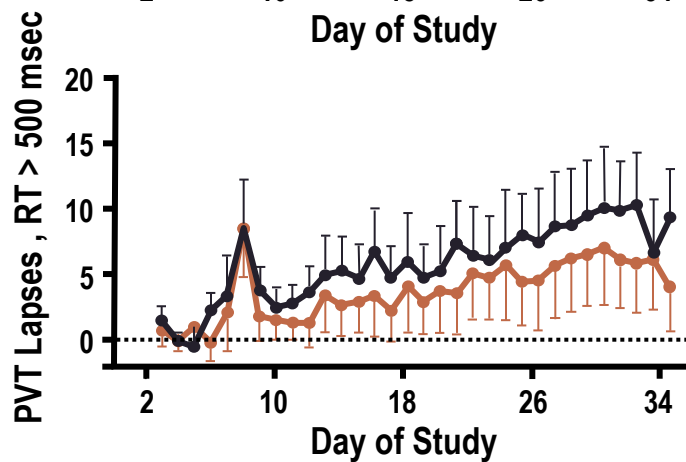
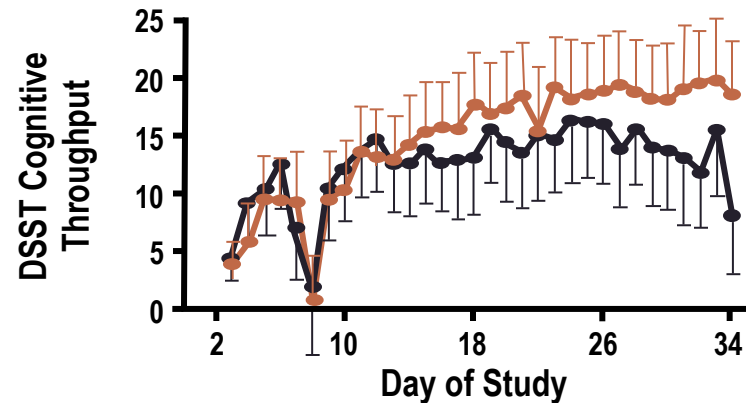
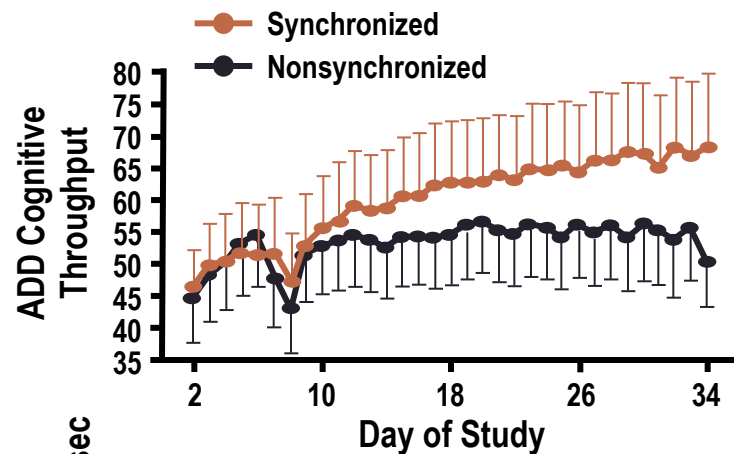


Major implications for:

- Depression
- Ulcers
- Hypertension
- Metabolic disorders
- Neurologic deficits
- Cancer

Drake CL, et al. In: *Principles and Practice of Sleep Medicine*. 5th ed. 2011.  
Wright KP Jr, et al. *Sleep Med Rev*. 2013;17(1):41-54. PMID: 22560640.

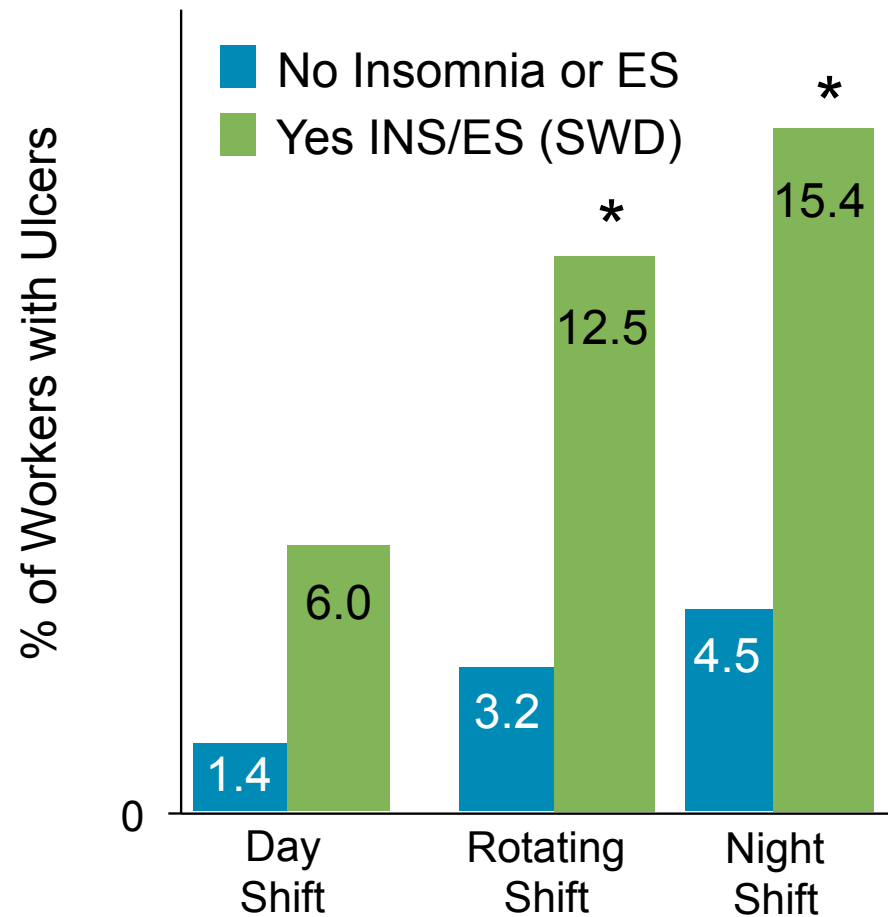
# Circadian Misalignment: Cognitive and Performance Deficits



ADD = mathematical addition test; DSST = digit symbol substitution test; PVT = psychomotor vigilance test; RT = reaction time. N = 7.

Wright KP Jr, et al. *J Cogn Neurosci*. 2006;18(4):508-521. PMID: 16768357.

# Ulcers in Night-Shift Workers

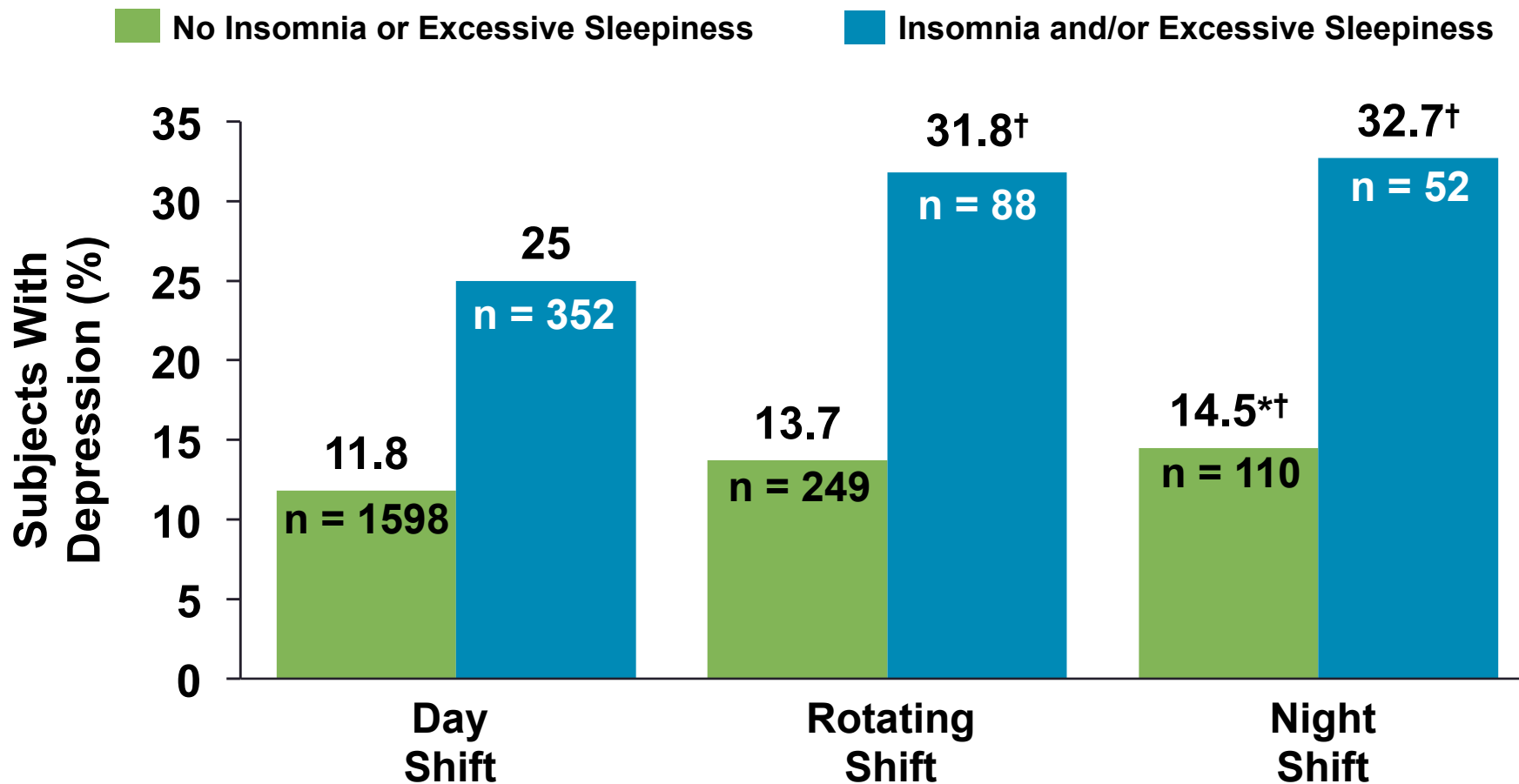


\* $p < .05$  vs. no insomnia.

INS = insomnia; ES = excessive sleepiness; SWD = shift work disorder.

Drake CL, et al. *Sleep*. 2004;27(8):1453-1462. PMID: 15683134.

# Shift Work Disorder and Depression\*



\* Depression was determined using the *Diagnostic Interview Schedule* based on *DSM-IV* criteria.

†p < .05 between insomnia or excessive sleepiness vs. no insomnia or excessive sleepiness.

Drake CL, et al. *Sleep*. 2004;27(8):1453-1462. PMID: 15683134.

# Circadian Rhythm Sleep Disorders: Diagnostic Criteria *ICSD-3*

- A chronic or recurrent pattern of sleep-wake rhythm disruption due primarily to an alteration of the circadian timing system or to a misalignment between the internal circadian rhythm and the sleep-wake schedule desired or required by an individual's physical environment or social/work schedules
- The circadian rhythm disruption leads to insomnia symptoms, excessive sleepiness, or both
- The sleep and wake disturbances cause clinically significant distress or impairment in mental, physical, social, occupational, educational, or other important areas of functioning
- Three months duration



*International Classification of Sleep Disorders, 3rd ed.* American Academy of Sleep Medicine; prepublication with anticipated publication October 2013.

# Evaluation of Circadian Rhythm Disorders

- Important strategy in circadian medicine is to understand:
  - “What time it is in the brain and body”
  - Use phase markers (e.g., core body temperature, melatonin) as “the hands on the clock”
- Prominent recommendation in *ICSD-3* for biomarkers
  - Salivary dim-light melatonin onset (DLMO)
  - 24-hour urinary melatonin



*International Classification of Sleep Disorders*, 3rd ed. American Academy of Sleep Medicine; anticipated publication October 2013.

Sack RL, et al. *Sleep*. 2007;30(11):1460-1483; Sack RL, et al. *Sleep*. 2007;30(11):1484-1501.



# Non-24-Hour Sleep-Wake Disorder (Non-Entrained, Free-Running)



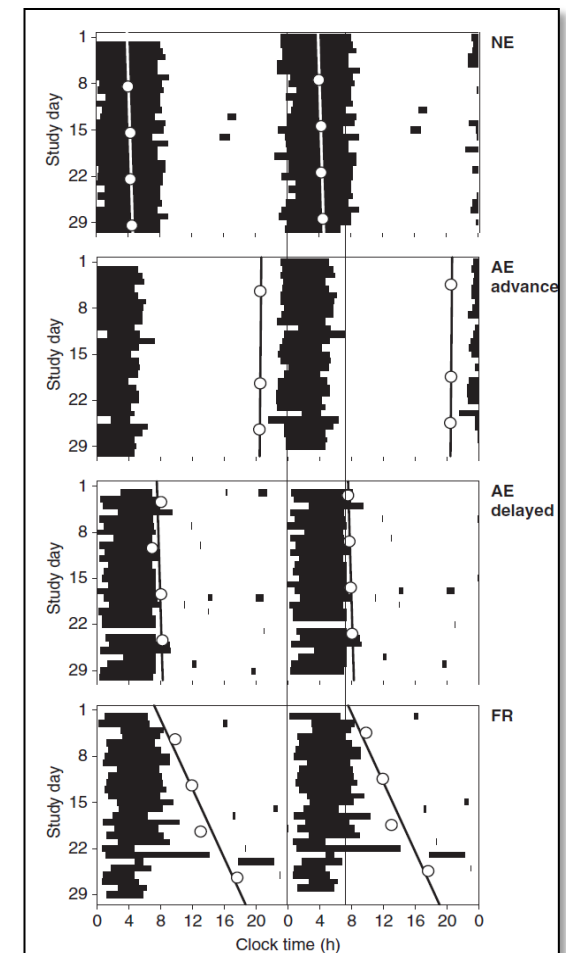
- History of insomnia, excessive daytime sleepiness, or both, which alternate with asymptomatic episodes, **because of misalignment between the 24-hour light-dark cycle and the non-entrained endogenous circadian rhythm of sleep-wake propensity**
- Patients may present with a progressively delaying sleep-wake pattern and intermittent insomnia
- Individual symptoms will depend on when an individual tries to sleep in relation to the circadian rhythm of sleep-wake propensity
- Symptoms persist over the course of at least 3 months
- Sleep diaries and actigraphy for at least 14 days, and preferably longer for blind persons demonstrate a pattern of sleep and wake times that typically delays each day with a circadian period usually longer than 24 hours
  - Note: In addition, other circadian rhythms, such as the dim light melatonin onset or urinary 6-sulfatoxymelatonin rhythm obtained at two time points 4 weeks apart is desirable to confirm the non-entrained rhythm

American Academy of Sleep Medicine. *International Classification of Sleep Disorders*, 3rd ed. Anticipated publication October 2013.

# Non-24-Hour Sleep-Wake Disorder: Highlights in Blind People

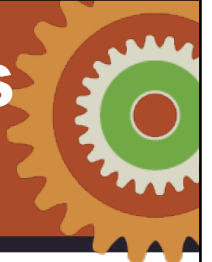


- Approximately 50% of totally blind people have non-24-hour sleep-wake disorder
  - Daily drift may be slow (period close to 24 hours)
  - Relative or weak entrainment to nonphotic stimuli
- Some blind people have intact retinal ganglion cells and retinohypothalamic tract

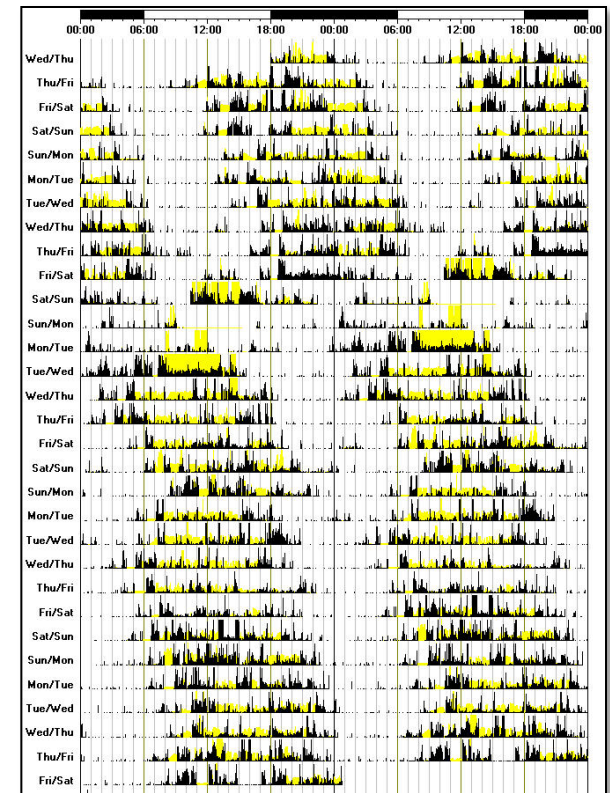


Barion A, Zee PC. *Sleep Med.* 2007;8(6):566-577. PMID: 17395535.  
Lockley SW, et al. *J Sleep Res.* 2008;17(2):207-216. PMID: 18482109.

# Clinical Characteristics of Sighted Patients With Non-24-Hour Sleep-Wake Disorder

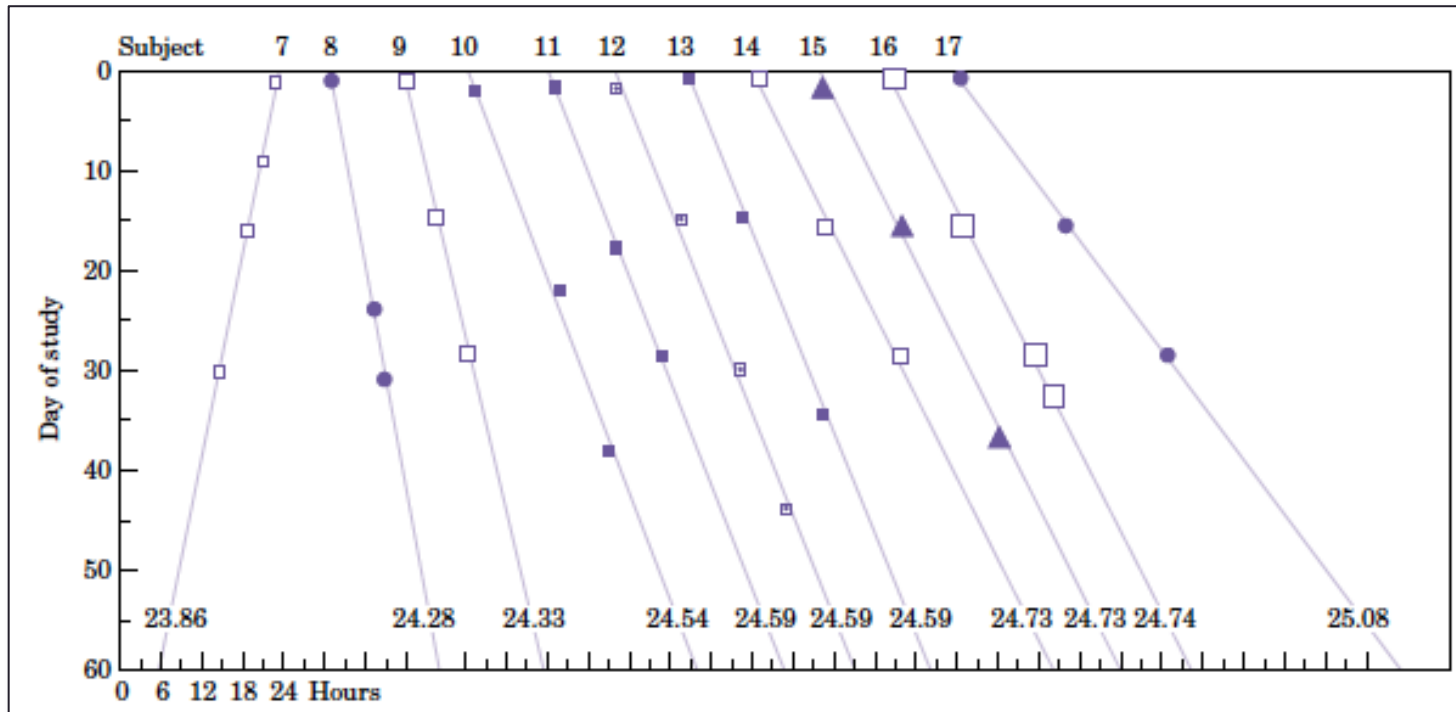


- Overlap between delayed sleep phase and non-24-hour sleep-wake disorders
  - Extreme, prolonged circadian period
- Social or environmental contributions
  - Lack of light exposure
  - Irregular schedules
- Onset in teenage years: 63%
- Mean sleep-wake period: 24.9 hours (range: 24.4 – 26.5)
- Mean total sleep time: 9.3 hours
- Psychiatric disorders preceded diagnosis in 28%; 34% of patients went on to develop major depression



Barion A, Zee PC. *Sleep Med.* 2007;8(6):566-577. PMID: 17395535.  
Hayakawa T, et al. *Sleep.* 2005;28(8):945-952. PMID: 16218077.

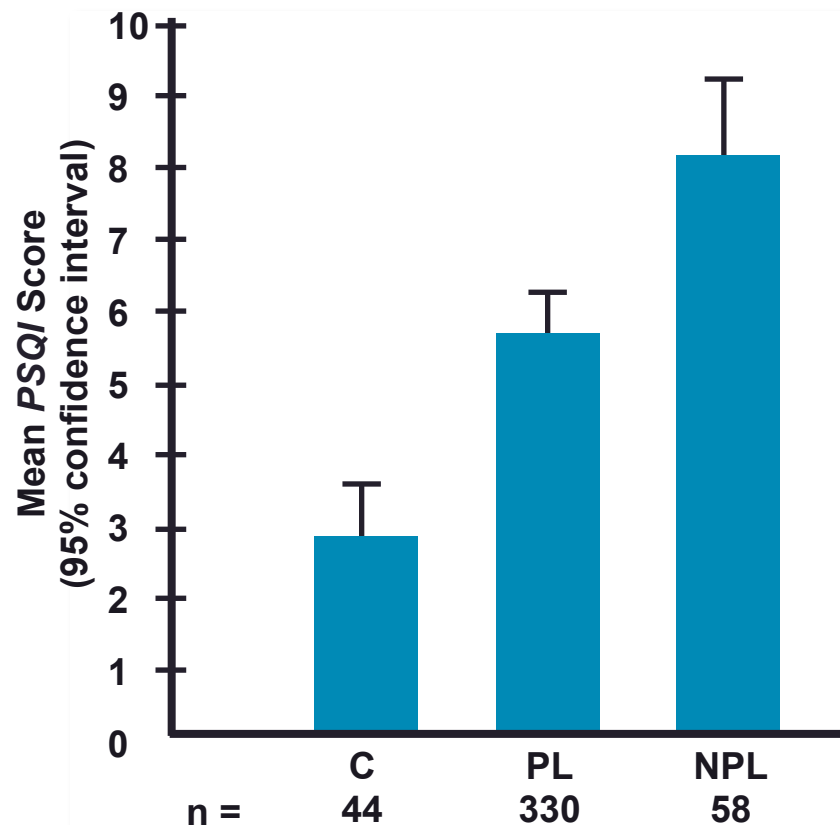
# Circadian Phase in the Blind



Melatonin onsets and circadian periods in 11 totally blind subjects with free-running rhythms. In this group of totally blind subjects, the melatonin onsets and regressions derived for each subject are shown. (The intercepts are evenly spaced so that the data could be displayed more clearly.) The calculated circadian period for each subject is listed with each regression. The slope of the line is proportional to the circadian period; a vertical slope would indicate a period of 24 h (normal entrainment).

Reprinted from Sack RL, et al. *J Clin Endocrinol Metab.* 1992;75(1):127-134. PMID: 1619000.

# Sleep Disturbances in the Blind



*Pittsburgh Sleep Quality Index (PSQI) scores of vision categories. The relationship between visual loss and PSQI score was significant (Pearson  $\chi^2 = 37.5$ ;  $p < .001$ ).*

- C = normally sighted comparisons
- PL = perception of light or better
- NPL = no perception of light

Tabandeh H, et al. *Am J Ophthalmol.* 1998;126(5):707-712. PMID: 9822235.

# Napping in the Blind

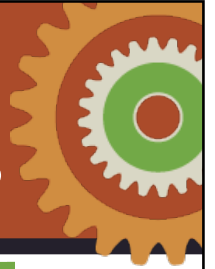
- Mean numbers and durations ( $\pm$  SD) of naps in and out of the normal, 6-sulphatoxymelatonin phase

Subject number	Number of naps per day		Duration of naps per day (minutes)	
	In phase (24:00 to 06:00 h)	Out of phase (06:00 to 24:00 h)	In phase (24:00 to 06:00 h)	Out of phase (06:00 to 24:00 h)
14	0.9 $\pm$ 0.9	2.6 $\pm$ 1.6*	17.9 $\pm$ 21.2	55.8 $\pm$ 54.3
18	0.4 $\pm$ 0.6	0.6 $\pm$ 0.5	18.0 $\pm$ 26.8	24.8 $\pm$ 26.6
20	0.0 $\pm$ 0.0	0.6 $\pm$ 0.5*	0.0 $\pm$ 0.0	84.0 $\pm$ 87.6
31	0.2 $\pm$ 0.4	0.7 $\pm$ 0.9	17.8 $\pm$ 38.3	37.3 $\pm$ 55.0

\*Compared to in phase ( $p < .05$ , one-way ANOVA)

Lockley SW, et al. *J Biol Rhythms*. 1997;12(1):16-25. PMID: 9104687.

# Frequency of Sleep Disorders in Blind Subjects Compared With Sighted Subjects



	Blind	Controls
<b>At least one sleep problem (%)</b>	83	57*
Difficulty falling asleep	35	25*
Awakenings during sleep	54	34*
Inappropriate early morning awakenings	45	23*
Poor sleep quality	34	19*
Curtailed sleep duration	49	25*
<b>Prevalence of insomnia (%)</b>		
According to <i>DSM-IV</i> criteria	35	26*
Psychophysiological insomnia according ICSD-90 minimum criteria	45	28*
Acute psychophysiological insomnia	34	25*
Chronic psychophysiological insomnia	34	24*
<b>Prevalence of daytime sleepiness</b>		
Involuntary napping at least once a day	14	6*
Voluntary napping at least 5 days a week	15	12 <sup>‡</sup>
Average number of naps per week per individual	3.63	3.35 <sup>‡</sup>
<b>ICSD minimum criteria for “free-running patterns”</b>	17	8
<b>ICSD minimum criteria for “obstructive sleep apnea”</b>	6	4 <sup>‡</sup>

\* $p < .001$ ; <sup>‡</sup>Non-significant ( $p > .05$ )

Leger D, et al. *Lancet*. 1996;348(9030):830-831. PMID: 8814013.

# Sleep, Sleep Propensity, Melatonin, and Phase-Angle Measures in Sighted Patients With Non-24-Hour Sleep-Wake Disorder and in Control Subjects



Non-24	SWperiod [95% CI]	HSlength	SPduration	MLduration	Intervals	
					SPon-MLmid	MLmid-SPoff
1	25.09 [24.91-25.27]	9.39	8.56	8.25	3.52	5.03
2	25.23 [25.07-25.39]	9.27	6.38	8.12	1.00	5.04
3	24.63 [24.51-24.75]	8.92	7.45	8.80	2.44	4.98
4	24.91 [24.75-25.07]	8.41	10.11	7.96	4.01	6.32
5	25.73 [25.54-25.92]	11.89	6.99	7.88	3.53	3.64
Mean	25.12	9.58	7.90	8.20	2.90	5.00
SE	0.18	0.60	0.66	0.16	0.54	0.42
Controls (n = 20)						
Mean	24.02	7.33	8.37	8.01	4.77	3.61
SE	0.02	0.31	0.21	0.23	0.30	0.28
<i>p</i>	< .0001	.002	.35	.64	.007	.02

SWperiod = period of sleep-wake cycle (h); HSlength = habitual sleep length (h); SPduration = duration of high sleep propensity (h); MLduration = duration of melatonin secretion (h); SPon-MLmid = interval between sleep propensity onset and melatonin midpoint (h); MLmid-SPon = interval between melatonin midpoint and sleep propensity offset (h)  
 Uchiyama M, et al. *Sleep*. 2002;25(1):83-88. PMID: 11833864.



# Polysomnographic Measures of Sleep in Blind Subjects and Sighted Control Subjects

PSG Indicators	Blind Subjects n = 20	Sighted Control Subjects n = 24	p Value
Total sleep time, min	289.7 ± 80.4	424 ± 50.6	.0001
Sleep latency, min	27.33 ± 52.8	12.16 ± 12.4	NS
REM latency, min	122.3 ± 79.4	72.4 ± 10.9	.004
Sleep efficiency, %	76.2 ± 17.4	92.3 ± 3.6	.0001
Sleep stage, %			
SWS	22.7 ± 10.5	20.7 ± 5.7	NS
REM	12 ± 6	23.7 ± 4.7	.0001

Values are shown as mean ± SD. Unpaired t tests and chi<sup>2</sup> between the two groups.  
PSG = polysomnography; REM = rapid eye movement sleep; SWS = slow wave sleep.  
From Leger D, et al. *Clin Neurophysiol.* 2002;113(10):1607-1614. PMID: 12350437.

# Tasimelteon\*

## Investigational Agent for Non-24-Hour Disorder

- Two Phase II studies
  - SET
    - Safety and Efficacy of Tasimelteon
  - RESET
    - Randomized-withdrawal study of the Efficacy and Safety of Tasimelteon to treat Non-24-Hour Disorder

\* Not FDA approved for treatment of Non-24-Hour Disorder  
Lockley SW, et al. Presented at Sleep 2013. Baltimore, Maryland.

# Tasimelteon\*

## Investigational Agent for Non-24-Hour Disorder

- SET Trial

- Achieved the primary endpoints of
  - Entrainment (synchronizing) of the melatonin (aMT6s) rhythm as compared to placebo
  - Clinical response as measured by entrainment plus a score of greater than or equal to 3 on the Non-24 Clinical Response Scale (N24CRS)
- Significantly improved total sleep time, nap duration, and timing of sleep, and global functioning, compared to placebo

\* Not FDA approved for treatment of Non-24-Hour Disorder  
Lockley SW, et al. Presented at Sleep 2013. Baltimore, Maryland.

# Tasimelteon\*

## Investigational Agent for Non-24-Hour Disorder

- RESET Trial

- Demonstrated that

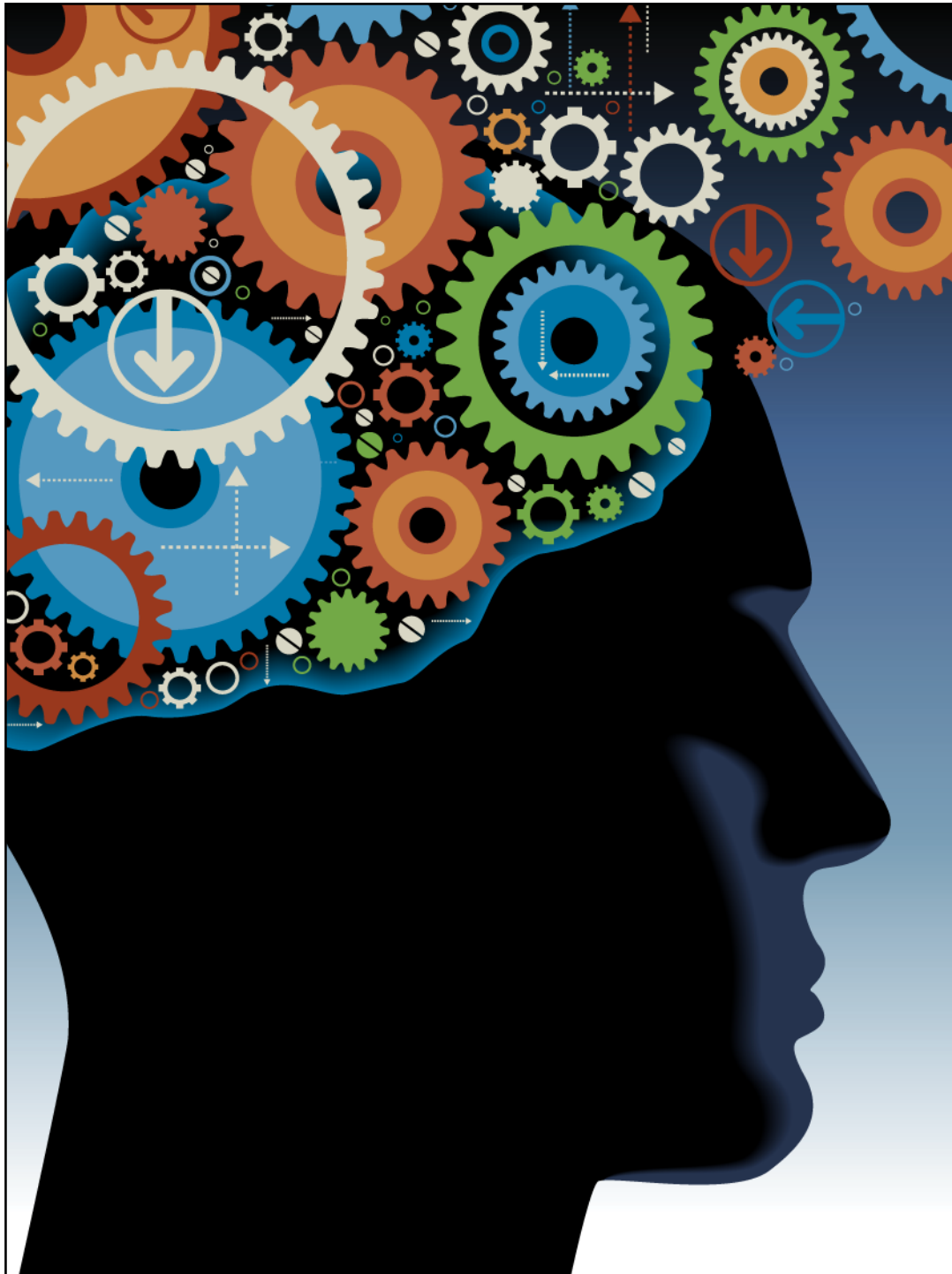
- Continued treatment with 20mg of tasimelteon was required to maintain entrainment of melatonin and cortisol circadian rhythms in individuals with Non-24 disorder

\* Not FDA approved for treatment of Non-24-Hour Disorder  
Lockley SW, et al. Presented at Sleep 2013. Baltimore, Maryland.

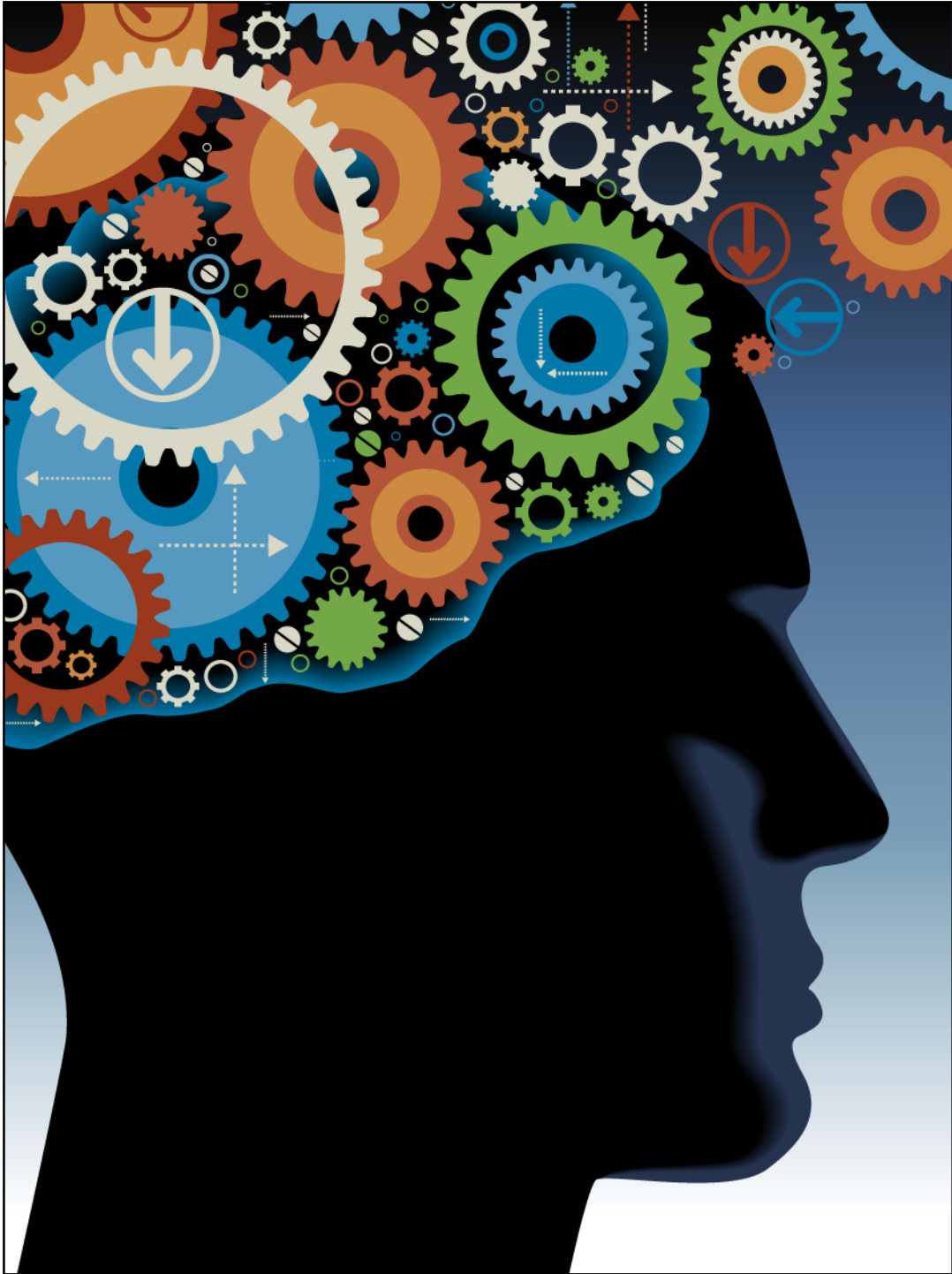
# Clinical Connections



- An important strategy in circadian medicine is to understand *what time it is in the brain and body*, using phase markers as *the hands on the clock*. Circadian rhythms can be assessed by evaluating the timing of biological events, with:
  - Questionnaires
  - Actigraphy
  - Measure of dim-light melatonin onset
  - Sleep diary
  - Core body temperature
- Compared with sighted individuals, blind people have a lower sleep efficiency, a longer sleep latency, a shorter total sleep time, and more frequent naps



# Questions & Answers



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