Helping Patients with Circadian Rhythm Disorders

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Caveats

• Actual biomarkers for a patient’s circadian time-phase position are not usually available in usual treatment settings.
• Empirical treatments are based on creatively applying underlying psychological and biological principles.
Objectives

• To describe the general circuitry for circadian neurobiology
• To describe the key biological interventions to shift a circadian rhythm
• To deploy some motivational interviewing techniques to help patients express expected ambivalence about adopting major schedule changes
• To review treatment principles for advanced sleep phase, shift work, and jet lag

A Core Attitude in Treating Circadian Rhythm Disorders

• Thinking about 24-hour functioning in relation to the 2-process model of sleep regulation
• Circadian Rhythm Disorders: as if the patient has a personality disorder in time functioning
• Therapy implications: One cannot effectively treat the problem without understanding the “time personality” of the patient
• So: Where is the patients time structure in relation to others’ time structures?
Process S: Builds up slowly, goes away quickly with initial sleep. Why one avoids naps in insomnia, why one uses naps in hypersomnia.

Process C: Why one needs to know where the patient’s internal clock is in time in relation to environmental time.

Anterior Hypothalamic Anatomy
The Molecular Clockworks in the Suprachiasmatic Nucleus (and other cells)

Figure 1. A network of transcriptional-translational feedback loops constitutes the mammalian circadian clock.

From Ko & Takahashi. Human Molecular Genetics, 15(Review Issue 2), R-271-277, 2006; Fellowship Teaching Only
Zeitgebers ("Timegivers")

- Light to the Eyes via the retinohypothalamic track from retinal ganglion cells containing melanopsin (blue-sensitive) pigment.
  - Dawn light the most potent
  - Dusk light 2nd most potent
- Melatonin (half-life ~ 1 hour, secreted continuously at night)
  - Evening early secretion reinforces phase advance (basis for using melatonin, tamelteon, tasimelteon as chronobiotics).
  - Morning dawn persistent secretion would tend to phase delay
- Food access (independent of SCN functioning)
- Activity and Posture
A light exposure at night (red arrow) will tend to delay the time setting, as if the person was traveling west to a new time zone. By contrast, a strong early light exposure after the temperature minimum (Blue Arrow) will advance the Clock's time setting, as if the person was traveling east to a new time zone. The time of 4:30 for the temperature minimum - when the hysteresis occurs - is common when tested in specialized labs, but in patients cannot be practically measured. So the native time setting in clinical patients is only assumed, and can be wrongly guessed. Light given too early relative to where the patient's clock actually is in time will not phase advance, but phase delay.

Melatonin at night (Blue Arrow) will tend to advance the time setting, as if the person was traveling east to a new time zone. By contrast, melatonin exposure after the temperature minimum (Red Arrow) will delay the Clock's time setting, as if the person was traveling West to a new time zone. Melatonin has a ½ life of ~ 1 hour. The hysteresis effect in the SCN is less clear because it is continuously secreted through the night by the Pineal Gland. Melatonin secretion can be inhibited by light exposure at night, beta blockers, and NSAIDS. Melatonin onset has been used as a useful overall proxy for circadian phase position but in patients cannot be practically measured.

Therapist’s Clock Toolbox

- Sleep logs
- Light Exposure intensity and timing
- Blocking Blue Light
- Melatonin as an evening zeitgeber
- Using native phase delay to advantage
- Managing other potential zeitgebers: Food, Social Rhythms, Exercise, etc.
- Therapist’s work with patient about personal behavioral choices and scheduling
- Working with the patient’s own motivations

Circadian Sleep Disorders

- Phase Delay Syndrome
  - Body clock runs late compared to other persons
- Shift Work Disorder
  - Work hours conflict with normal diurnal pattern
- Jet Lag
  - Rapidly Changing Time Zones
- Phase Advance Syndrome
  - Body clock runs early compared to other persons
- Irregular Sleep-Wake Rhythm Disorder
- Non-24-Hour Sleep-Wake Rhythm disorder
  - Clock is so out of phase or disrupted that any entrainment to normal environment is impossible
Delayed Sleep Phase Syndrome

- A: Delay in major sleep period compared to conventional sleep wake times (esp > 2 hours).
  - Example: Bedtime at 3 AM and wake time at 11 AM
- B: For 3 months
- C: When allowed to sleep when wanted in phase delay, normal sleep quality and sense of restfulness
- D: Sleep log (actigraphy better) for > 6 days (14 better) demonstrating stable advance, for times including work/school and free days
  - Dim-Light Melatonin Onset (DLMO) measurements can be confirmatory
  - May have delayed Forbidden Zone
- E: Not due to another Dx (e.g. shift work disorder)
- Population prevalence: 0.17%, in adolescence 7-16%

International Classification of Sleep Disorders, 3rd ed

Phase Delay Mimics

- Restless Legs Syndrome: Symptoms occur late, so patient stays up late to avoid symptoms.
- Insomnia: Patient has problems with sleep onset.
- Sleep Inertia: In AM, pt has trouble waking up from sleep as such.
- Social Jet Lag: Staying up late, but only on weekends
- “Motivated delayed sleep-wake phase disorder” – “sometimes unconscious” (ICSD 3rd ed.)
  - Affective d/o, ADD, learning disabilities
  - Chronic fatigue, Mono episodes, pain
- Pediatric: Autism Spectrum, ADHD
Delayed Sleep Phase Rx

• Phase advance strategy
  - **Morning Bright Light** (30+ minutes, 5000 lux) - but not too early, before the cross-over time at the temperature minimum
  - **Avoid Blue Light in the evening** (Wear dark sunglasses esp with blue filtered)
  - **Timed evening melatonin** (<3 mg)in the evening about 8 PM.

• Or: Phase delay strategy
  (“Chronotherapy”) Delay bedtimes 3 hours daily till in correct phase position

• Some may: Work 2nd Shift

Case Presentation

• 22 yo Caucasian woman, in college, having trouble getting to morning classes
• CC: Delayed Sleep Phase since HS
• Comorbidities: Bipolar disorder, Type 2
• Hx:
  - Phase Delay since High School
  - Total Sleep Time: 10 hours
  - Initially Dx with ADHD, but in retrospect was actually Bipolar disorder
  - Under stable psychiatric follow-up, on ziprasidone and bupropion
Case Presentation, II

- Treatment: Educated about
  - 2-Process model
  - Phase response curves
  - Adverse role of circadian disturbances in Bipolar Disorder

- Plan included
  - Using bright light for 30 minutes at the moment of awakening
  - Melatonin 3 mg hs
  - Blue blocker glasses

Case Presentation, III

- Treatment effects:
  - Pt more able to get up for classes, less of a rush; academics going better
  - Pt made compromises about bedtime agenda
  - No melatonin side effects
  - Total Sleep Time: 9 hours
  - Greater sense of self-efficacy about managing sleep-wake problems
  - Continued stability of Bipolar illness
Case Presentation, IV

- Individual Differences:
  - Still had morning difficulties, but these were less and now workable for pt
  - Asked about blue blocker contact lenses!
  - Initially had moody spells on blue blockers for a few days
  - Over Christmas holidays, went back to phase delay, especially one night when wanted to be out till bar closing
  - No obvious need for follow-up

Aristotle’s Observations from the Rhetoric

Rhetoric: “the faculty of observing in any given case the available means of persuasion“
Divisions: (1) the speaker’s power of evincing a personal character which will make his speech credible (ethos ); (2) his power of stirring the emotions of his hearers (pathos ); (3) his power of proving a truth, or an apparent truth, by means of persuasive arguments (logos )

“We are moreover ashamed of having done to us, having had done, or being about to have done to us acts that involve us in dishonor and reproach.”
Motivational Interviewing

- Core Idea: Patients are in charge of making changes for themselves
- Core trap for providers: Feeling responsible for the treatment outcome (and not the medical art)
- Subsidiary traps (i.e. risk of shaming the patient):
  - Assessment trap: must complete it for who?
  - Expert trap: Imposing, not negotiating, plans
  - Premature focus trap: Who gets to choose?
  - Labeling trap: Labels may be too totalitarian.
  - Blaming trap: Emotional punishment
  - Chat trap: Not attending to pt’s concerns


OARS, with examples

- Open-ended questions:
  - “How has your sleep-wake pattern affected your life?”
  - “What things have you tried to help yourself do better with it?”
- Affirming supports:
  - “You have really been working hard on getting up on time for classes.”
  - “That’s something I would not have thought of.”
OARS, with examples

- Reflecting:
  - “Your teachers don’t understand what is going on with your sleep-wake schedule.”
  - “It is really important to you to be on-line with your friends.”
- Summarizing:
  - “It is valuable to be part of your social network that be up late, but on the other hand you would like help to be awake in the morning.”
  - “You have been doing your best to manage your schedule, but now are wondering if there might be other approaches to think about.”

Introducing Knowledge

- First, hearing out what the patient already knows or believes
- Second, asking permission to divulge new information
  - Why? Pushing unwanted knowledge can be an emotional harm of shaming – an interpersonal assault!
- Third, inquiring with pt what the new information may mean to him/her
  - To check out comprehension, and to encourage questions
- Fourth, ask permission to elaborate what would be practically implied by the new knowledge
Examples of Knowledge Development

• “Frank, can you tell me what you might know about how the body adjusts to time schedules?”
• “The science around body time changes can be a bit tricky. Would you like to know more about how we think it works in most people?”
• “… so that’s how we think one’s body works when adjusting to time. After hearing this, what to you make of it for how it affects you? What would it mean for changes you might consider?”
• “…Yea, what you mentioned about … is usually right for people. Could we explore more what would be involved perhaps in more detail?”

Working with Ambivalence

• Ambivalence is normal and expected.
  - It is a sign of mental health that one can be ambivalent some of the time, especially for important life decisions.
• One outcome is not necessarily better than another for a particular person at a particular time.
• No outcome should be stigmatized.
  - Why? Stigmatizing/shaming is emotionally injurious.
• No one is perfect.
• Bringing out an ambivalence often helps to resolve it, particularly if the patient can does so him/herself with interpersonal ease and voluntarily.
Examples of Encouraging Verbalization of Circadian Ambivalence

- “Well, we’ve gone over some facts about how the body handles sleep-wake changes. What do you see as the bad things and the good things about making the changes that might be needed?”
- “If I understand what you said, you really like being up to be with your friends, but you also want to be doing well at school. This must make it hard to know what to do. Am I getting that right?” (N.B. the new goal comes second).
- “I’m glad that today we had this discussion. It may be a bit sudden to make some of these changes, but I’m here to help you if you decide to do some of them.”

Shift Work Disorder (SWD)

- A: C/O insomnia EDS, with reduction in TST, assoc with a recurrent work schedule that overlaps the usual time for sleep
- B: 3 months Associated with work schedule
  - Example: Waketime at 3 am to start shift at 5 am
  - Relative to the normal sleep requirement
- C: Ideally, sleep log or actigraphy monitoring > 6 days shows disturbed sleep & wake pattern
- E: Not due to another Dx (e.g. Depression, medications, etc)
- E*: Usually remits when not doing shift work
- 20% of population does shift work; SWD prevalence estimated at 2-5%

International Classification of Sleep Disorders, 3rd Ed.
Consequences of Shift Work Disorder

• Fatigue, Chronic Sleep Disturbances
• GI, Metabolic (weight gain), Reproductive, Neoplastic, Cardiovascular Disorders
• Drug/Alcohol abuse/dependency
• Disturbances to family and social life
• Impaired alertness at work
  - Lowered work efficiency
  - Threats to safety
    • Public (transportation/Nuclear/etc)
    • Personal
• Long-term physiological (Tim Monk’s Hypothesis)
• Note: Melatonin secretion timing generally not changed (Grundy, et al. (2009). Chronobiol Int 26(7): 1443-1461.)
  • International Classification of Sleep Disorders, 3rd eds

Shift Work Disorder Rx

• Find a day shift if nightshift is a big problem.
• If possible, sleep promptly at shift’s end, with blackout-type curtains.
• Phase delay shift changes are better than phase advance shift changes.
• Countermeasures at night: Remain standing, bright lighting, caffeine, modafinil (FDA indication 100-400 mg at night), etc.
• Thoughtful choices about needs to be awake for family and social needs
• Awareness that shift work is a relative risk for metabolic syndrome and the urge to eat.
Jet Lag Disorder

- C/O Insomnia or EDS, with reduction in TST, associated with jet travel across at least 2 time zones
- Associated impairment of daytime function, general malaise, or somatic symptoms (e.g. GI) < 2 days after travel
- Not better explained by other disorder
- Cause: The SCN and slave clocks have temporal inertia, wanting to stay more or less in the time zone of origin, but the prompt time zone change is
  - Acutely outside the range of entrainment for the clocks, so they cannot adjust rapidly.
  - The link between the SCN and body slave clocks involves secondary delay shifting in the organ clocks.

International Classification of Sleep Disorders, 3rd ed

Jet Lag Rx

- Anticipate the phase shift before traveling
  - Adopt light exposure regimen at destination before doing travel.
  - Use melatonin at the destination’s 8 PM time
- Avoid Bright Light during the dark phase.
- Avoid sleep deprivation, poor sleep practices before and after travel.
- Empirical: Sleep on the plane, draining off Process S, so that it is not a factor at time of arrival (a reason for using hypnotics on the plane).
- Note: SCN probably shifts fast, but there is a lot of individual variability wrt Jet Lag.
Jet Lag *in situ*

- **Types:**
  - Weekday/Weekend shifting of bedtimes and wake-up times (Inconsistent time zone)
  - Wake/Sleep Disorganized Structure
    - Lack of external structure (e.g. in retirement, during unemployment)
    - Lack of any structure (e.g. ICU, depressive disorder, mania, etc.)
- **General Treatment Principles**
  - If you do not know the pt’s time zone, then the patient is lost in the sea of formless time.
  - Daily time structures allow other physiological and psychological rhythms to be therapeutically organized.

Advanced Sleep Phase Syndrome

- **A:** The onset of nocturnal sleepiness and offset of sleep in morning earlier compared to others
- **B:** For at least 3 months
- **C:** If socially isolated: Normal SQ and TST
- **D:** Sleep log (actigraphy better) for > 6 days (14 better) demonstrating stable advance, for times including work/school and free days
- **E:** Not better explained by other diagnosis
  - Typical Major Depression (EMA-implicated)
  - Chronic Insomnia with Early Morning Awakenings (EMA)
  - Schedule irregularity & Poor Sleep Hygiene
  - “Advance-related sleep complaints” (no evening sleepiness)

*International Classification of Sleep Disorders, 3rd ed.*
Advanced Sleep Phase Syndrome

- Cause: Tau (the intrinsic period of the clock) is shorter than in most other persons
  - Some shortening of Tau is a normal developmental process in all mammals from young adulthood to old age.
  - In some lineages, due to Clock mutations
    - hPER2 phosphorylation site mutation with decreased phosphorylation, more activity.
    - CK1δ mutation leading to slower clearance
    - Autism spectrum (assumed)
    - Smith-Magenis syndrome (interstitial deletion of 17p11.2)

*International Classification of Sleep Disorders, 3rd ed.*
*Science* 288, 483-492
*Nature* 434, 640-644

Advanced Sleep Phase Rx

- Bright Light in the Evening
- Avoid Bright Light in the Morning
- Melatonin in the morning (theoretical)
Key Practice Points

• Imagine where in time the patient’s biological clock might be,
• Biological effects follow from how the phase response curves for light and melatonin change circadian clock time.
• Positive outcomes are more likely when patients feel interpersonally safe, unrushed, and free to decide which outcomes they prefer over others.

Potential Reads
