

# Circadian Rhythms

Ryan G. Wetzler, Psy.D., C.BSM, ABPP  
Director, Behavioral Sleep Medicine  
Sleep Medicine Specialists, Louisville, Kentucky

**Date:**

October 14-15, 2016

**Location:**

Marriott Louisville East



# Conflict of Interest Disclosures

## Speaker:

1. I do not have any potential conflicts of interest to disclose, **OR**

2. I wish to disclose the following potential conflicts of interest

Type of Potential Conflict	Details of Potential Conflict
Grant/Research Support	
Consultant	Mindware Consulting, Inc
Speakers' Bureaus	
Financial support	
Other	

3. The material presented in this lecture has no relationship with any of these potential conflicts, **OR**

4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:

- 1.
- 2.
- 3.

## Disruption of circadian clocks has ramifications for metabolism, brain, and behavior

- *Circadian rhythms are phylogenetically ancient and are present in almost all plants and animals.*
- *Modern industrialized society and the ubiquity of electric lighting has resulted in a fundamental alteration in the relationship between an individual's endogenous circadian rhythmicity and the external environment.*
- *The ramifications of this desynchronization for mental and physical health are not fully understood, although numerous lines of evidence are emerging that link defects in circadian timing with negative health outcomes.*

# Symptoms of Short Term Circadian Disruption (Jet Lag)

- indigestion
- constipation
- diarrhea
- nausea
- loss of appetite
- difficulty concentrating
- feeling disorientated
- anxiety
- irritability
- memory problems
- clumsiness
- lethargy (lack of energy)
- lightheadedness
- confusion
- headaches
- sweating
- muscle soreness
- irregular periods
- generally feeling unwell

# Health Consequences of Chronic Circadian Disruption

- Increased risk for premature death, cancer, metabolic syndrome, cardiovascular dysfunction, immune dysregulation, reproductive problems, mood disorders, and learning deficits (Evans & Davidson, Prog Mol Biol Transl Sci. 2013;119:283-323)
- Cardiovascular disease, diabetes and obesity (Reutrakul & Knutson. Sleep Med Clin. 2015 Dec;10(4):455-68).
- Neurodegenerative disorders such as Alzheimer, Parkinson, and Huntington diseases (Videnovic & Zee. Sleep Medicine Clin. 2015 Dec; 10(4), 469-480).
- Inflammatory Bowel Disease (Swanson, Burgess & Kesharvarzian. Expert Rev Clin Immunol. 2011; 7(1). 29-36.

# Circadian Rhythm Disturbance

- Circadian rhythm sleep disorders are characterized by complaints of insomnia and excessive sleepiness.
- These complaints are primarily due to alterations in the internal circadian timing system or a misalignment between the timing of sleep and the 24-hour social and physical environment

(Barion & Zee, 2007)

# Circadian Rhythm Sleep Disorders (CRSD's)

- Advanced Sleep-Phase Syndrome (ASPS)
- Delayed Sleep-Phase Syndrome (DSPS)
- Shift-Work Sleep Disorder (SWSD)

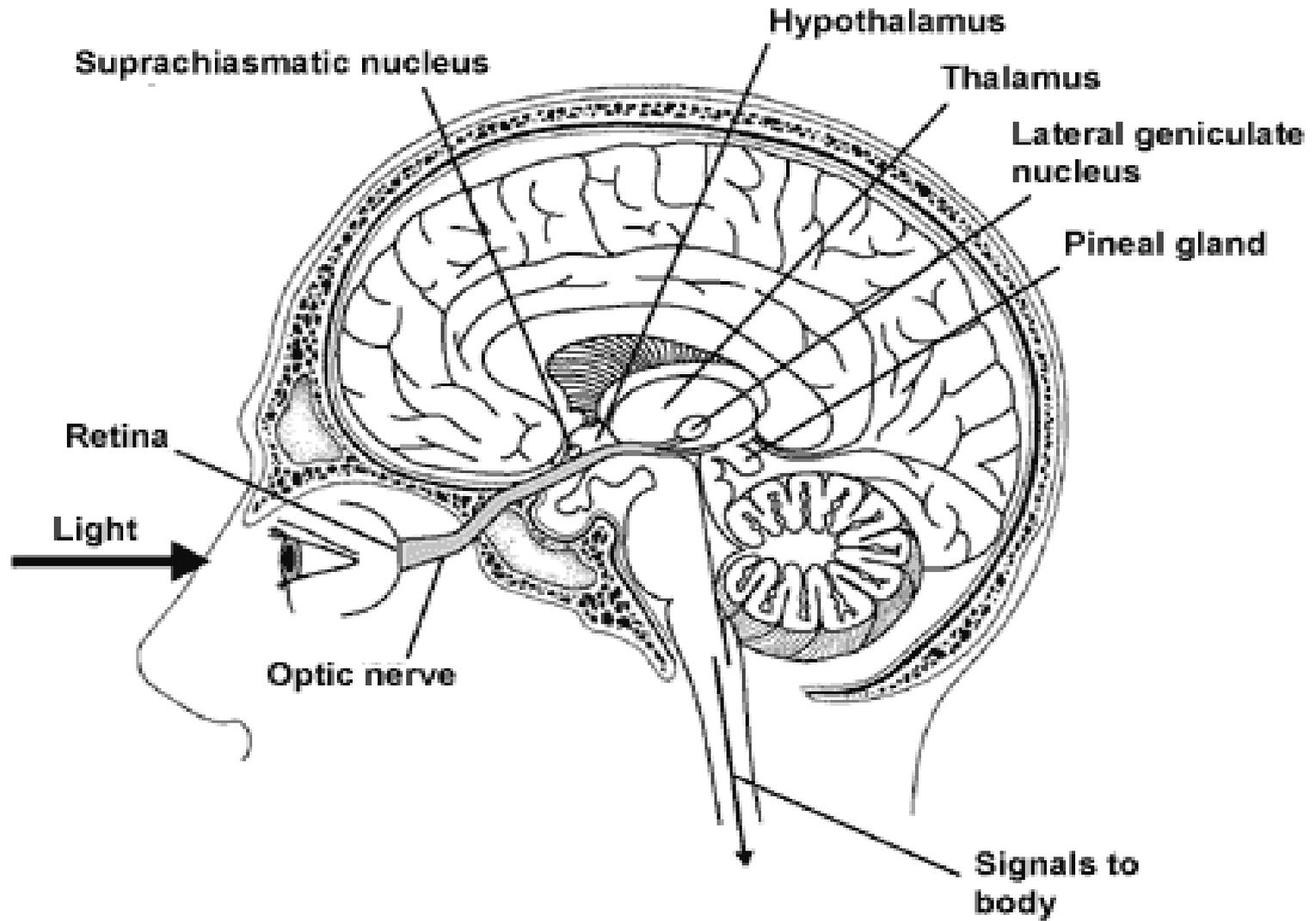
# Evaluation Procedures

- Sleep History Questionnaire
- Insomnia Severity Index
- Morningness-Eveningness Scale
- Epworth Sleepiness Scale
- Pre-Sleep arousal Scale
- Daytime Alertness Scale
- Beliefs and Attitudes About Sleep Scale
- Sleep Logs
- Actigraphy
- Personality Assessment Inventory
- There are others, yet probably impractical for clinical practice.

# Treating CRSDs: Basic Concepts

- Master Circadian Clock
- Zeitgebers (entrainment cues)
- Circadian Rhythms
- Core Body Temperature Minimum (CTmin)
- Phase Response Curve
- Light Therapies
  - Natural Light
  - Light Boxes

# Master Circadian Clock

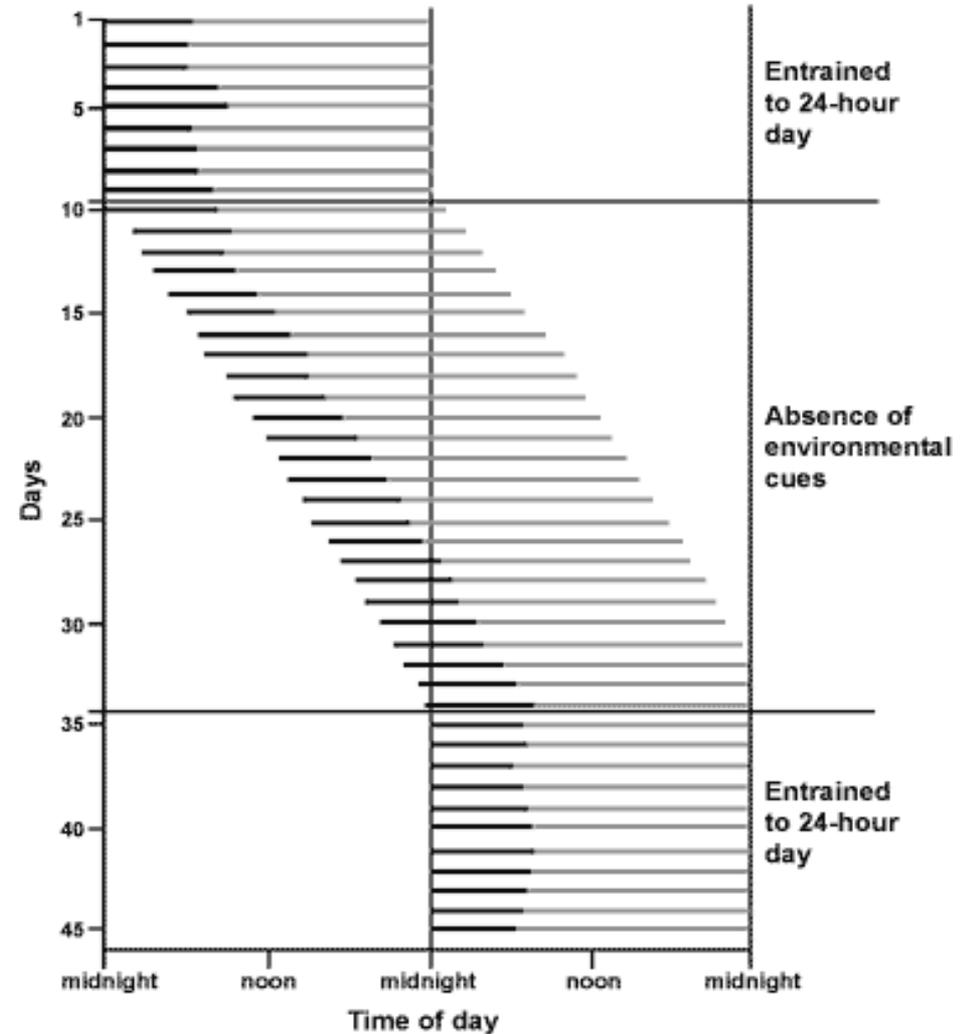


# Zeitgebers

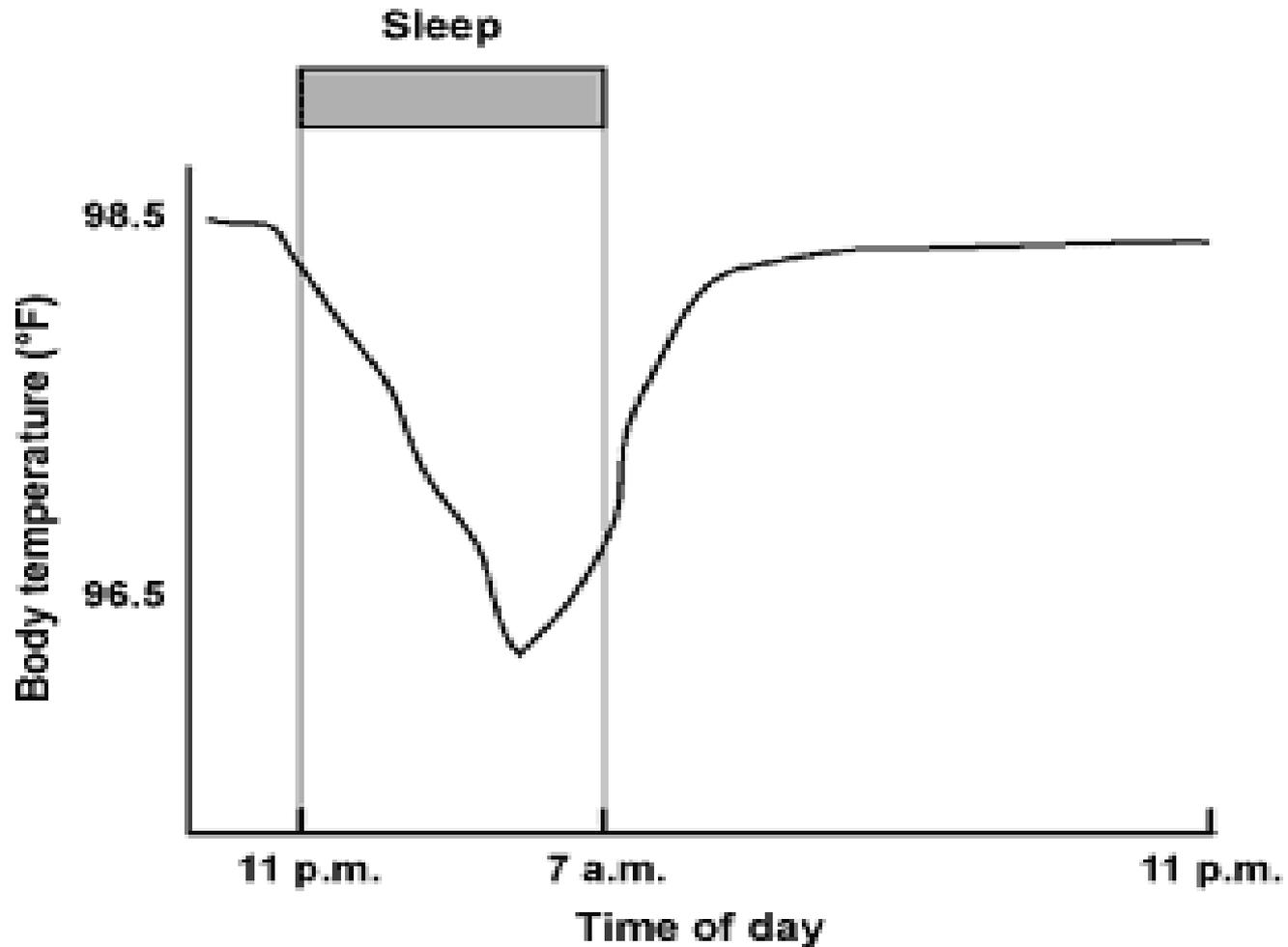
- The cues or entraining forces that operate to keep the large majority of us appropriately synchronized to the 24-hour world.
  - Light (primary)
  - Others include:
    - Physical Activity
    - Social interactions
    - Meal Times
    - Temperature variations.

# Circadian Rhythms

- Initial estimates suggested an average of 25 hours.
- More recent estimates suggest it is actually closer to 24.15-24.18 hours, range of roughly 23.9-24.5 hours



# Core Body Temperature



# Assessment of Core Body Temperature

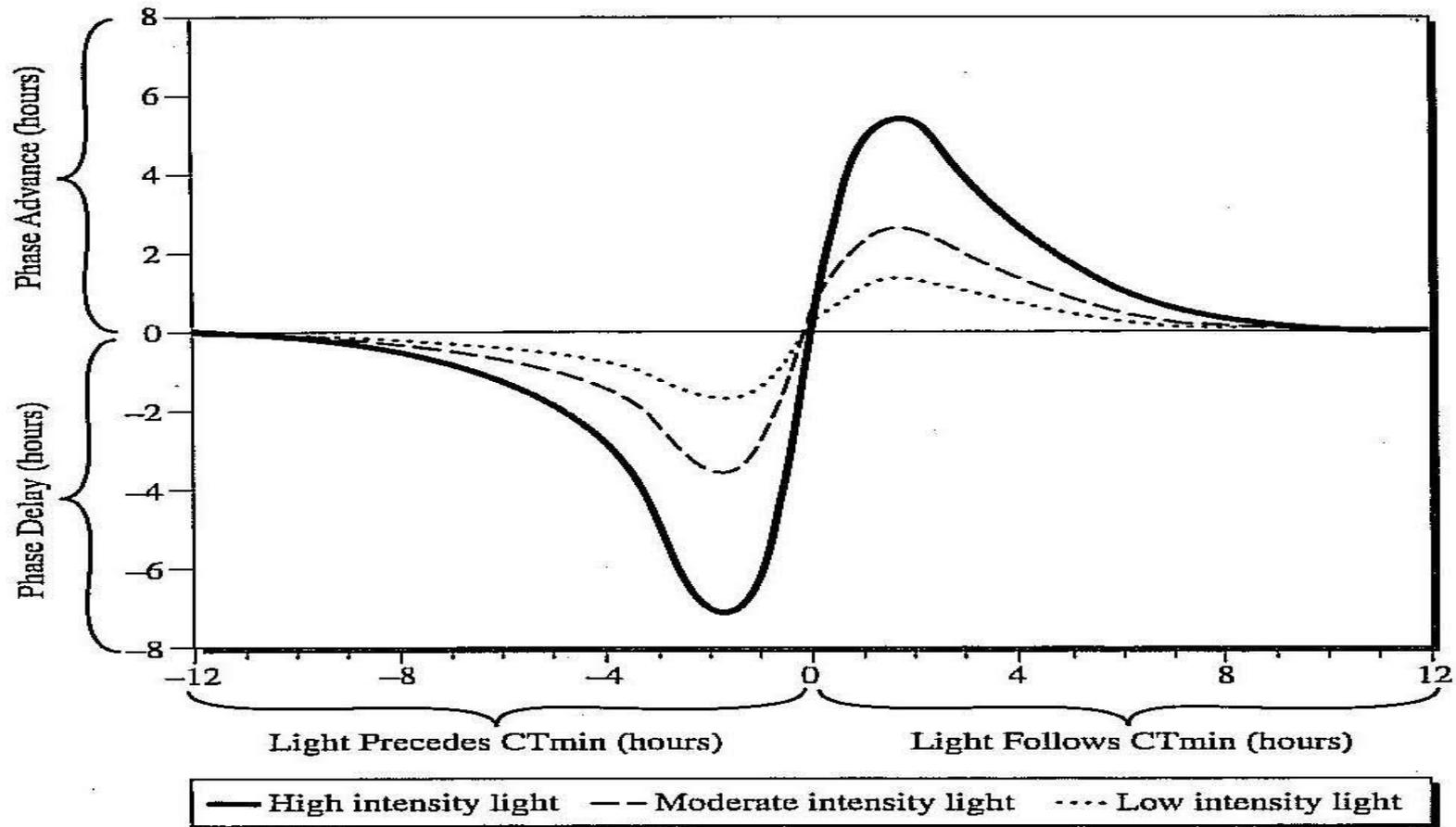


- **Or.....you can just use typical out of bed times as a clinical estimate.**
- **This is accurate within 1-hour for 92% of patients (Burgess et al., 2003; Martin & Eastman, 2002).**

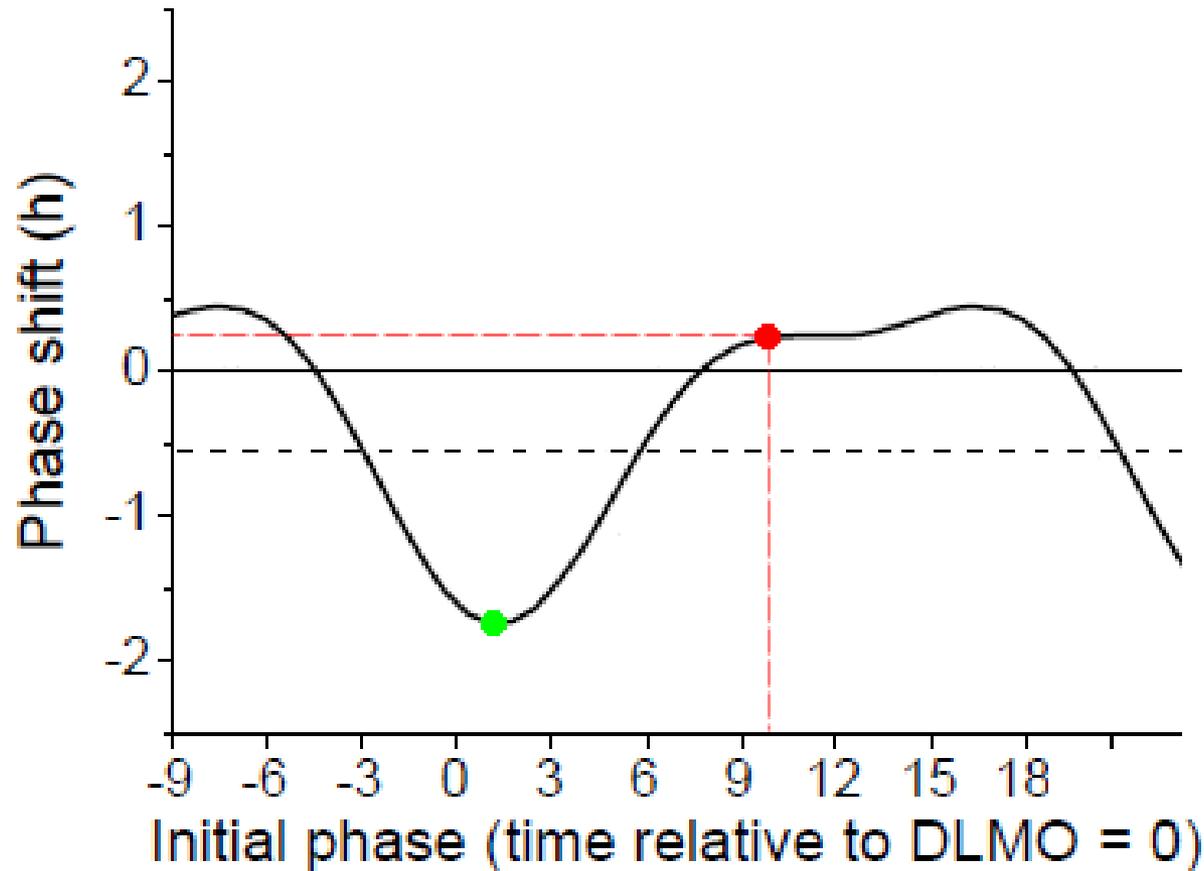
# Dim Light Melatonin Onset (DLMO)

- The time of the onset of melatonin secretion
- The onset of melatonin secretion in the evening is the most reliable and most widely used index of circadian timing in humans.
- Saliva (or plasma) is usually sampled every 0.5–1 hours under dim-light conditions in the evening 5–6 hours before usual bedtime to assess the dim-light melatonin onset (DLMO).
- DLMO typically occurs about 2 hours prior to sleep onset.

# Phase Response Curve relative to CTmin

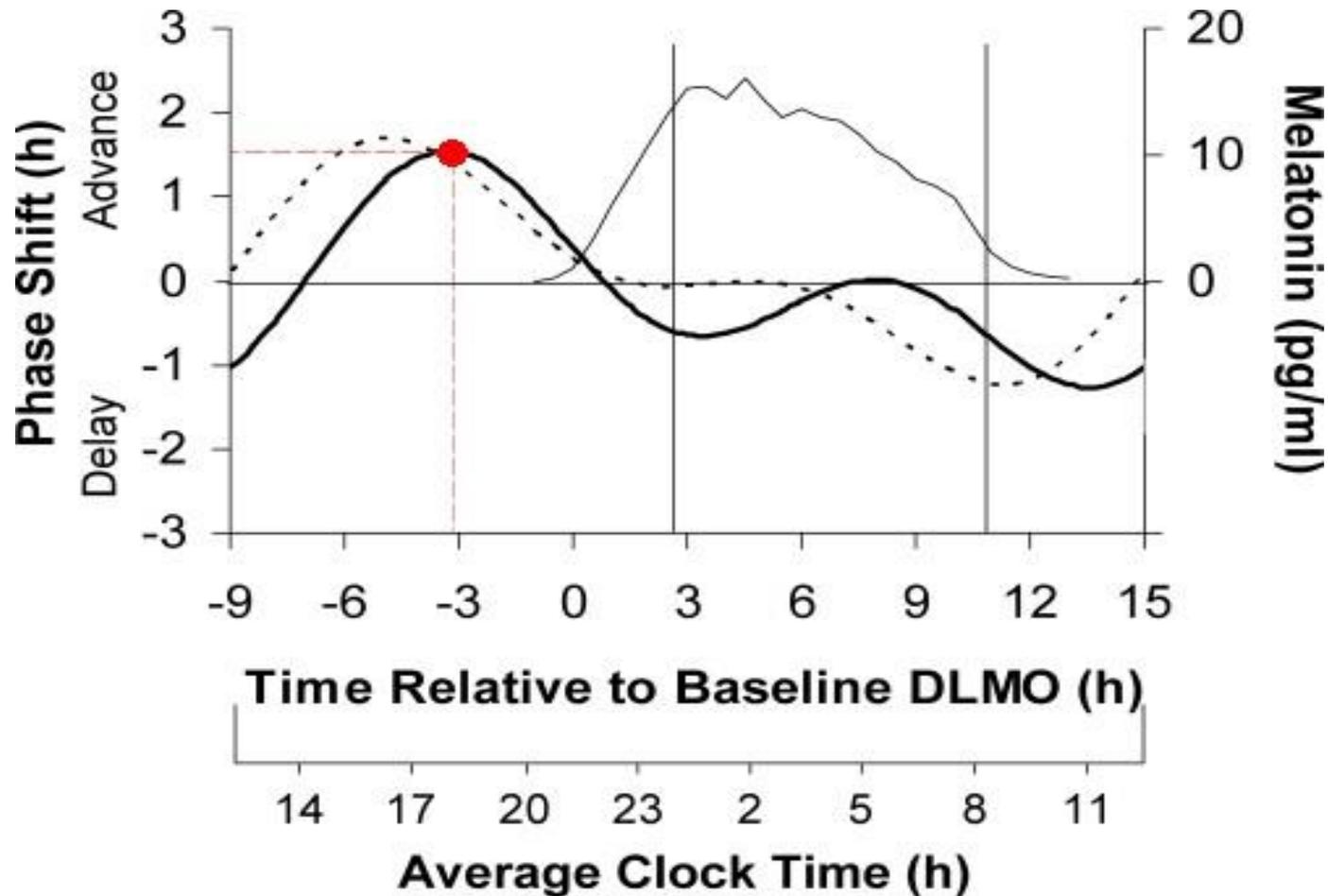


# PRC for One Hour Light Exposure relative to DLMO



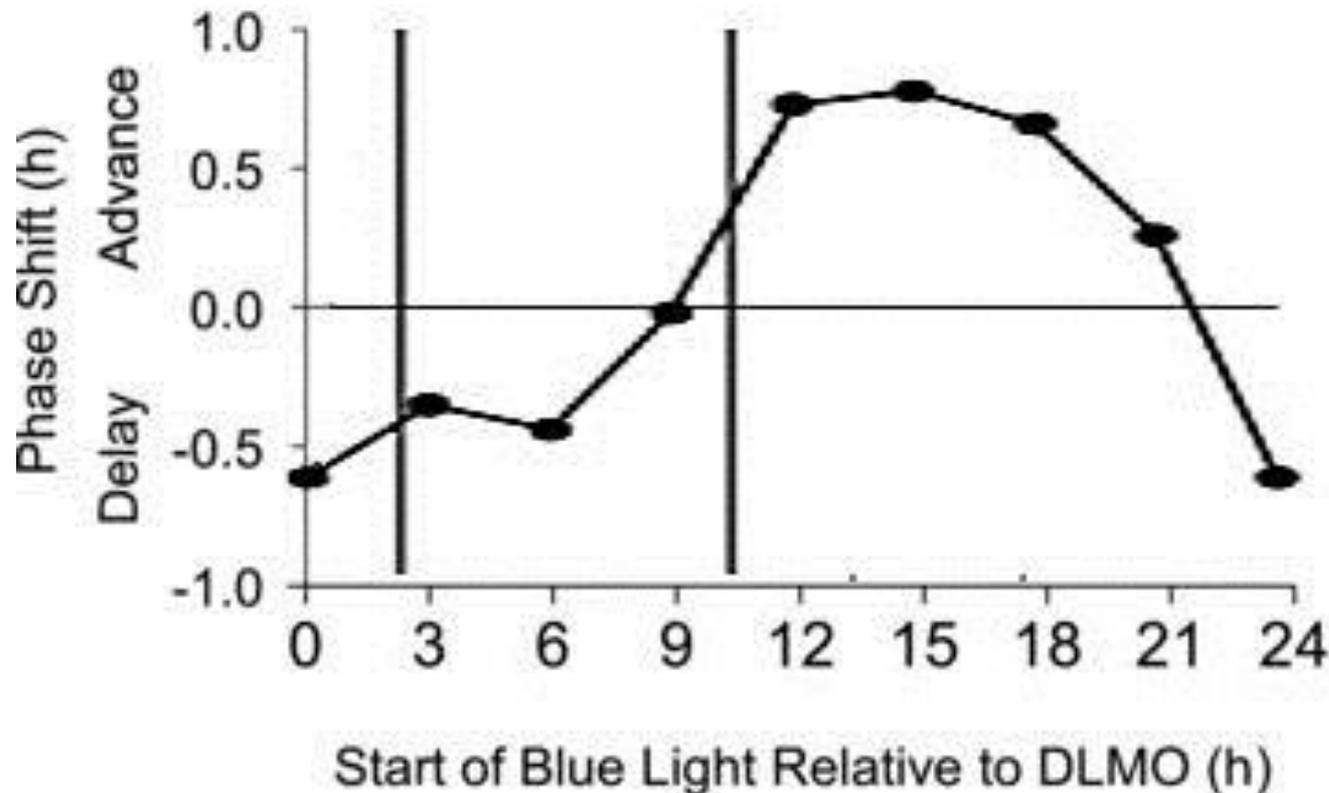
St. Hilaire MA, Gooley JJ, Khalsa SBS, Kronauer RE, Czeisler CA, Lockley SW, [Human Phase Response Curve to a 1-hour pulse of bright white light](#) (*J Physiol.* 2012 Jul 1;590(Pt 13):3035-45)

# PRC for melatonin relative to DLMO



Modified from Burgess HJ, Revell VL, Molina TA, Eastman CI, [Human phase response curves to three days of daily melatonin: 0.5 mg versus 3.0 mg](#) (*J Clin Endocrinol Metab.* 2010 Jul;95(7):3325-31)

# PRC for 1.5 hour Blue Light Relative to DLMO



Revell VL, Molina TA, Eastman CI, [Human phase response curve to intermittent blue light using a commercially available device](#) (*J Physiol.* 2012 Oct 1;590(Pt 19):4859-68)

# Treating CRSD's:

## Basics of Bright Light Therapies

- Light Intensity
  - 100-300 lux = indoor light
  - 10,000 lux = dawn or dusk
  - 150,000 lux = summer noon
  - Bright Light Boxes 2,500-10,000 lux
- Light Timing
  - The closer the time between the light stimulation and the time of the CTmin, the greater the magnitude of phase change
- Light Duration
  - Varies from patient to patient. Need to closely monitor progress.
  - 12-25 days of exposure may be enough to effectively phase shift.
  - Depends on light intensity from 1 hour at 10,000 lux to 4 hours at 2,500 lux

# Clinical Considerations of Bright Light Therapies

- Light therapy appears to be a safe treatment option for circadian rhythm disorders when used within guidelines for light intensity and time limits.
  - In one study light intensity of 10,000 lux for 1250 hours over 5 years produced no major side effects.
- Side Effects
  - Hypomania, irritability, headache and nausea.
    - These symptoms typically subside after several days of treatment and can be reduced or eliminated with dose decreases.

# Treating Advanced Sleep Phase Syndrome

- Phototherapy: Provide light exposure in the early evening and prevent light exposure in the early morning.
- Scheduled activities: Encourage activity in the evening (i.e. Walking outdoors after dinner).
- Address the problem that wakes them up early (i.e. daytime napping).
- Melatonin given in the early morning?
  - In theory would result in a phase delay, although little data exists to support use in this situation.



# Treating Delayed Sleep Phase Syndrome

- Goal is to resynchronize the circadian clock with the desired 24-hour light/dark cycle.
- Gradual (15 minutes every 1-2 days or 30 minutes per week) advance of sleep/wake schedule.
- Avoidance of bright light in the evening
- Phototherapy: 30 minutes at time of awakening
- Exogenous melatonin in the evening (5-6 hours before habitual sleep time).

# Managing Shift Work Sleep Disorder

- Change in work pattern
- Stay on nights 7 days per week
  - Complete circadian adaptation to night shifts and day sleep has been achieved.
    - However, this approach leaves the worker completely out of phase with family and friends on days off, which is a sacrifice few night workers are likely willing to make.
- Scheduled Naps
- Wakefulness promoting agents
  - Modafinil and armodafinil are recommended by the AASM as a guideline to enhance alertness during night shift work.
- Melatonin
  - Some melatonin studies have demonstrated decreased sleep latency and increased sleep duration, others have failed to demonstrate any subjective or objective benefits.
  - Regardless, the AASM recommends the use of melatonin as a guideline in the treatment of patients with SWSD



# Night Shift Performance is Improved by a Compromise Circadian Phase Position

Smith and Eastman, *SLEEP*, Vol. 31, No. 12, 2008

- Night shifts from 11:00pm – 07:00am.
  - Sleep starting at 8:30am after night shifts and at 3:00am on days off.
  - Goal was to delay the sleepest circadian time out of the night work period so that it fell within sleep episodes after night shifts and on days off, but to keep it from delaying too far, beyond the scheduled sleep episodes on days off.
- Sleep was scheduled from 8:30am to 3:30pm (7 h) after the first 2 night shifts, from 08:30 to 1:30pm (5 h) after the third night shifts, from 3:00am to 12:00pm (9 h) on the 2 weekend days off, and again from 8:30am to 3:30pm after the final 4 night shifts.
  - Experimental subjects were required to go outside for  $\geq 15$  minutes of light exposure within 2 h after the end of these scheduled sleep periods (the “light brake”).
- Subjects in the experimental groups were exposed to five 15-min intermittent bright light pulses each night shift. The first pulse began at 00:45 and the last pulse ended at 05:00. Pulses were interspersed by 45 min of normal room light ( $< 50$  lux).
- All subjects wore sunglasses at all times when outside during daylight hours.
  - Sunglasses for experimental subjects more strongly attenuated short wavelength light.



# Night Shift Performance is Improved by a Compromise Circadian Phase Position

- The average final DLMO of the experimental group was about 04:30, which is slightly later than the target compromise phase position of 03:00. The average final DLMO of the control group was about 00:30.
- The control group had longer reaction times on the SRT (simple reaction time) task than the experimental group.

# Summary

- Circadian disruption in both the short and long-term is associated with a number of physical and mental consequences.
- Great advances have been made regarding our understanding of the functioning of the circadian timing system.
- Treatment approaches are available for all major circadian rhythm sleep disorders.
- Bottom line: Humans are designed to function optimally on the natural light/dark schedule.