Treating Circadian Rhythm Disorders

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Disclosures

- I have nothing to disclose

Learning Objectives

- Briefly review the functioning of the circadian system
- Discuss different methods of treatment for delayed sleep phase syndrome
- Review other types of circadian rhythm disorders and their treatment

The Circadian Rhythm

- Circadian – “about a day”
- Regulated by internal pacemakers
- Entrains to external cues

The Two-Process Model

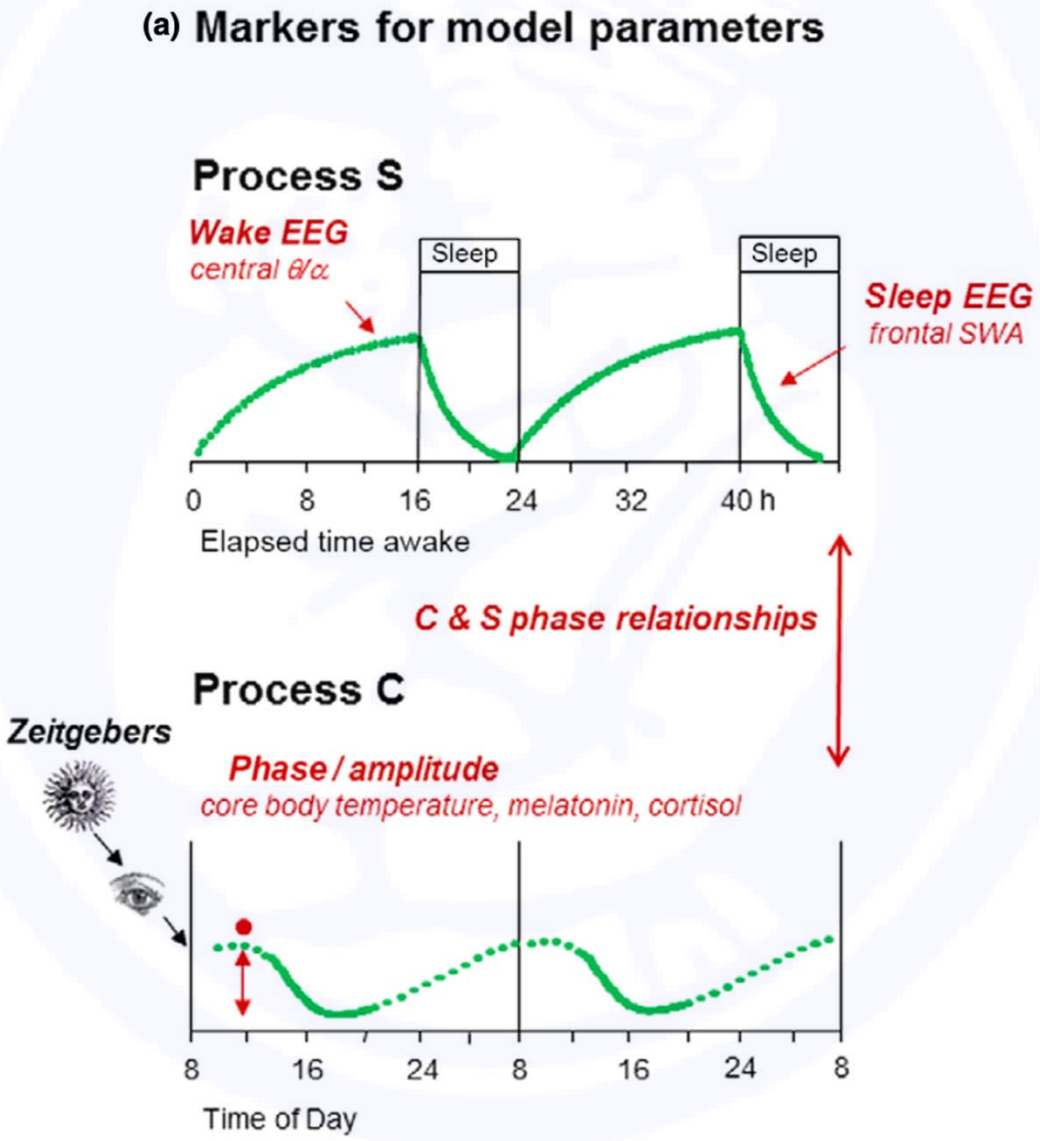


Image from: Borbely, AA, et al. (2016)

Borbely, AA, et al. (2016)
Kryger, M, Roth, T, and Dement, WC (Ed.). (2017)

The Two-Process Model

- Not a perfect explanation
- Slow-wave activity does show variation in rate of build-up
- Alertness and sleep inertia have also been postulated to play a role and vary across different points
- Difficult to separate and study

Borbely, AA, et al. (2016)
Kryger, M, Roth, T, and Dement, WC (Ed.). (2017)

The Circadian System

Image from: Kryger, M, Roth, T, and Dement, WC (Ed.). (2017)

Adolescence – Process S

- Alterations in sleep homeostasis
  - Taylor, et al. (2005) studied 9 pre-pubertal and 11 post-pubertal teens
  - Post-pubertal teens took longer to fall asleep past typical bedtimes

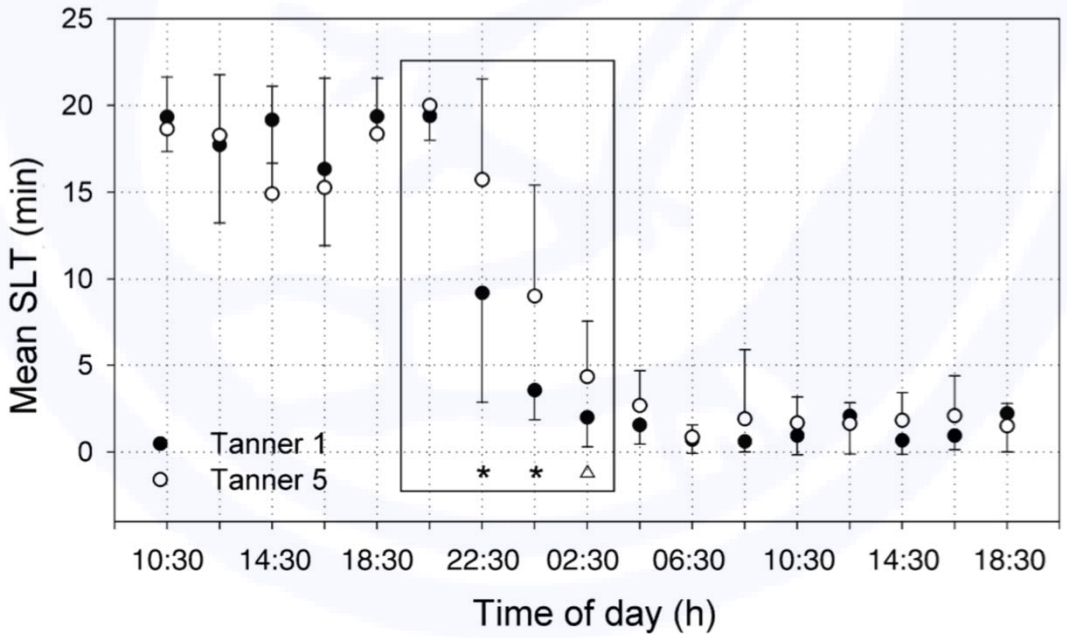


Image from: Taylor, DJ, et al. (2005)

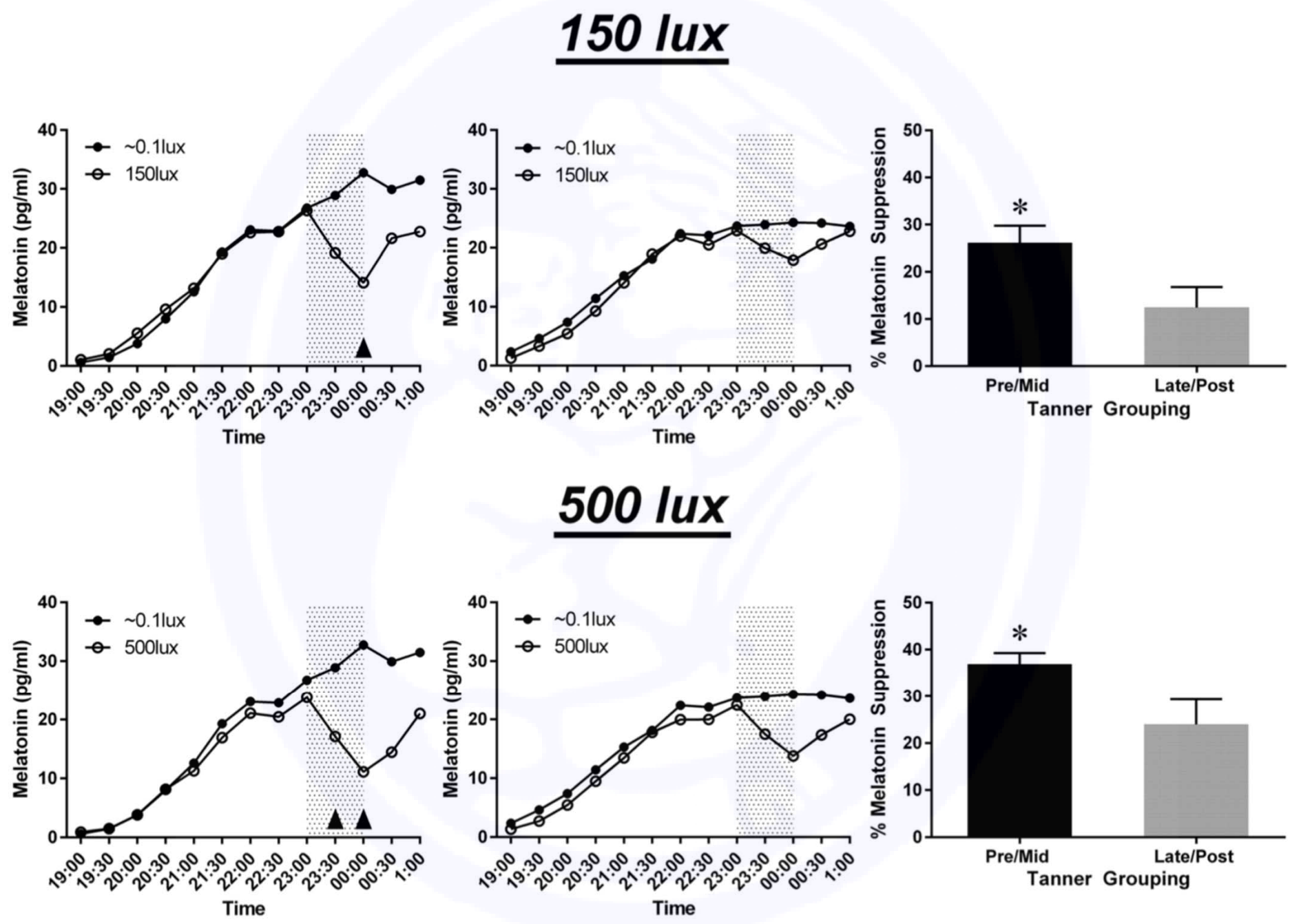


Image from: Crowley, et al. (2015).

Diagnosis

- Primarily clinical diagnoses
- Thorough sleep history, including:
  - Bedtime routine
  - Time to sleep onset
  - Wake time for school
  - Weekend differences
  - Improvement on vacations/on preferred schedule
  - Screen time and light exposure

Sleep Logs

Image from Boston Children's Hospital Sleep Disorders Clinic

0=would never doze or sleep
1=slight chance of dozing or sleeping
2=moderate chance of dozing or sleeping
3=high chance of dozing or sleeping.

Circle the most appropriate number for each situation:

1. Sitting and reading	0	1	2	3
2. Watching television	0	1	2	3
3. Sitting inactive in a public place (for example, a movie theater or classroom)	0	1	2	3
4. As a passenger in a car for an hour without a break	0	1	2	3
5. Lying down to rest in the afternoon when circumstances Permit	0	1	2	3
6. Sitting and talking to someone	0	1	2	3
7. Sitting quietly after lunch	0	1	2	3
8. Doing homework or taking a test	0	1	2	3

Actigraphy

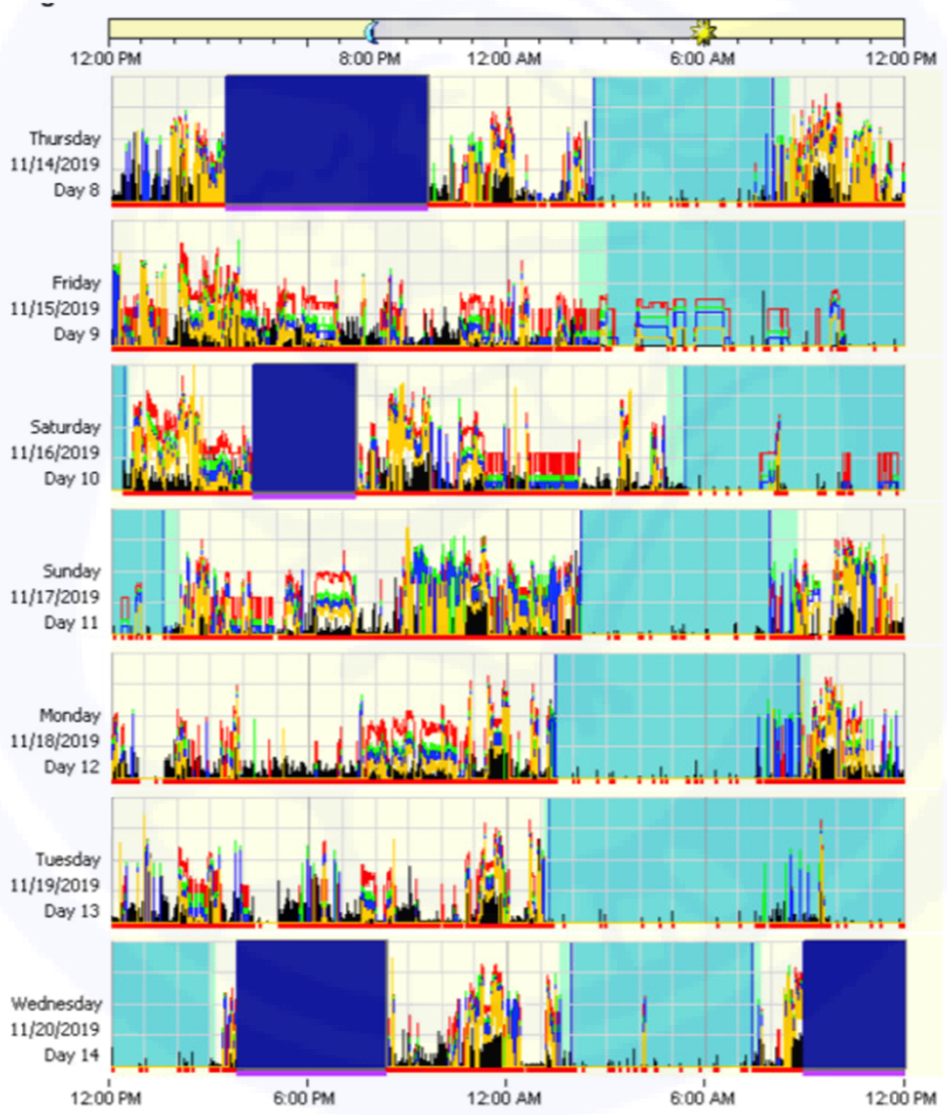
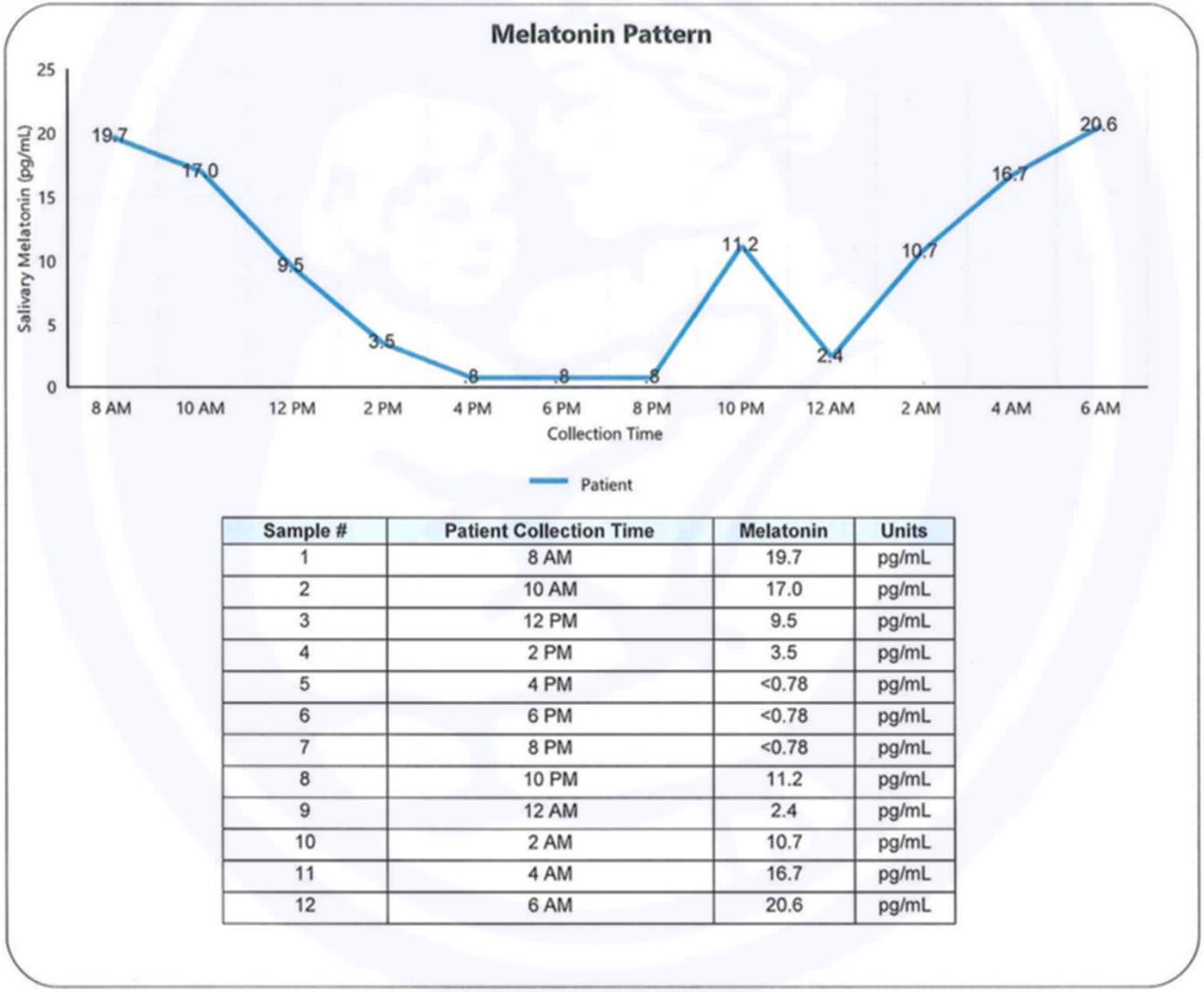


Image courtesy of Joshua August

Melatonin Profiling



Sample #	Patient Collection Time	Melatonin	Units
1	8 AM	19.7	pg/mL
2	10 AM	17.0	pg/mL
3	12 PM	9.5	pg/mL
4	2 PM	3.5	pg/mL
5	4 PM	<0.78	pg/mL
6	6 PM	<0.78	pg/mL
7	8 PM	<0.78	pg/mL
8	10 PM	11.2	pg/mL
9	12 AM	2.4	pg/mL
10	2 AM	10.7	pg/mL
11	4 AM	16.7	pg/mL
12	6 AM	20.6	pg/mL

Image courtesy of Joshua August

Delayed Sleep-Wake Phase Disorder

- "Significant" delay in the phase of the major sleep episode in relation to the desired schedule
- Present for at least 3 months
- Improved on an ad-lib schedule
- Sleep logs or actigraphy demonstrate the delay
- Not better explained by something else

American Academy of Sleep Medicine. (2014)

Sleep Need

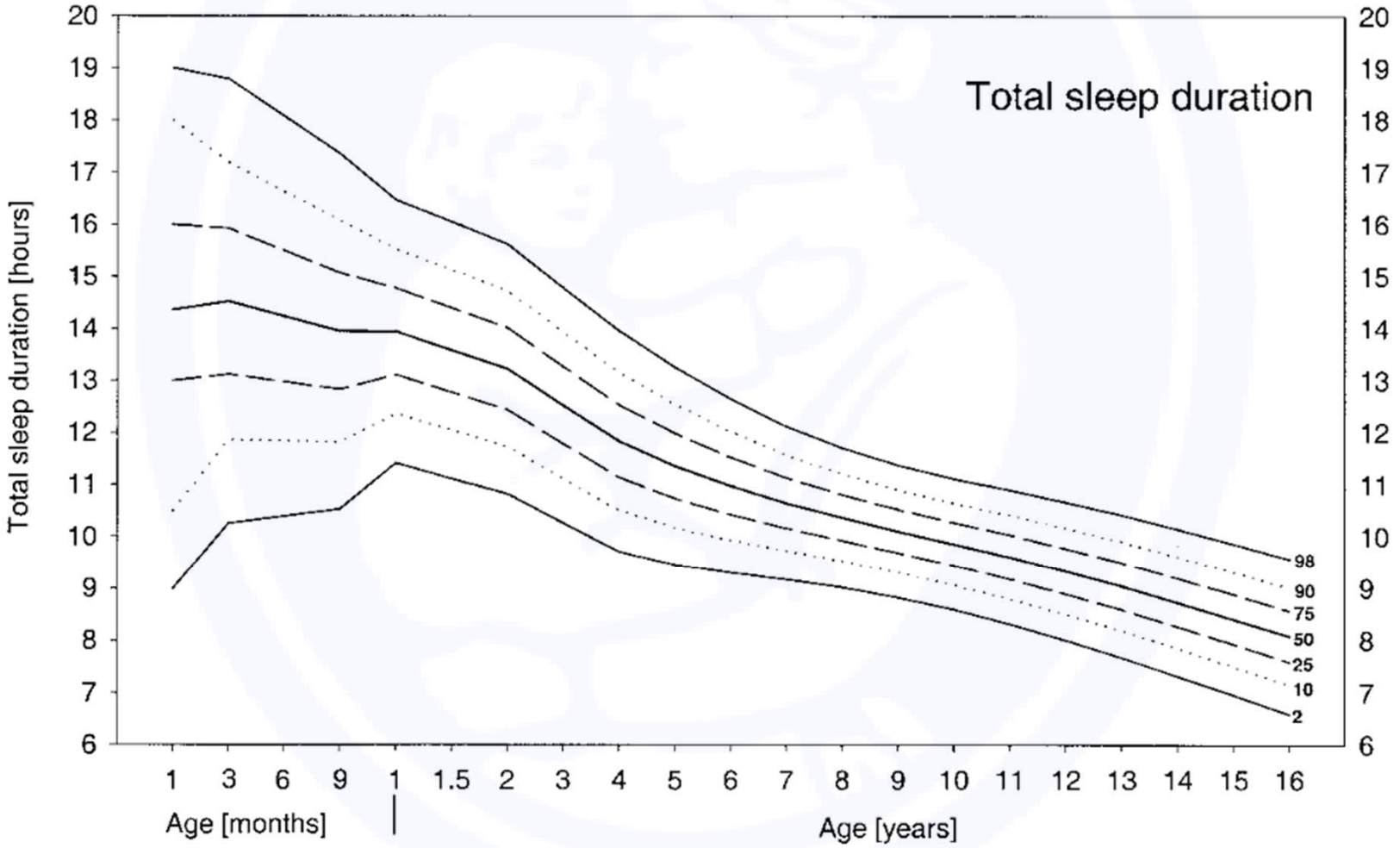


Image from: Iglowstein, I, et al. (2003)

Image from: Auger, RR, et al. (2015)

Treatment Strategies

Table 6—Recommendation statements for treatment of patients with intrinsic CRSWDs.

Treatment (PICO Question)	Recommendation Statement	Direction and Strength of Recommendation	Quality of Evidence	Benefits/ Harms Assessment	Patients' Values and Preferences
Advanced Sleep-Wake Phase Disorder (ASWPD)					
5.1.4 Light therapy (PICO Question 4)	**5.1.4a** The TF suggests that clinicians treat adult ASWPD patients with evening light therapy (versus no treatment)	WEAK FOR	VERY LOW	Benefits closely balanced with harms	The majority of patients would use this treatment.
Delayed Sleep-Wake Phase Disorder (DSWPD)					
5.2.6 Timed oral administration of melatonin or agonists (PICO Question 6)	**5.2.6.1a** The TF suggests that clinicians treat DSWPD in adults with and without depression with strategically timed melatonin (versus no treatment)	WEAK FOR	LOW	Uncertainty in the estimates of benefits/ harms	The majority of patients would use this treatment.
	5.2.6.2.1a The TF suggests that clinicians treat children and adolescents with DSWPD (and no comorbidities) with strategically timed melatonin (versus no treatment)	WEAK FOR	MODERATE	Uncertainty in the estimates of benefits/ harms	The majority of patients would use this treatment, with appropriate informed consent from the patient and caregiver.
	5.2.6.2.2a The TF suggests that clinicians treat children and adolescents with DSWPD comorbid with psychiatric conditions with strategically timed melatonin (versus no treatment)	WEAK FOR	LOW	Uncertainty in the estimates of benefits/ harms	The majority of patients would use this treatment, with appropriate informed consent from the patient and caregiver.
5.2.9 Combination Treatments	**5.2.9.2a** The TF suggests that clinicians treat children/adolescents with DSWPD with post-awakening light therapy in conjunction with behavioral treatments (versus no treatment)	WEAK FOR	LOW	Benefits outweigh harms	The majority of patients would use this treatment, particularly with active caregiver support.

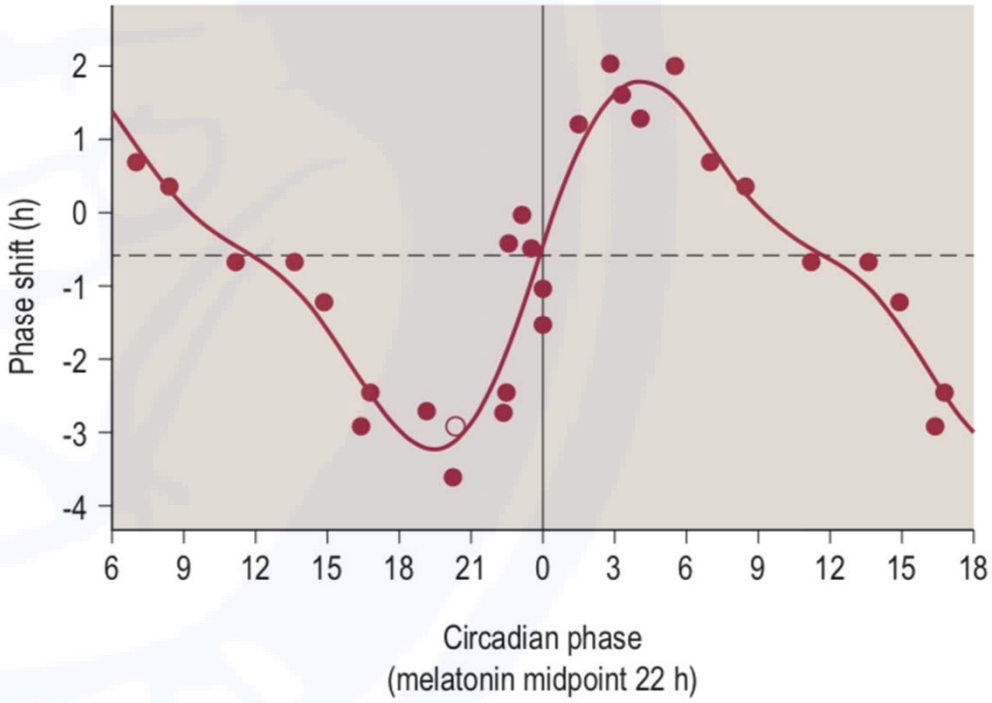
Optimal sleep hygiene

- Unclear effect due to minimal research, but will set groundwork for other portions
- Negotiate a reasonable sleep schedule based on sleep needs and social obligations
- Restrict naps
- Avoid electronics before bed and during the sleep zone

Bartlett, DJ, et al. (2013)

Morning Light Therapy

- Optimally given after waking
- Start with habitual wake time
- Advance by 15-30 minutes every 2-3 days



Bartlett, DJ, et al. (2013)
Figueiro, MG. (2016)
Sharkey, KM, et al. (2011)
Wilhelmsen-Langeland, A, et al. (2013)

Image from: Sheldon, SH, et al (Ed.). (2014)

Morning Light Therapy

- Natural light, when available
- 10,000 lux lightbox
- Blue light enriched lightbox
- Goal is for 30 minutes

Cautions with Light Therapy

- Headache
- Visual discomfort
- Risk of hypomania?

Wilhelmsen-Langeland, A, et al. (2013)
Zhou, T, et al. (2018)

Melatonin

- Even small doses (0.1 to 0.3 mg) have been shown to have circadian re-timing effects
- Optimally timed with knowledge of DLMO

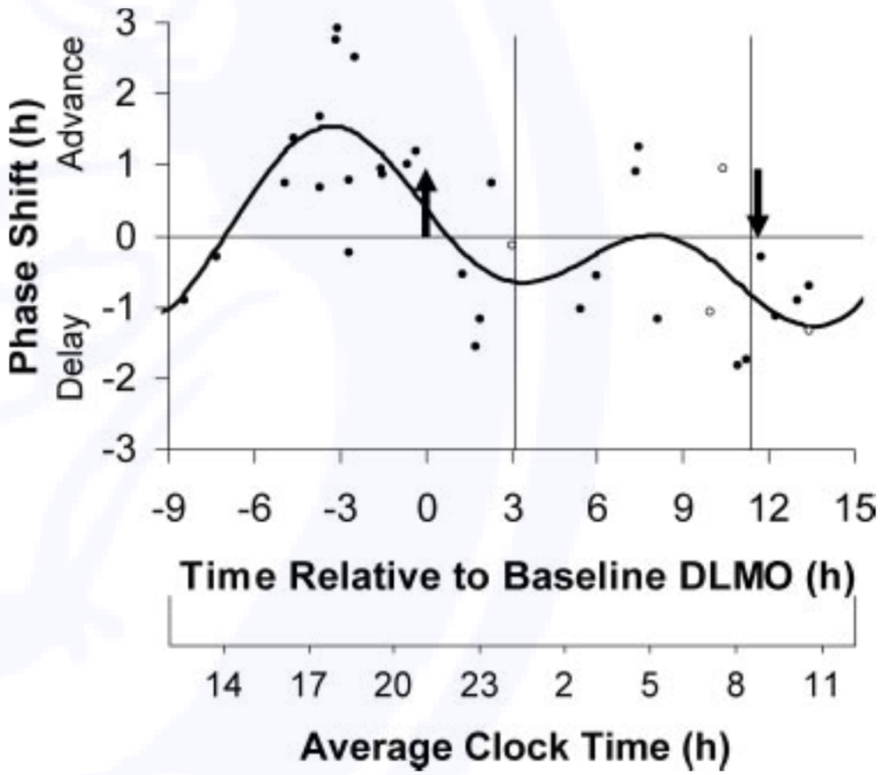


Image from: Burgess, HJ, et al. (2010)

Melatonin

- Generally well-tolerated
- Somnolence
- Headaches
- Risk of seizure
- No effect – may be related to variability of preparations

Erland, LAE, and Saxena, PK. (2017).
Heussler, H, et al. (2013).

Light Restriction

- Field studies have shown later DLMO when maximizing home light compared to maintaining a dim environment
- Blue light block glasses may have potential effects
  - Less alerting effects of light
  - Less melatonin suppression
  - But NO actual delay in DLMO seen

Burgess, HJ and Molina, TA. (2014)
Van der Lely, S, et al. (2015)

Additional Avenues?

- Timed exercise
- Diet?

Bartlett, DJ, et al. (2013).
Sherman, H, et al. (2012).

Chronotherapy

- Delay the sleep schedule progressively further until reaching the desired time
- Very disruptive to families attempting the protocol
- Rare case-report of transitioning to a free-running circadian rhythm

Auger, RR, et al. (2015).
Hayakawa, T, et al. (2005).

General Approach

- Start with the habitual sleep zone with an age-appropriate amount of sleep
- Advance wake times gradually with morning light exposure
- Avoid electronics and light exposure prior to bedtime
- May consider the addition of chronobiotic melatonin

Co-Morbid Conditions

- "Evening" chronotype
- Mood disorders
- ADHD
- Neurodevelopmental disorders
- Family history

American Academy of Sleep Medicine. (2014)

Advanced Sleep-Wake Phase Disorder

- "Significant" advance in the phase of the major sleep episode in relation to the desired schedule
- Present for at least 3 months
- Improved on an ad-lib schedule
- Sleep logs or actigraphy demonstrate the delay
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American Academy of Sleep Medicine. (2014)

Treatment Strategies

- Similar to DSWPD, but the goal is to advance
- Using the phase response curve, this means:
  - Evening light therapy
  - Morning melatonin administration
  - Gradual sleep delay

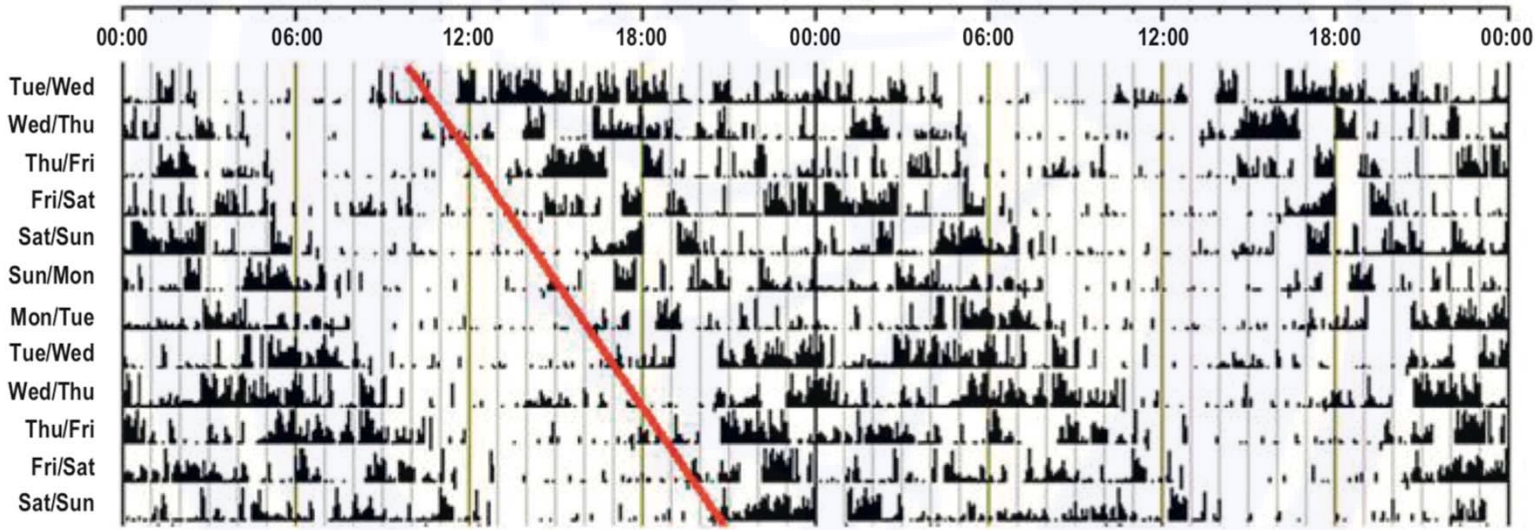
Non-24-Hour Sleep-Wake Rhythm Disorder

- Alternating periods of insomnia, excessive daytime sleepiness, and relatively normal sleep
- Present for at least 3 months
- Sleep logs or actigraphy demonstrate a typical delay in sleep timing each day
- Not better explained by something else

American Academy of Sleep Medicine. (2014)

Diagnosis

- Actigraphy/Sleep Diaries



- Repeated melatonin profiles

Image from: Sheldon, SH, et al (Ed.). (2014)

Treatment

- No large-scale trials on treatment
- Timed-constant melatonin may help with entrainment, as may constant light therapy
- Tasimelteon was recently approved in adults, but is just emerging in clinical use

Uchiyama, M, and Lockley, SW. (2015).

Summary

- The circadian system helps to regulate sleep timing, with light being the primary entrainment signal
- Delayed sleep-wake phase syndrome is most commonly seen, and both behavioral, light, and melatonin manipulation may be needed
- Understanding of circadian processes and entraining signals can help treat other disorders

References

- American Academy of Sleep Medicine. (2014). *International Classification of Sleep Disorders, Third Edition*. Darien, IL: American Academy of Sleep Medicine.
- Auger, RR, et al. (2015). Clinical practice guildeline for the treatment of intrinsic circadian rhythm sleep-wake disorders: advanced sleep-wake phase disorder (ASWPD), delayed sleep-wake phase disorder (DSWPD), non-24-hour sleep-wake rhythm disorder (N24SWD), and irregular sleep-wake rhythm disorder (ISWRD): an update for 2015. *JCSM* 11(10): 1199-1236.
- Bartlett, DJ, et al. (2013). Circadian rhythm disorders among adolescents: assessment and treatment options. *MJA* 199(8): S16-S20.
- Borbely, AA, et al. (2016). The two-process model of sleep regulation: a reappraisal. *J Sleep Res* 25: 131-143.
- Burgess, HJ and Molina, TA. (2014). Home lighting before usual bedtime impacts circadian timing: a field study. *Photochem Photobiol* 90(3): 723-726.
- Burgess, HJ, et al. (2010). Human phase response curves to three days of daily melatonin: 0.5 mg versus 3.0 mg. *J Clin Endocrinol Metab* 95(7): 3325-3331.
- Crowley, SJ, et al. (2015). Increased sensitivity of the circadian system to light in early/mid-puberty. *J Clin Endocrinol Metab* 100: 4067-4073.
- Erland, LAE, and Saxena, PK. (2017). Melatonin natural health products and supplements: presence of serotonin and significant variability of melatonin content. *J Clin Sleep Med* 13(2): 275-281.
- Figueiro, MG. (2016). Delayed sleep phase disorder: clinical perspective with a focus on light therapy. *Nature and Science of Sleep* 8: 91-106.
- Hayakawa, T, et al. (2005). Clinical analyses of sighted patients with non-24-hour sleep-wake syndrome: a study of 57 consecutively diagnosed cases. *SLEEP* 28(8): 945-952.
- Heussler, H, et al. (2013). Pharmacologic and non-pharmacologic management of sleep disturbance in children: an Australian Paediatric Research Network survey. *Sleep Medicine* 14: 189-194.

References

- Iglowstein, I, et al. (2003). Sleep duration from infancy to adolescence: reference values and generational trends. *Pediatrics*; 111(2): 302-307.
- Kryger, M, Roth, T, and Dement, WC (Ed.). (2017). *Principles and Practice of Sleep Medicine, Sixth Edition*. Elsevier, Inc.
- Sharkey, KM, et al. (2011). Effects of an advanced sleep schedule and morning short wavelength light exposure on circadian phase in young adults with late sleep schedules. *Sleep Medicine* 12: 685-692.
- Sheldon, SH, et al (Ed.). (2014). *Principles and Practice of Pediatric Sleep Medicine, Second Edition*. Elsevier, Inc.
- Sherman, H, et al. (2012). Timed high-fat diet resets circadian metabolism and prevents obesity. *The FASEB Journal* 26: 3493-3502.
- Taylor, DJ, et al. (2005). Sleep tendency during extended wakefulness: insights into adolescent sleep regulation and behavior. *J Slep Res* 14: 239-244.
- Uchiyama, M, and Lockley, SW. (2015). Non-24-hour sleep-wake rhythm disorder in sighted and blind patients. *Sleep Med Clin* 10: 495-516.
- Van der Lely, S, et al. (2015). Blue blocker glasses as a countermeasure for alerting effects of evening light-emitting diode screen exposure in male teenagers. *Journal of Adolescent Health* 56: 113-119.
- Wilhelmsen-Langeland, A, et al. (2013). A randomized controlled trial with bright light and melatonin for the treatment of delayed sleep phase disorder: effects on subjective and objective sleepiness and cognitive function. *Journal of Biological Rhythms* 28(5): 306-321.
- Zhou, T, et al. (2018). Clinical efficacy, onset time and safety of bright light therapy in acute bipolar depression as an adjunctive therapy: a randomized controlled trial. *Journal of Affective Disorders* 227: 90-96.