EVALUATION AND MANAGEMENT OF THE CIRCADIAN RHYTHM SLEEP-WAKE DISORDERS

James K. Wyatt, Ph.D., D. AB, FAASM, C.BSM
Director, Section of Sleep Disorders and Sleep/Wake Research,
Associate Professor
Department of Behavioral Sciences
Rush University Medical Center / Rush Medical College

For ISS Conference: COI: Royalties from UpToDate

Conflict of Interest Disclosures

Speaker:

1. I do not have any potential conflicts of interest to disclose, OR
X 2. I wish to disclose the following potential conflicts of interest

<table>
<thead>
<tr>
<th>Details of Potential Conflict</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant/Research Support</td>
</tr>
<tr>
<td>Consultant</td>
</tr>
<tr>
<td>Speakers' Bureaus</td>
</tr>
<tr>
<td>Financial support</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Royalties, UpToDate</td>
</tr>
</tbody>
</table>

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

X 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:


LEARNING OBJECTIVES

By the end of this educational activity, learners will be able to:

• Design age-appropriate assessment strategies for patients of varying ages with circadian rhythm disorders
• Design, implement, and monitor evidence-based treatment strategies for the circadian rhythm sleep-wake disorders

SLEEP HOMEOSTASIS

• During each hour you are awake (“cost” of being awake):
  – Sleep-promoting substances build up in the brain (e.g. adenosine)
  – Wake-promoting substances are used up in the brain (e.g., NE, 5-HT)
• During sleep
  – Sleep-promoting substances are cleared
  – Wake-promoting substances are replenished
SLEEP HOMEOSTASIS

INTRANSCIC CIRCADIAN TIMEKEEPING SYSTEM

- 24-hour clock in the brain
- Suprachiasmatic nucleus (the “SCN”)
- Regulates timing of (for example):
  - Core body temperature
  - Appetite
  - Amount of urine production
  - Alertness / sleepiness
- Coordinates clocks throughout the body
CIRCADIAN SYSTEM

CSMZ: sleep$^{3,4}$

WMZ: wake$^{1,2}$

1 Strogatz et al., *Am J Physiol* 253, 1987
3 Stepanski & Wyatt, *Sleep Medicine Reviews* 7, 2003
4 Wyatt et al., *Sleep* 27, 2004

2-PROCESS MODEL OF SLEEP-WAKE CONTROL

Borbély, *Hum Neurobiol*, 1982;
Borbély et al model, *HFSP*, 2000
THE BRAIN IS PROGRAMMED FOR 14-17 HOURS OF STABLE WAKEFULNESS

In normal sleepers:
- Increased sleep drive with hours of wake + offset by
- Circadian drive for wake during daytime =
- ~16 hours of stable daytime alertness
- Midafternoon dip is part of biology

HELPFUL HINT

- Midafternoon dip
- Supposed to be there
- Not too deep
- Not too wide
- Minimal but some effort to maintain alertness
HELPFUL HINT

- Sleep Inertia vs.
- Patient wants “refreshed” upon awakening

![Graph showing subjective alertness and cognitive throughput over time.](image)

---

CIRCADIAN TIMEKEEPING SYSTEM: EXTENDED INFORMATION
SCN = master circadian pacemaker

Multiple output pathways

HELPFUL HINT

• Night eating syndrome
• Appetite should be lower at night
• Consider circadian phase delay
ENDOGENOUS CIRCADIAN PERIOD

- SCN relies on light/dark cycle for “entrainment” to external 24-hr day
- Without “zeitgebers”, circadian system drifts (“free-running” conditions) slightly
- True “circadian period” is best measured in core body temperature and melatonin rhythms
- Average adult human period 24.18hr
  - Czeisler, et al., Science, 1999
  - In teens, slightly longer at 24.3hr (Carskadon)

Normal mouse: $\tau = 23.7\text{h}$
Jumps on the wheel 0.3h earlier each day
“free running” circadian system
WHAT CRSD DOES THIS RESEMBLE?

Top: Constant conditions: wheel running pattern very consistent, but free running

Bottom: SCN destroyed, NO consolidated bouts of sleep or activity, arrhythmic
DEVELOPMENTAL CHRONOBIOLOGY

• Maternal circadian rhythm
  – Impact on fetal cardiac rhythms
  – Impact on newborn (e.g., via breastfeeding)
• 2-3 months old, circadian patterns of
  – 24-hr pattern of core body temperature
  – Cortisol (or perhaps months later)
  – [spindles/K’s, sleep EEG maturing]
  – Implications for sleep training
• 6-9 months
  – Melatonin rhythms (via diapers !)

HELPFUL HINT

• Breastfeeding moms
• Melatonin present in breast milk
• Many label time of pumping
• Bottle feed at similar clock time as pumping

• (not very evidence-based yet)
EFFECTS OF BRIGHT LIGHT

- “Phase response curve”
- Late evening
  - Pushes the clock later
- Evening or during the night
  - Suppresses melatonin production
  - Weakens the clock’s sleep drive
- Early morning
  - Pushes the clock earlier
- Morning / post normal awakening
  - Keeps the clock lined up correctly
- “Entrainment” – is circadian phase properly aligned with the sleep schedule?
- Dose response (brighter light = stronger shifting)
- Spectrum of light (IPRGCs tuned for blue light)

Stable sleep-wake schedule =
Stable light-dark schedule =
Optimal entrained circadian phase

© Wyatt, 2013
NORMAL SLEEPERS
PHOTOTHERAPY DURING SLEEP

- 2msec flash
- 3,000 lux
- (eyes closed, so around 300 lux)
- Every 30 sec
- From 2-3hr after bedtime
- 30 min phase delay

Zeitzer JM et al, 2014, JBR

HELPFUL HINT

- Bedrooms should be dark
- Open blinds/curtains only after wake-up time
Evening reading: 4 hours of pre-bedtime iPad vs. book

HELPFUL HINT

- Dim the room lights for evening homework
- Modern, blue-enriched screens
- Dim the screens in the evening
  - TV
  - Tablet
  - Smart phone

Change A-M et al, 2015, PNAS
**PHASE RESPONSE CURVE for EXOGENOUS MELATONIN (The “Melatonin PRC”)**

NOTE: Clock times denote only to habitual sleep schedule for sample patient, not to absolute clock time for all

- **Late Afternoon / Early Evening MEL**
  - Phase Advance (move earlier)
- **Late night / Early morning**
  - Phase Delay (move later)

**MELATONIN caution**

- Concern about sedation or sleepiness if given at the optimal time for phase advancing (e.g., for DSPD: late afternoon dosing, then they work, study, drive, or perform sports)
MELATONIN AS A CIRCADIAN PHASE-DEPENDENT HYPNOTIC

CAVEAT

- Patients on beta blockers
- 2.5mg melatonin incr. TST 36 mins.
SLEEP HOMEOSTASIS:
EXTENDED INFORMATION

IMPLICATIONS FOR SLEEP DISORDERS

• Naps
  – Decrease homeostatic drive
  – Delays sleep onset, lighter sleep
• Late wake times
  – Shorter duration of subsequent wake
  – Lower homeostatic drive for sleep initiation and consolidation
• Shorter sleep duration (e.g., DSPD)
  – EDS, fatigue, cognitive and mood dysfunction
ADENOSINE BUILDS DURING EXTENDED WAKE (cat)

Strecker et al., Behav Brain Res 115, 2000

CAFFEINE

THE GOOD:
• 3-7 hr half life
• 100mg coffee, 45mg soda, 200mg No-Doz
• Adenosine receptor antagonist
• **Attenuates the expression of sleep homeostatic pressure**
  • Beneficial effect on homeostatic-related (not circadian) cognitive deficits with extended wakefulness

THE BAD:
• Increases sleep latency
• Suppresses slow wave activity (deep sleep)
• “sensitivity”: insomnia, nervousness, irritability, tachycardia

1 Wyatt, et al., Sleep, 2004
2 Landolt, et al., Neuropsychopharmacology, 1995
3 Landolt, et al., Brain Res., 1995
HELPFUL HINT

• Look for all sources of caffeine intake
• Follow AAP recommendations about age(s) for caffeine initiation
• With sufficient sleep, caffeine is not needed

ICSD-3: CIRCADIAN RHYTHM SLEEP-WAKE DISORDERS
General Criteria for Circadian Rhythm Sleep-Wake Disorder

• 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.
ASSESSMENT TOOLS

- Sleep diary
  - Required for most
- Wrist actigraphy
  - Strongly encouraged
- Chronotype assessment
  - May be helpful
- Circadian phase assessment (CBT, DLMO, aMT6s)
  - On the horizon

MELATONIN

Endogenous
- Secreted by the pineal gland at night
- Suppressed by ocular light exposure
- 2 receptors on the SCN—phase shifting and suppressing the alerting system

Exogenous
- 45min half-life (unless SR)
- 0.1 - 0.5mg physiologic peak dose
- Can shift circadian phase
- Circadian-phase dependent hypnotic
  - suppresses circadian alerting

Side effects
- EDS, headache, vivid dreams
- Antigonadotropic data in seasonal breeding animals
DIM LIGHT MELATONIN ONSET

DLMO
- 10 pg/ml in blood, 3-4 pg/ml in saliva
- May drop to 2 pg/ml in blood, 0.7 pg/ml in saliva as assays improve
- Occurs approximately 2 hrs. prior to habitual bedtime

Collection procedure
- Dim lighting (less than 20 lux)
- Blood or saliva samples every 30-60 minutes
- Sampling prior to and following presumed DLMO time

FIGURE FROM: Lewy & Sack, Neuropsychopharmacology, 2002
Advanced Sleep-Wake Phase Disorder

- Early phase of the major sleep episode vs. the desired or required sleep time and wake-up time,
- Chronic or recurrent complaint of inability to reach the desired bedtime and EMA.
- Symptoms for **at least three months**.
- When sleeping at this earlier phase, sleep quality and duration are **improved (may not be WNL)**
- Sleep log (and ideally actigraphy) for **at least 7 days** (ideally 14 days) show advance timing of the habitual sleep period. Look for both work/school days vs. free days
- The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder

ASWPD Developmental Issues

- ASWPD is most common in older adults
- ASWPD in children or young adults
  - Look for family history
  - Unrealistic parent/guardian expectation about normal wake-time for kids
  - “motivated” early wake time (e.g., Saturday morning cartoons)
  - Early bedtime may reflect insufficient sleep syndrome / sleep deprivation

ICSD-3
ASPD IS SUPPOSED TO EXIST IN KIDS/YOUNG CHILDREN; NEVER SEEN IT

Delayed Sleep-Wake Phase Disorder

- There is a **delay in the phase of the major sleep episode** in relation to the **desired or required** sleep time and wake-up time, as evidenced by a chronic or recurrent complaint by **patient or caregiver** of inability to fall asleep and difficulty awakening at a desired or required clock time.
- The symptoms are present for at least **three months**.
- When patients are allowed to choose their ad libitum schedule, they will exhibit **improved sleep quality and duration for age** and **maintain a delayed phase** of the 24-hour sleep-wake pattern.
- Sleep log and, whenever possible, actigraphy monitoring for **at least seven days** (preferably 14 days) demonstrates a delay in the timing of the habitual sleep period. **Both work/school days and free days must be included within this monitoring.**
- The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.
DSPD NOTES

- Standardized **chronotype questionnaires are useful** tools to assess the chronotype of “eveningness” and “morningness.” Individuals with this disorder typically score as “evening types.” This tool can also be useful in determining whether an “eveningness” circadian preference contributes to sleep initiation difficulties among those who do not meet full criteria for the disorder.

- Demonstration of a delay in the timing of other circadian rhythms, such as melatonin (measured by dim light melatonin onset or urinary 6-sulfatoxymelatonin sampled across a 24-hour period) is desirable to confirm the delayed circadian phase.

ICSD-3

ASSOCIATED FEATURES

- DSPD and evening types
  - Higher rates of psychiatric disorders
  - E.g., mood disorders, suicide risk

- Potential overlap/alternation with free running disorder

- KEY POINT: can develop conditioned (or other) insomnia over time – both may require treatment

ICSD-3
PREVALENCE OF DSPD

- 374 Australian teens
- Sleep diary + actigraphy + questionnaires
- DSPD: 1%
- 1 ICSD2 criterion: 52%
- 2 ICSD2 criteria: 14%
- 0 ICSD2 criteria: 33%

- Differentiation of evening type vs. delayed phase vs. delayed sleep vs. DSPD

ICSD-3

**DSPD Subtype: motivated delayed sleep phase disorder**

- “a subgroup typically comprised of adolescents who have little intrinsic motivation to successfully complete treatment and thereby resume a “normal” lifestyle (regular school attendance, developmentally appropriate peer interactions, etc).”
- Psychiatric comorbidity is high
- Factors to avoid school (e.g., learning disability)
- Exaggerated parental response of “inability to awaken” with extreme measures
- Parent vs. child motivation

ICSD-3
Irregular Sleep-Wake Rhythm Disorder

- The patient or caregiver reports a chronic or recurrent pattern of irregular sleep and wake episodes throughout the 24-hour period, characterized by symptoms of insomnia during the scheduled sleep period (usually at night), excessive sleepiness (napping) during the day, or both.
- Symptoms are present for at least three months.
- Sleep log and, whenever possible, actigraphy monitoring for at least seven days, preferably 14 days, demonstrate no major sleep period and multiple irregular sleep bouts (at least three) during a 24-hour period.
- The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

ICSD-3

Non-24-Hour Sleep-Wake Rhythm Disorder (‘free running’)

- There is a history of insomnia, excessive daytime sleepiness, or both, which alternate with asymptomatic episodes, due to misalignment between the 24-hour light-dark cycle and the non-entrained endogenous circadian rhythm of sleep-wake propensity.
- Symptoms persist over the course of at least three months.
- Daily sleep logs and actigraphy for at least 14 days, preferably longer for blind persons, demonstrate a pattern of sleep and wake times that typically delay each day, with a circadian period that is usually longer than 24 hours.
- The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

ICSD-3
N24SWD

- Patients may present with a **progressively delaying sleep-wake pattern and intermittent insomnia and excessive sleepiness**. Individual symptoms will depend on when an individual tries to sleep in relation to the circadian rhythm of sleep-wake propensity.
- The symptomatic episode will typically begin with a gradual increase in sleep latency and delayed sleep onset. As the sleep propensity rhythm shifts into the daytime, patients will have difficulty falling asleep at night and staying awake during the day. As the sleep-wake propensity rhythm drifts further, patients will eventually complain of late afternoon and evening sleepiness and naps as well as an early sleep onset time and short sleep latency.
- Other circadian rhythms, such as the dim light melatonin onset or urinary 6-sulfatoxymelatonin rhythm obtained at two time points four weeks apart is desirable to confirm the non-entrained rhythm.

**ICSD-3**

Shift Work Disorder

- There is a report of **insomnia and/or excessive sleepiness**, accompanied by a reduction of total sleep time, which is associated with a recurring work schedule that overlaps the usual time for sleep.
- The symptoms have been present and associated with the shift work schedule for **at least three months**.
- **Sleep log and actigraphy monitoring** (whenever possible and preferably with concurrent light exposure measurement) for at least **14 days** (work and free days) demonstrates disturbed sleep and wake pattern.
- The sleep and/or wake disturbance are not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, poor sleep hygiene, or substance use disorder.
- Outside the 7am-6pm window = shift work
- Don’t’ forget about teens! (evening after-school jobs)

**ICSD-3**
Jet Lag Disorder

- There is a complaint of **insomnia or excessive daytime sleepiness**, accompanied by a reduction of total sleep time, associated with transmeridian jet travel across **at least two time zones**.
- There is associated **impairment** of daytime function, general malaise, or somatic symptoms (e.g. gastrointestinal disturbance) within one to two days after travel.
- The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.
- [no data in kids]

**TREATMENT OPTIONS**
### PHOTOTHERAPY

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Guideline</th>
<th>Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSPD</td>
<td></td>
<td>Indicated</td>
<td></td>
</tr>
<tr>
<td>ASPD</td>
<td></td>
<td></td>
<td>Indicated</td>
</tr>
<tr>
<td>Free-run</td>
<td></td>
<td></td>
<td>Indicated</td>
</tr>
<tr>
<td>Irregular</td>
<td></td>
<td></td>
<td>Indicated</td>
</tr>
<tr>
<td>Jet Lag</td>
<td></td>
<td></td>
<td>Indicated</td>
</tr>
<tr>
<td>SWSD</td>
<td></td>
<td></td>
<td>Indicated</td>
</tr>
</tbody>
</table>

**comments**
- Brightness, duration not discussed
- Precision of timing relative to C phase

Adapted from Morgenthaler et al., *Sleep*, 2007

### ORAL MELATONIN

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Guideline</th>
<th>Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSPD</td>
<td></td>
<td>Indicated</td>
<td></td>
</tr>
<tr>
<td>ASPD</td>
<td></td>
<td></td>
<td>Indicated</td>
</tr>
<tr>
<td>Free-run</td>
<td></td>
<td>Indicated&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Indicated&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Irregular</td>
<td></td>
<td></td>
<td>Indicated&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Jet Lag</td>
<td></td>
<td>Indicated</td>
<td></td>
</tr>
<tr>
<td>SWSD</td>
<td></td>
<td></td>
<td>Indicated</td>
</tr>
</tbody>
</table>

**comments**
1: Blind patients
2: Sighted patients
3: For MR, not for elderly/dementia

Adapted from Morgenthaler et al., *Sleep*, 2007
## PRESCRIBED SLEEP SCHEDULE

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Guideline</th>
<th>Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSPD</td>
<td></td>
<td>Indicated</td>
<td></td>
</tr>
<tr>
<td>ASPD</td>
<td></td>
<td>Indicated</td>
<td></td>
</tr>
<tr>
<td>Free-run</td>
<td></td>
<td>Indicated</td>
<td></td>
</tr>
<tr>
<td>Irregular</td>
<td></td>
<td>Indicated</td>
<td></td>
</tr>
<tr>
<td>Jet Lag</td>
<td></td>
<td>Indicated</td>
<td></td>
</tr>
<tr>
<td>SWSD</td>
<td>Indicated</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**comments**

1: dementia / institutionalized elderly
2: mental retardation, moderate to severe

---

## UPDATE FROM 2015 (Auger et al.)

**ASWPD**: The TF suggests that clinicians treat adult ASWPD patients with evening light therapy (versus no treatment). [WEAK FOR]

**N24SWD**: The TF suggests that clinicians use strategically timed melatonin for the treatment of N24SWD in blind adults (versus no treatment). [WEAK FOR]

**DSPD**

- The TF suggests that clinicians treat **DSWPD** in adults with and without depression with strategically timed melatonin (versus no treatment). [WEAK FOR]

- **The TF suggests that clinicians treat children and adolescents with DSWPD (and no comorbidities) with strategically timed melatonin (versus no treatment). [WEAK FOR]**

- **The TF suggests that clinicians treat children and adolescents with DSWPD comorbid with psychiatric conditions with strategically timed melatonin (versus no treatment). [WEAK FOR]**

- **The TF suggests that clinicians treat children and adolescents with DSWPD with post-awakening light therapy in conjunction with behavioral treatments (versus no treatment). [WEAK FOR]**
2015 UPDATE: CONTINUED

ISWRD
• The TF suggests that clinicians treat ISWRD in elderly patients with dementia with light therapy (versus no treatment). [WEAK FOR]
• The TF recommends that clinicians avoid the use of sleep-promoting medications to treat demented elderly patients with ISWRD (versus no treatment). [STRONG AGAINST]
• The TF suggests that clinicians avoid the use of melatonin as a treatment for ISWRD in older people with dementia (versus no treatment). [WEAK AGAINST]
• The TF suggests that clinicians use strategically timed melatonin as a treatment for ISWRD in children/adolescents with neurologic disorders (versus no treatment). [WEAK FOR]
• The TF suggests that clinicians avoid the use of combined treatments consisting of light therapy in combination with melatonin in demented, elderly patients with ISWRD (versus no treatment). [WEAK AGAINST]

CRSD TREATMENT OPTIONS

1. Understand the homeostatic and circadian contributions to sleep/wake complaints
2. Fight the EDS
   • Caffeine (not great for children)
   • Stimulants / “Alerting Agents” (same concern)
   • Prevent or encourage napping
3. Put you to sleep
   • Melatonin / ramelteon
   • Hypnotics
4. Shift circadian phase
   • Melatonin
   • Phototherapy
   • Sleep scheduling (e.g., chronotherapy, naps, no naps)
PATIENT EDUCATION POINTS: DSPD Example

- Napping is bad for DSPD
  - Decreases homeostatic drive, worsens sleep onset delay
- Relatively late wake-time / early bedtime
  - Shorter duration of sustained wakefulness
  - Insufficient homeostatic drive to fall asleep
- Relatively late sleep-onset / early wake time
  - Shorter duration of sleep
  - Higher EDS from leftover homeostatic sleep drive

SLEEP SCHEDULING

- Chronotherapy – progressive shift of S-W schedule (DSPD, ASPD)
- Enforcing a daily S-W cycle vs. patient’s ad lib schedule (free-running, irregular)
- Major sleep episode with scheduled napping (jet lag, shift work)
CHRONOTHERAPY
[indicated: option for DSPD]

- 3hr DELAY OF BT/WT SCHEDULE
- RIGID ADHERENCE TO SLEEP SCHEDULE
- SMALLER SHIFT IF REQUIRED

- BASELINE / STABILIZATION

NOTE: Clock times denote only to habitual sleep schedule for sample patient, not to absolute clock time for all
modified from Czeisler et al., Sleep, 1982

PHOTOTHERAPY
[indicated: guideline for DPSD]

- Need to advance phase to an earlier hour
- Light exposure in the “morning” (see PRC)
  - natural light, artificial bright light

- NO STANDARD PROTOCOL; I suggest:
  - stabilize S-W schedule x 3 days
  - start 60+ min. light, starting at late wake time
  - dose of 2,000-10,000 lux
  - 30 min. per day advance of BT/WT schedule
  - 30 min. per day advance of light onset
  - *** dim light in the evening (prevent phase delay)
  - 30 min. maintenance dose of light at wake time
  - evaluation by ophthalmologist if ? ocular risk

Wyatt, Sleep Medicine Clinics, 2007
PHOTOTHERAPY
[indicated: guideline]

**BASELINE / STABILIZATION**

1. 30min. ADVANCE OF BT/WT SCHEDULE PER DAY
2. 60min. BRIGHT LIGHT AT WT
3. 2hr DIM LIGHT PRIOR TO BT

**STRICT SLEEP SCHEDULE**

30min. MAINTENANCE LIGHT

NOTE: Clock times denote only to habitual sleep schedule for sample patient, not to absolute clock time for all

Wyatt, Sleep Medicine Clinics, 2007

Morning light exposure occurs in the region of maximal phase delays for DSPD patients likely MAINTAINING the phase delay

DSPD PATIENTS
RCT: CBT + PHOTOTHERPY

- Age 11-18, DSPD diagnosis
- CBT (n=23)
  - sleep education (Session 1)
  - heavy cognitive component (Sessions 2-5)
  - Wrap-up (Session 6)
  - 30-120 minutes of post-awakening light of 1,000 lux or sunlight
  - 30min phase advance of sleep schedule/day
- Wait list control (n=17)
- Daily sleep diary
- Wrist actigraphy: insufficient data

RESULTS

- School night sleep
  - 56 minute decrease in sleep latency
  - 38 minute earlier sleep onset time
  - 60 minutes more total sleep time
  - 26 minute earlier wake-up time
- Some improvement in weekend sleep
- **Good maintenance of gain at 6 months**
- Improved EDS and fatigue
MELATONIN – phase shifting

- Max phase advance: give 5 hr prior to DLMO\(^1\)
  - DLMO is \(~1.5\) to \(2\) hr. prior to BT

- Relapse reported as high after stopping
  - May have to be a chronic treatment
- ? if really just phase-dependent hypnotic effect
- Sedation concern with afternoon (phase advancing) or morning (phase delaying) dosing

\(^1\) Burgess et al., 2008, *J Physiol*
MELATONIN FOR DSPD

• Meta-analysis of 9 suitable studies
  – 0.3-5 mg
  – Fixed time, time range, or X hours prior to DLMO
  – Up to 4 weeks
  – n’s =8 to 105
  – Mix of sleep diary, actigraphy, PSG
  – Most measured DLMO

van Geijlswijk et al., Sleep, 2010

META-ANALYSIS RESULTS

• Adults
• DLMO advanced 1.69 hours (1.13 hr/children)
• Sleep onset time 0.7 hours (0.64 hr/children)
• Wake-up time earlier in children only
• Sleep latency shorter in only in children
• Total sleep time increased only in children
• Most studies didn’t advance dose timing

van Geijlswijk et al., Sleep, 2010
MELATONIN cautions

- Concern about sedation or sleepiness if given at the optimal time for phase advancing (e.g., late afternoon dosing, then they study, drive, or perform sports)
- Neuroendocrine concern for use in young children & adolescents
  - Different risk : benefit evaluation with severe neurodevelopmental disorders

DSPD: PHOTOTHERAPY + MELATONIN

- N-40, age 16-25, DSPD
- 2 weeks: DL+PLA, BL+PLA, DL+MEL, BL+MEL
- All: gradual advance of WT 1hr/day
- 3 months open label, BL+MEL or no tx

- ALL GROUPS: advance of BT, WT, DLMO
- High relapse rate with no treatment f/u
- Good durability with long-term treatment

Saxvig et al., 2013, Chronobiol Int; Wilhelmsen-Langeland et al., 2013, JRB
PREVENT FURTHER PHASE DELAY

• Block evening blue light, 2hrs prior to BT
  – Avoid “daylight” bulb use in evenings
  – Dim the lighting, TV, e-devices
  – f.lux or other computer app
  – ”Night shift” on iPhone, iPad, laptops and desktops

DECISIONAL BALANCE

<p>| WHAT ABOUT HAVING THIS SLEEP PROBLEM IS: |</p>
<table>
<thead>
<tr>
<th>BAD</th>
<th>NEUTRAL</th>
<th>GOOD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
NON-24-HOUR SLEEP-WAKE RHYTHM DISORDER (“FREE RUNNING”): TREATMENT

TREATMENT OF FREE RUNNING

• Sleep scheduling (option)
  – Fixed S-W schedule
  – Eliminate naps

• Phototherapy (option)
  – Light on awakening in sighted patients
  – Not for use in most retinally blind patients
FREE-RUNNING TYPE

- “Phase lock” with exogenous melatonin [indicated: guideline/option]
  - 1 hr prior to desired bedtime
  - 10 mg dose (Sack NEJM 2000)
  - lowered to ~0.5 mg dose (Lewy JBR 2004)
  - drifting phase eventually “captured” by melatonin PRC phase advance region
  - 9 pm administration of 0.5 mg (Hack JBR 2003)

Melatonin at bedtime as hypnotic, OR shifting circadian phase PRIOR TO jet travel
M = melatonin; L = light box; S = sunlight

From Eastman & Burgess, SleepMedClin, 2009
SHIFT WORK

- Nap before or during night or extended shifts [indicated: standard]
- Hypnotic for day sleep [indicated: guideline]
- Melatonin for day sleep (guideline)
- Caffeine (option)
- Modafinil (guideline)

- Recovery sleep
  - rebound sleep, telephone & doorbell off, protected sleep time (kids, pets)
  - catch up prior to next night shift
- Error detection systems, redundancy
- Light exposure at work for stimulatory effect
- Don’t work shifts
  - some individuals are more intolerant of shift work