OSU Sleep Symposium 2019
Circadian Rhythm Sleep-Wake Disorders
Interactive Cases

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Disclosures

Current research funding

- National Institutes of Health
- Jazz
- Harmony Biosciences
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- Merck
- Philips
- Harmony
- Eisai
- Jazz
- Weight Watchers

Other
Stock ownership: Teva

Evaluation of Circadian Rhythm Sleep Wake Disorders

- Important strategy in circadian medicine is to understand

  "what time it is in the brain and body" using phase markers

  (eg, melatonin) as "the hands on the clock."

- Recommendation in ICSD-3 for biomarkers, including salivary

  DLMO or 24 hour urinary melatonin (in special populations)

  BUT NOT REQUIRED!

- **50% of DSWPD are not circadian delayed relative to desired sleep time!**

  (Murray JM et al, Sleep, 2017)

Sack RL, et al. *Sleep*. 2007;30(11):1460-1483; Sack RL, et al. *Sleep*. 2007;30(11):1484-1501; ISCD-3, 2014

Clinical Measures of Circadian and Sleep Timing

- **Chronotype questionnaire**

    - Horne-Ostberg

    - Munich Chronotype:

http://www.imp.med.uni-muenchen.de/index.html

- **Sleep diary (14 days)**

- **Actigraphy (**CPT code: 95803)

- Melatonin (DLMO)

    - salivary, serum

    - **urinary 24 hour** aMT6s

Clinical estimate of circadian phase: Using sleep wake data (sleep log, actigraphy)
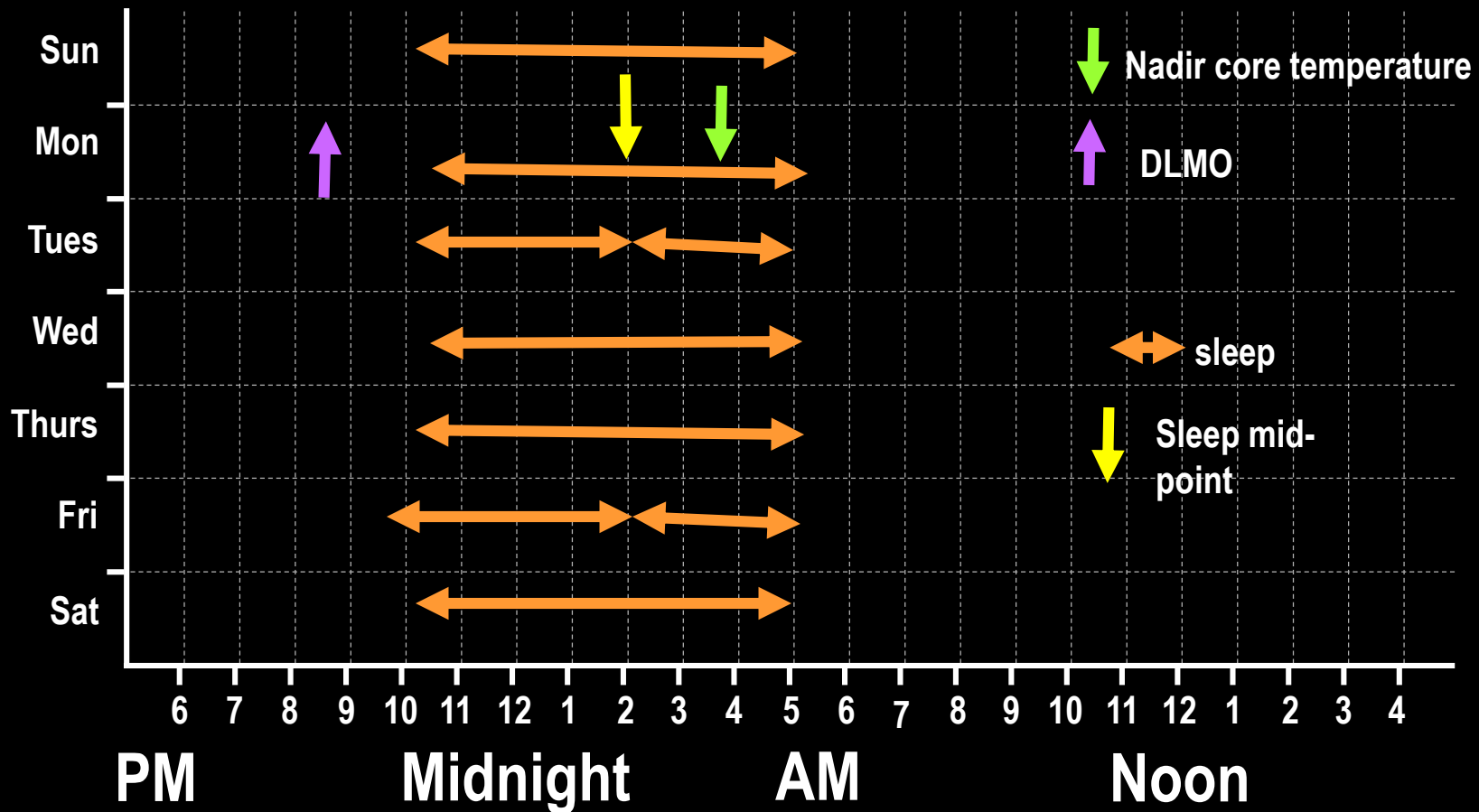
Home Salivary Melatonin Assessment

1) Instructions:

    - Dim light (<20 lux) (glasses)

    - 30-60 min sampling start 5-6 hours before average falling asleep time until fall asleep

    - 10-15 minutes before sampling: sitting position, no eating or drinking

    - cotton roll under tongue until saturated with saliva

    - place in container (cooler)and refrigerate next morning

2) Package of salivettes (12-18) for shipping

DIM LIGHT MELATONIN ONSET
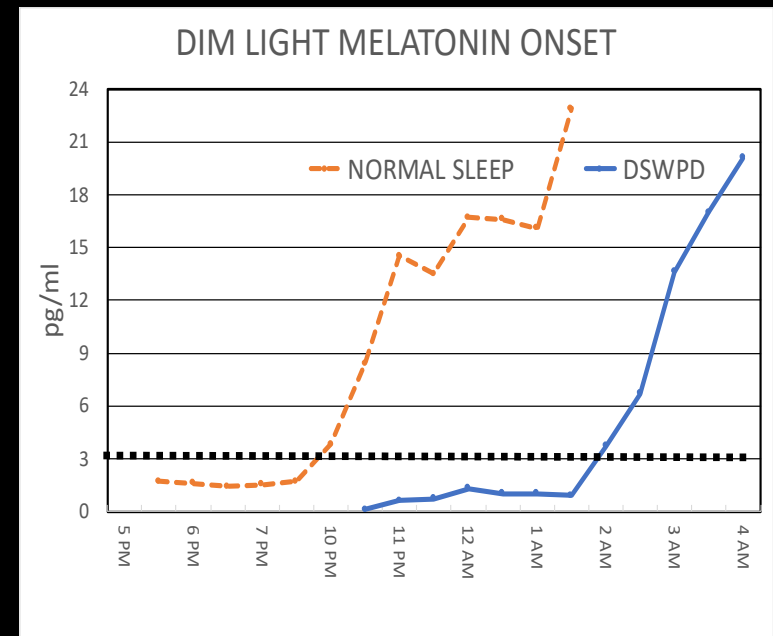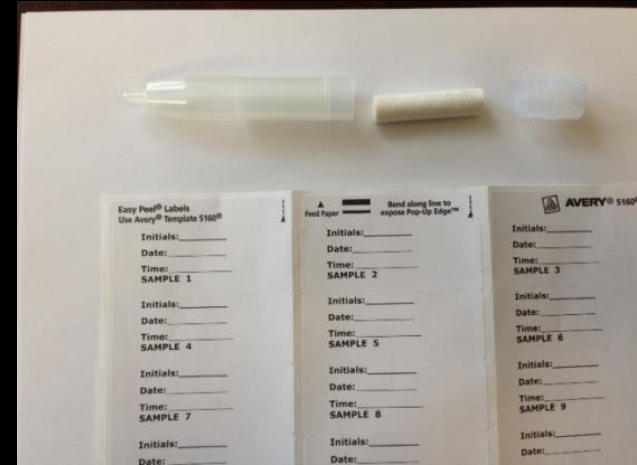
Phase Response Curves to Light and to Melatonin
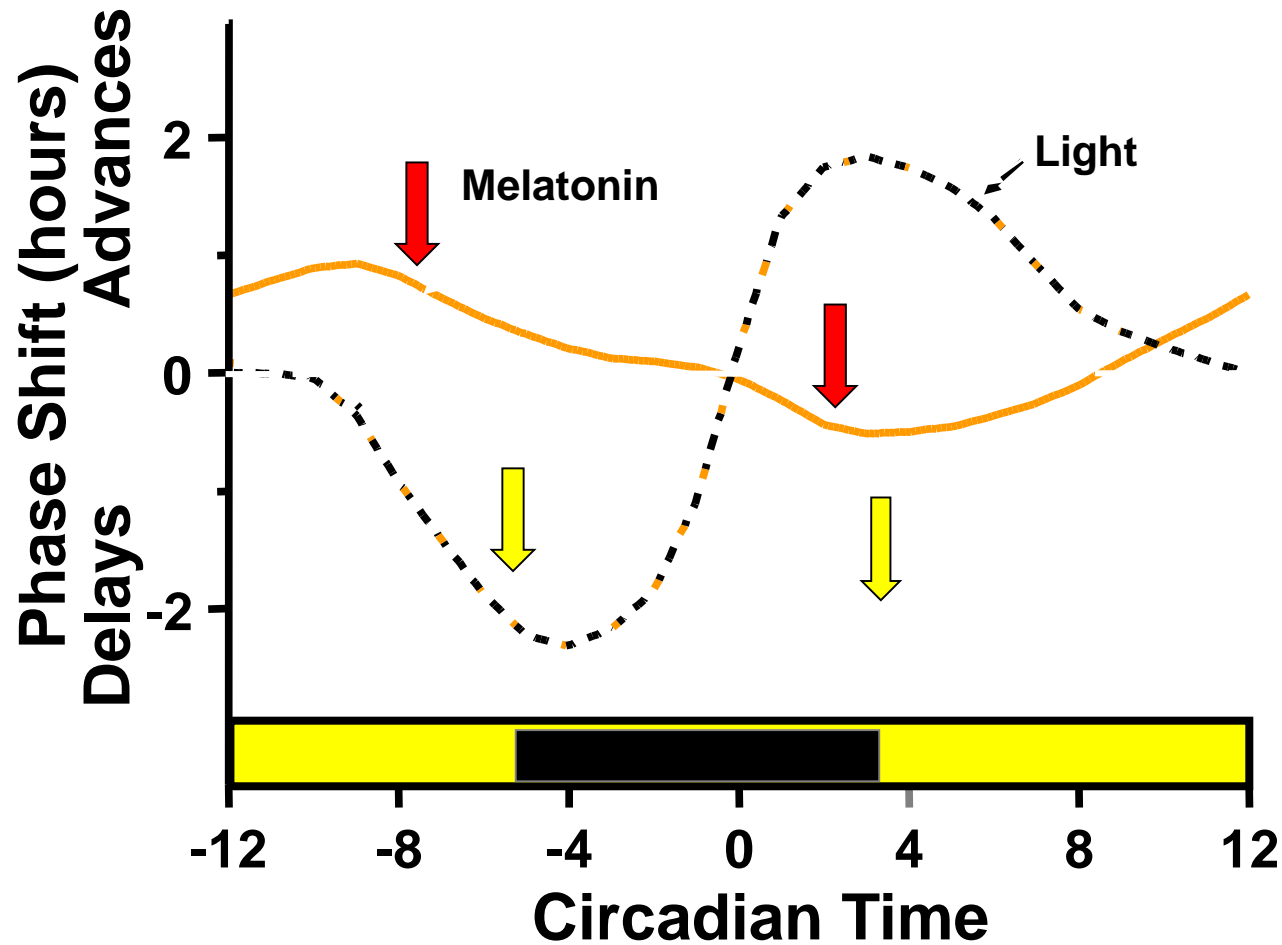
Case 1: I Can't Stay Asleep and falling asleep at work

- 43 year old woman with a history of temporal lobe epilepsy.

- She has always been a morning type who used to wake up at 5-6 am

- But for the last 2 years, she can't sleep past 230-3 AM

- Bedtime: 10 PM; Wake time (out of bed): 5 AM

- Estimates getting about 3-4 hours of sleep

- She is excessive sleepy in the afternoon and early evening

- Often naps when she gets home

- Denies snoring

- Feels "down" and tired most of the time and poor memory

- Referred for CBT for insomnia

Is this sleep maintenance insomnia?

Case 1: Salivary DLMO
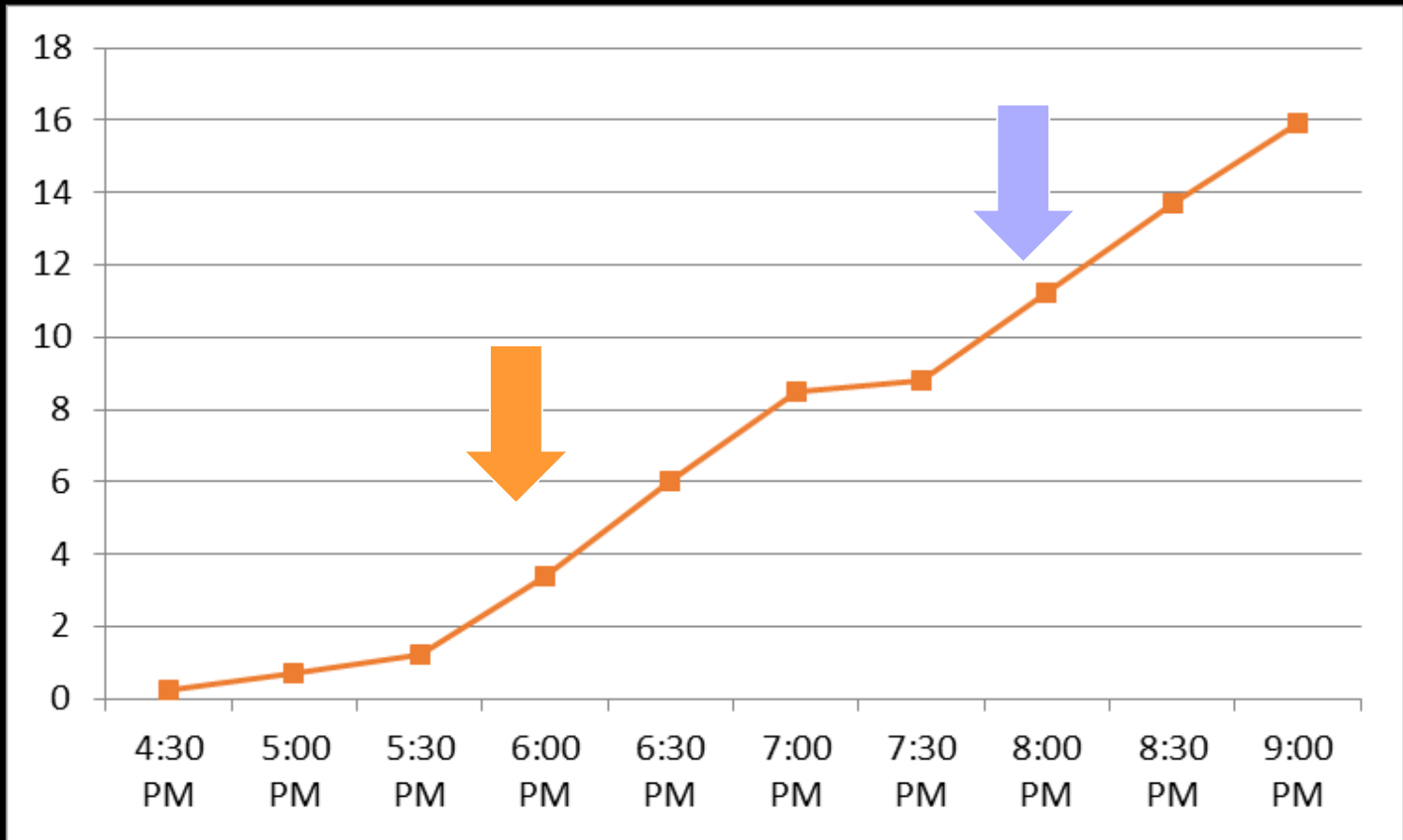
Case 1: I Can't Stay Asleep
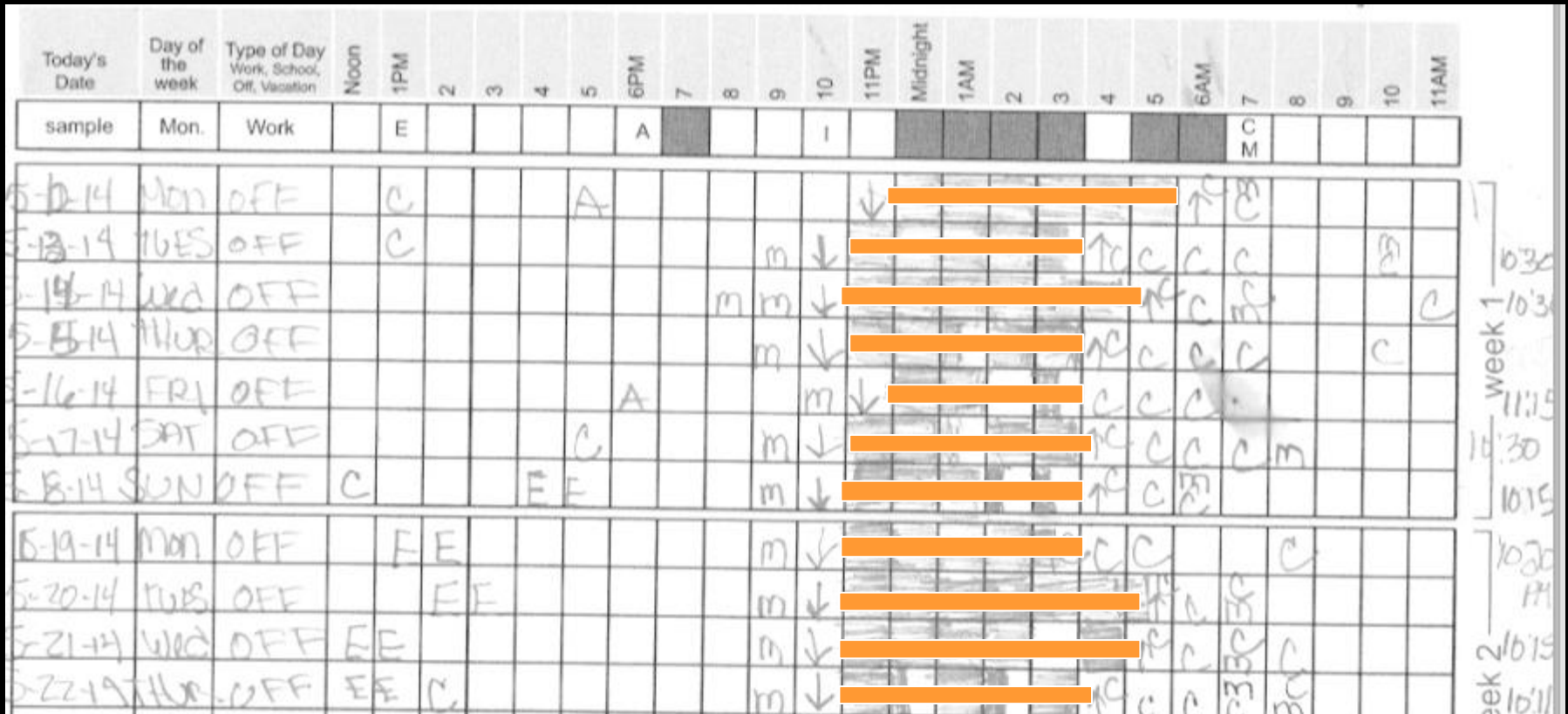
Average wake time moved from 3:00 am to 4:30 am
Average sleep time increased from 3.5 hours to 5 hours

Case 2: I'm never awake to see my family

- 41 year old woman who initially presented at age 25 with complaints of insomnia and daytime sleepiness.

- Had seen several other sleep physicians, with an unclear diagnosis

- PSGs with frequent PLMS but no evidence of obstructive sleep apnea.

- MSLT with sleep latency of 5.3 minutes (though no record of what time the naps were). No SOREMs.

- Previously had tried melatonin (5mg) at 9-10pm, light 'in the morning' and modafinil without significant improvement

Case 2: I'm never awake to see my family

Case 2: I'm never awake to see my family

2400   0700
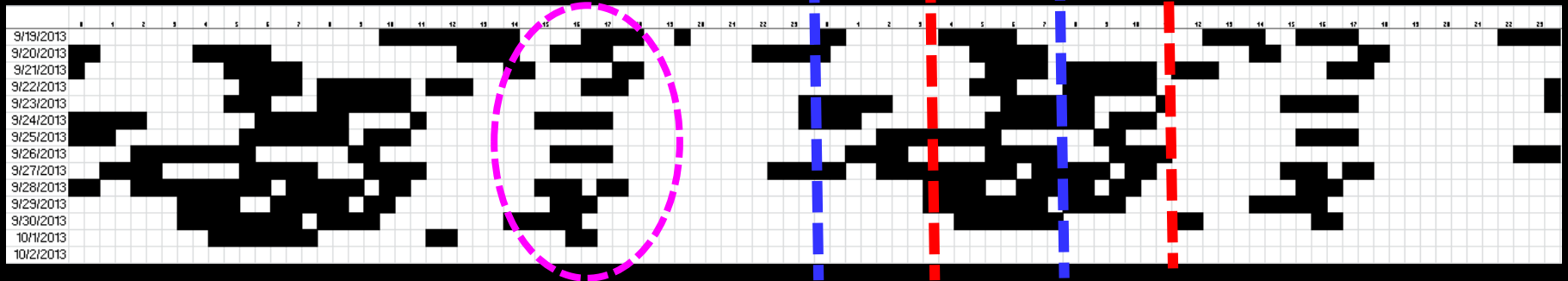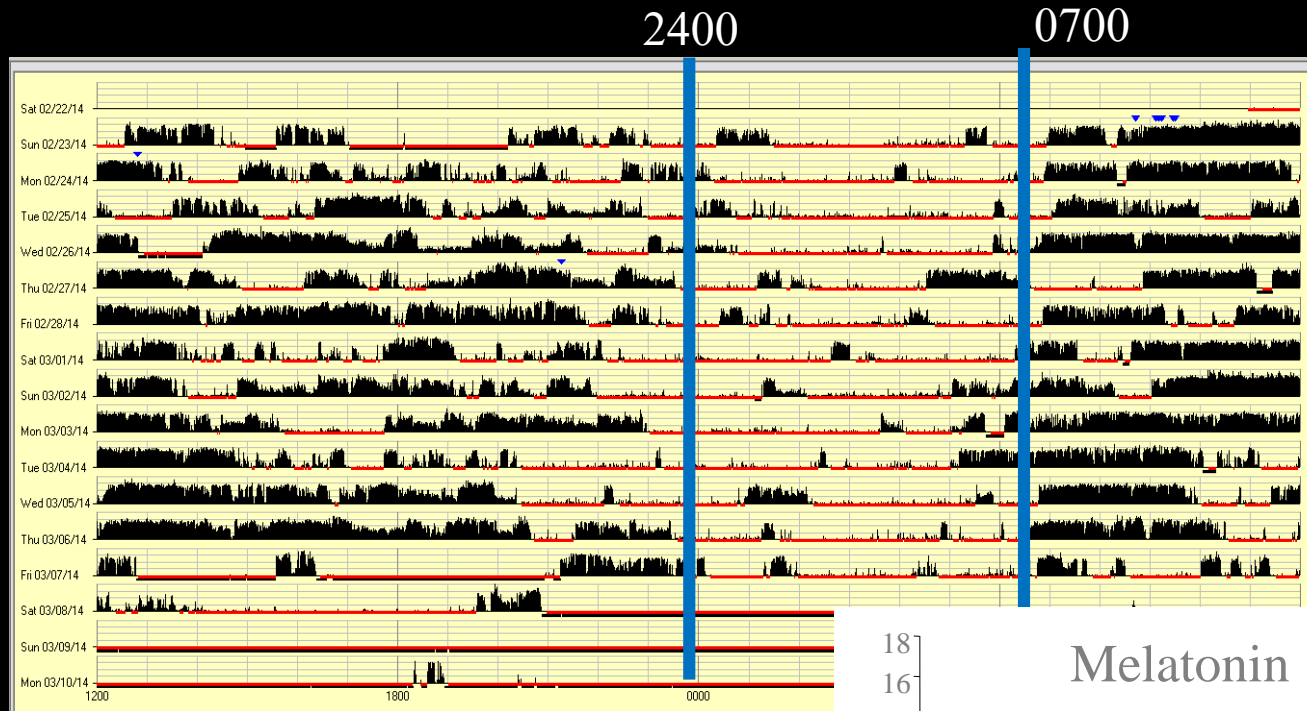
Doesn't look too bad…until you realize the watch is set on Chicago time and she is in Israel (average sleep time is actually ~5:30am)
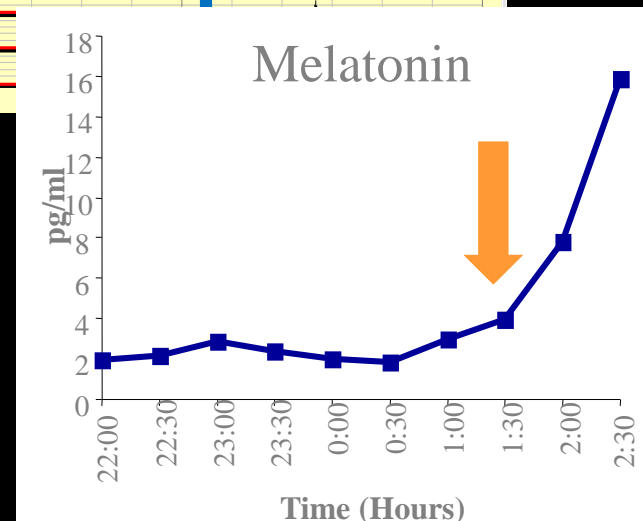
Melatonin

Case 2: I'm never awake to see my family

- Recommended:

- Bright light for 1 hour on awakening (starting at 11 am, advancing by 30 min every 1-2 weeks until desired wake up time)

- Dim light starting 9-10 pm

- 0.5 mg of melatonin 12 hours later (11 pm)

- Gradual advance of the entire light melatonin schedule

Case 2: I'm never awake to see my family

"I wanted to tell you about a miracle that happened three days ago. I opened my eyes and looked at the clock. It was eight o'clock in the morning. The sky was blue and I was wide awake! I got out of bed, had breakfast with my partner and children, went out and had a wonderful day.

One might ask, but where is the miracle? The miracle was that after twenty years of always being tired, or worse, sleeping the whole day, I was wide awake and able to do what everybody else does."

Gift for conducting a light phase response curve to light in DSPWD and program for circadian telemedicine!

Melatonin for DSPWD: Meta-Analysis

Figure 4—Meta-analysis of data for DLMO in response to melatonin treatment of children/adolescents with DSWPD and comorbid psychiatric conditions.

Study or Subgroup	Melatonin Tx Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Smits, 2001	1,233	57	10	1,296	75	17	20.2%	-63.00 [-113.19, -12.81]
van der Heijden, 2007	1,193	66	53	1,245	66	52	79.8%	-52.00 [-77.25, -26.75]
Total (95% CI)			63			69	100.0%	-54.22 [-76.78, -31.67]

Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 4.71 (P < 0.00001)

Favors melatonin   Favors control
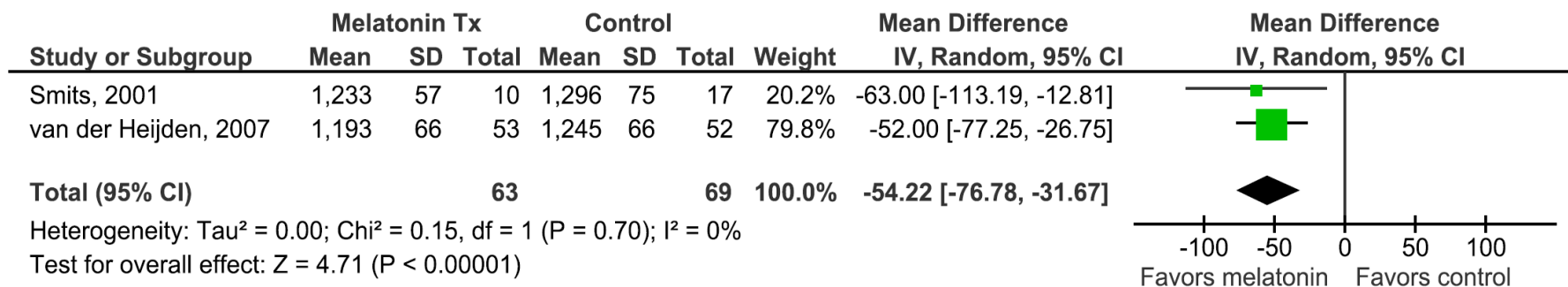
Figure 5—Meta-analysis of data for actigraphically-determined SOT in response to melatonin treatment of children/adolescents with DSWPD and comorbid psychiatric conditions.

Study or Subgroup	Melatonin Tx Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Smits, 2001	1,269	75	13	1,326	108	12	7.1%	-57.00 [-130.46, 16.46]
van der Heijden, 2007	1,273	58	53	1,308	48	52	92.9%	-35.00 [-55.35, -14.65]
Total (95% CI)			66			64	100.0%	-36.57 [-56.18, -16.96]

Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 3.65 (P = 0.0003)

Favors melatonin   Favors control

Auger RR et al, JCSM, 2015
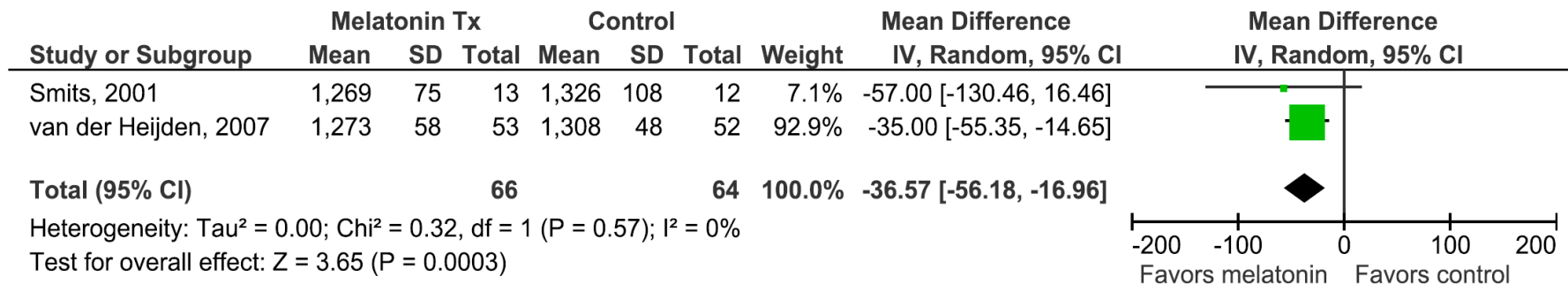
Combined low dose melatonin and behavioral therapy

- 104 DSWPD with DLMO delayed relative to desired bedtime
  (DLMO within 30 min of desired bedtime or later)
- Melatonin (0.5 mg) or placebo with sleep at desired bedtime each night (4 wks)
  (5 consecutive days minimum)

Sletten TL, et al, Plos Med, 2018
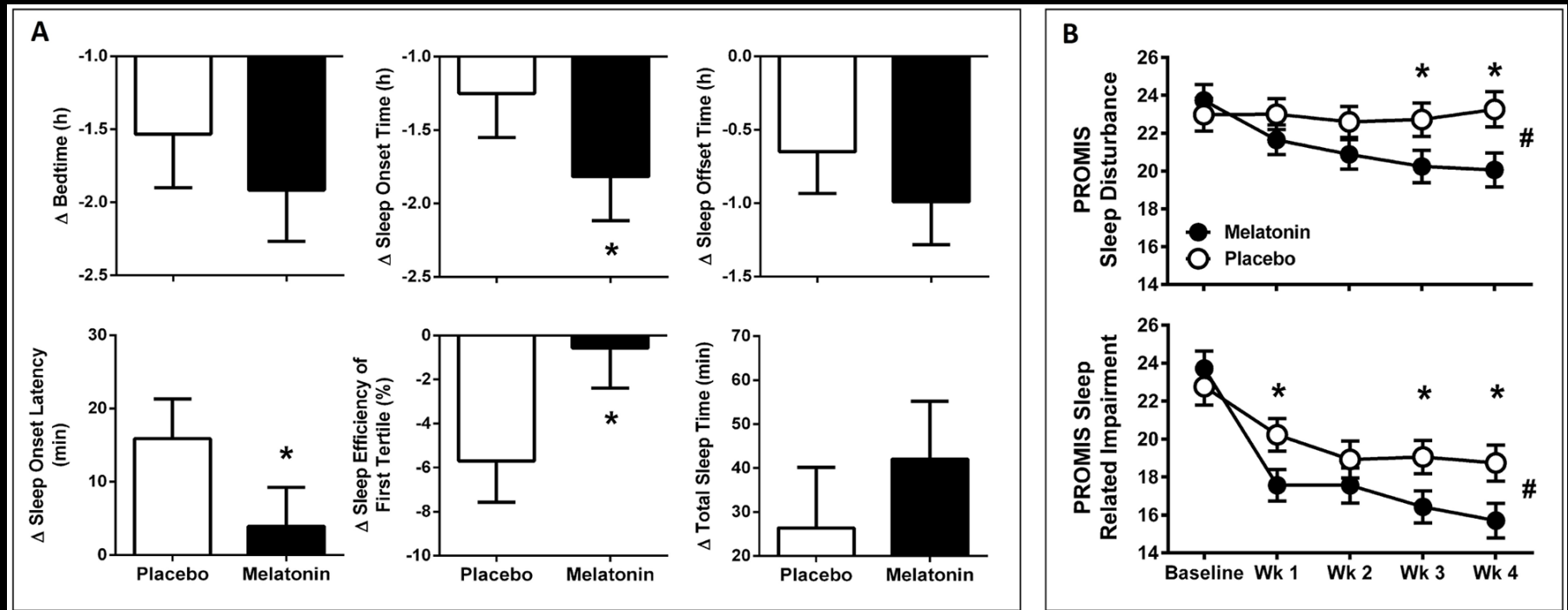
Using Light and Melatonin to Treat ASWPD and DSWPD

DLMO

Core body temperature

Normal Sleep Phase

Advanced Sleep – Wake Phase Disorder

Delayed Sleep – Wake Phase Disorder

MLT

Noon   15   19   21   Midnight   3   6   9   Noon

▲ Dim light melatonin onset   ▼ Minimum core temperature
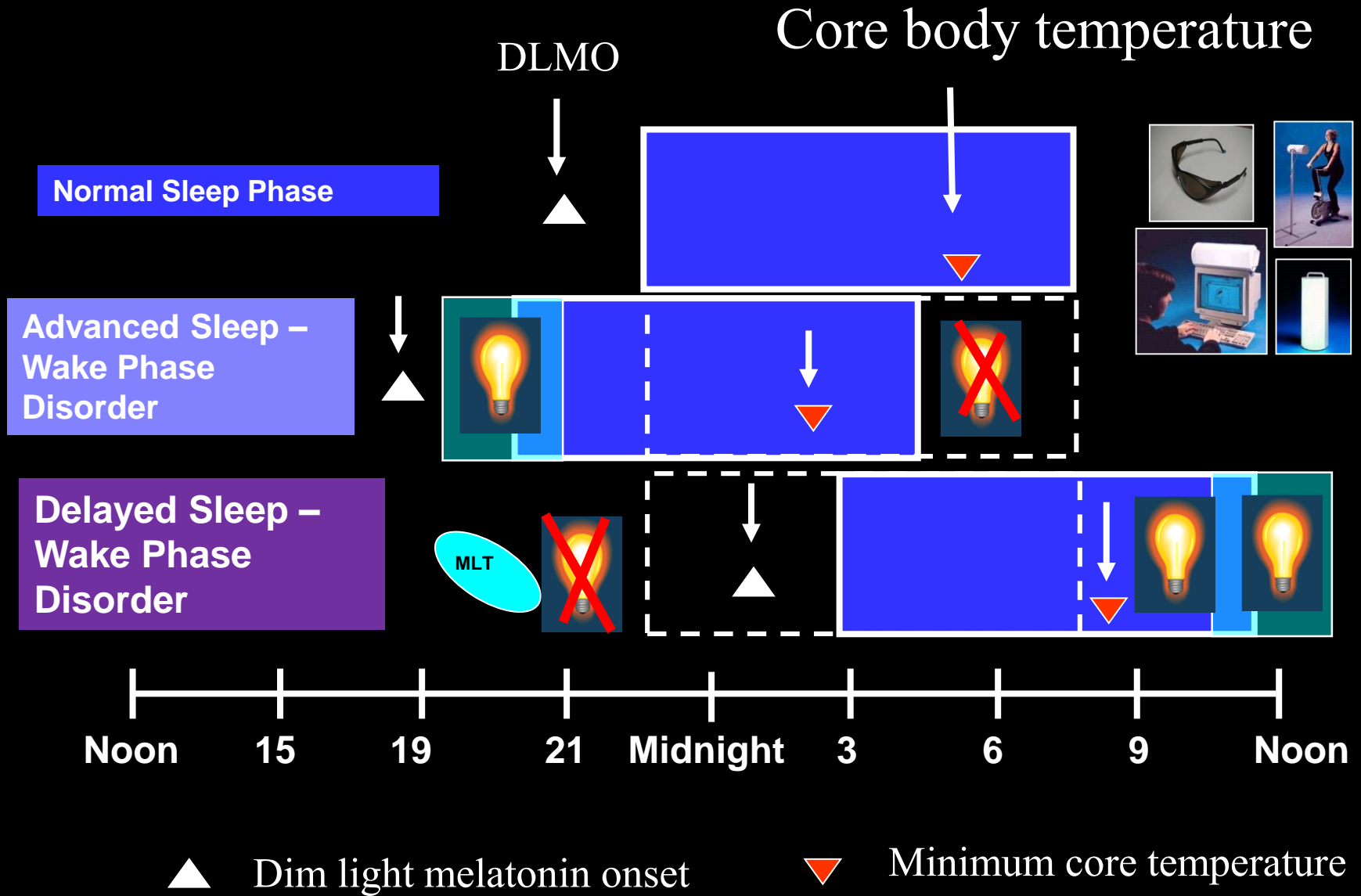
Case 3. I Can't stay on a regular sleep schedule

- 34 year old male with history of periodic insomnia and excessive sleepiness

- He has always been an "evening type", difficulty falling asleep before 1-2 am.

- Over the past 3 years sleep times drift later and later by almost an hour a day.

- He was no longer able to work because he was unable to predictably get to work during working hours.
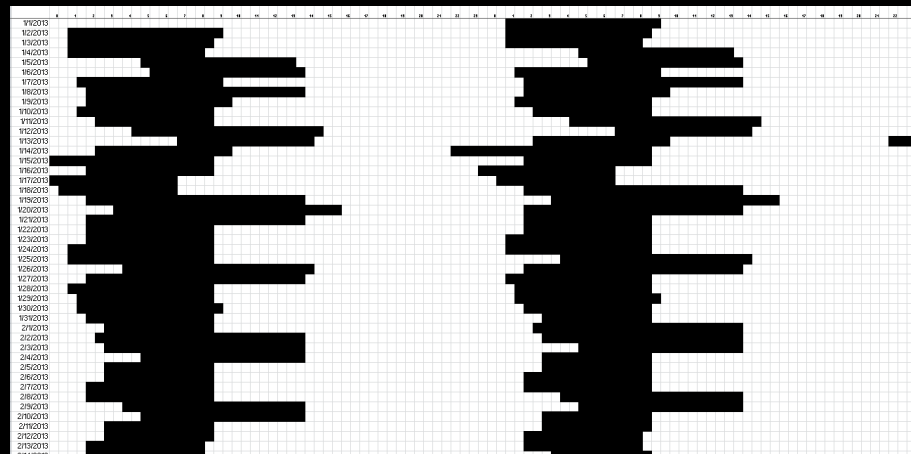
Case 3: I can't stay on a regular sleep/wake schedule

Clinic Based Treatment of Non-24 h Sleep/Wake Rhythm in Sighted Patient

Circadian phase shifting by timed light exposure in sighted (option)
Circadian phase shifting by melatonin in sighted (option)

- Light and melatonin to lock phase
- Regulate bedtime and wake time
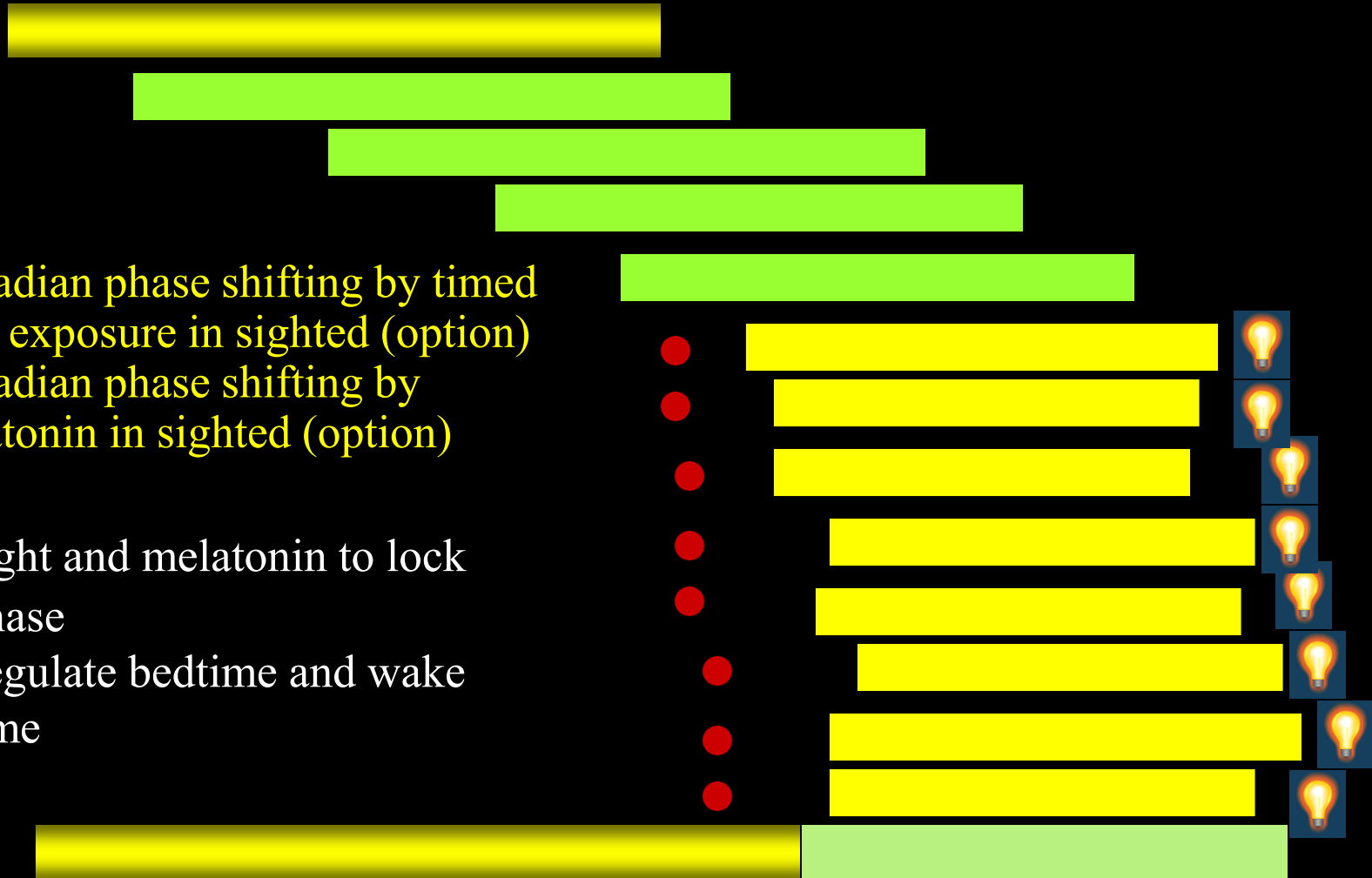
I can't keep a 24 hour schedule

Initial attempts at stabilizing his sleep with light (yellow), melatonin (green) and exercise (blue)
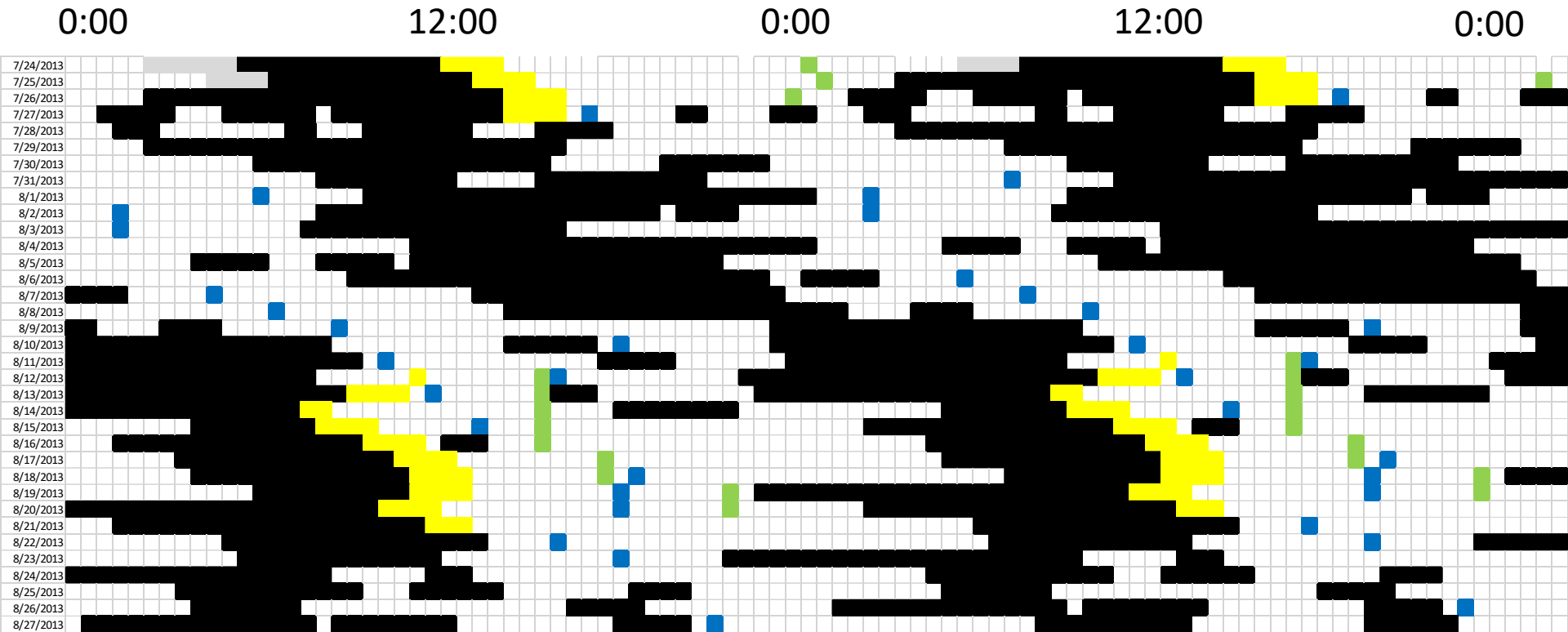
It really feels like my body has 3 different schedules. My physical self now seems to follow a more stable schedule. My mental self seems to be highly nocturnal, and my metabolism has changed to require only one small meal every 24hrs instead of 12 hours." Light worsened his migraine and hurt his eyes.

- **0130**

- **1900-2345**

- **0150 - 0300**

11/11/13
12:00 am – 20 oz Coke

11/12/13
1:30 am – 20 oz Coke
   – 15 oz Digiorno's pizza (three meat rising crust)

7:00 pm – 1.5 bowls chicken chili with 20 Keebler Club multi-grain crackers
   – 20 oz Coke

8:00 pm – 1 small bowl of snack mix

10:45 pm – 32 oz water

2200 calories

939 calories

11/13/13
6:00 am – 1 cup decaf Constant Comments tea

7:00 pm – 20 oz decaf sweet tea

11:00 pm – 14 oz Stouffer's lasagna
   – 20 oz decaf sweet tea
   – 1.6 oz garlic bread

840 calories

11/14/13
12:00 am – 20 oz decaf sweet tea
   – 1 small bowl of snack mix

11/15/13
12:15 am – 20 oz decaf sweet tea

1:50 am – 20 oz decaf sweet tea
   – 3 hard shell ground turkey tacos
   – 3 soft shell ground turkey tacos

3:00 am – 20 oz decaf sweet tea
   – 1 small bowl of tortilla chips

3124 calories

6:30 am – 20 oz decaf sweet tea

9:20 am – 20 oz decaf sweet tea

11/16/13
1:00 am – 2.5 oz bread
   – 20 oz decaf sweet tea

5:45 am – deli turkey and cheese sandwich

I can't keep a 24 hour schedule

Single dose melatonin 0.5 mg at 10 pm
Scheduled feeding times

Case 4: Can't stay awake during the day and can't stay asleep at night

- 77 year old man with cognitive impairment and Parkinson's Disease
- Over past 5 months sleep has been increasingly problematic
  - Falls asleep easily and sleeps for a few hours on and off during the night
  - He sleeps in the guest bedroom on the first floor because he has fallen while walking down the stairs at night
- Bed time: 8:30 -10:00 PM; Wake time: 5:30 AM
  - Usually falls asleep within an hour, sleeps for 2-3 hours, then sleeps on and off every 2-3 hours for the remainder of the night
- Daytime: Falls asleep during the day, mostly in the late morning and afternoon
  - several naps during the day
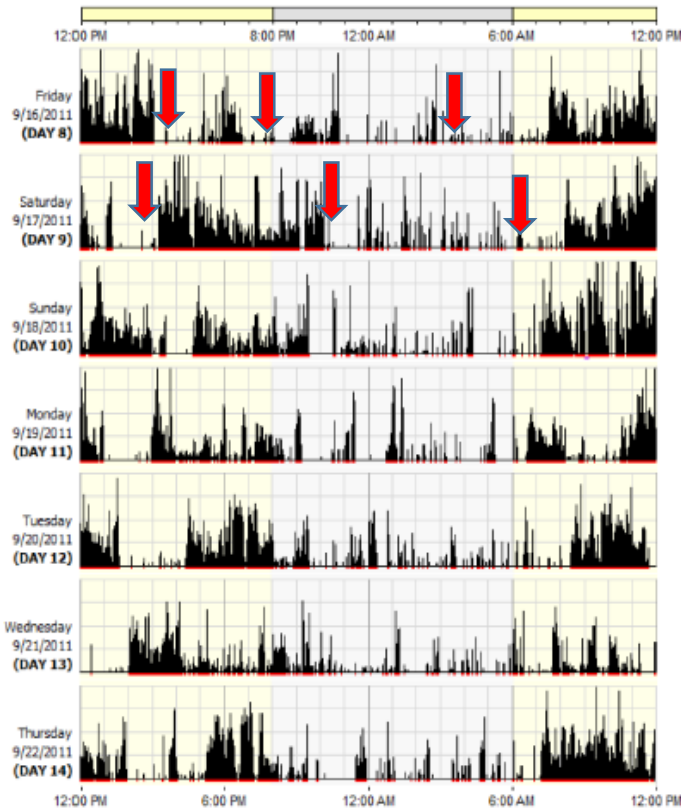- Snores loudly even during naps

Case 4- Sleep Log

Case Actigraphy

Actogram:

Polysomnography

Lights out: 2100
Lights on: 0500
TST: 274 minutes
SE: 57%
SL: 42 minutes
WASO: 164 minutes
Arousal index: 18
PLMI: 8
AHI: 9.5 (4% desaturation criteria)
Lowest Oxygen saturation: 88%
Increased chin muscle activity in REM and non-REM

Irregular Sleep Wake Rhythm Clinical Practice Parameters

- Most common in disorders of neurodevelopment and neurodegeneration

- Daytime bright light may improve rest/activity and consolidate sleep in nursing home residents

  - 8/9 studies reported positive results

  - Average of 2 hours; 1500-8000 lux

  - 1/9 negative study tested morning light (2500 lux)

- Melatonin may be effective

  - indicated in children with ISWR

- Mixed modality approaches including light, activity and other behavioral elements (guideline)

Morgenthaler TL et al, Sleep 30(11), 2007

Timed Light Therapy Improves Daytime Sleepiness Associated with Parkinson's Disease

- Bright: 3000 lux
- Dim Red: 300 lux
- 0900-1100; 1700-1900 (2 weeks)

	Bright Light	Dim Red Light	*p*
△EES score	4.75 ± 1.84	1.79 ± 2.89	0.005

- sleep quality (PSQI, PDSS)
- sleep fragmentation
- sleep latency
- daily physical activity level (actigraphy)
- improved total UPDRS score

Case 5. Insomnia, Excessive Sleepiness and Depression

- A 55-year-old female with excessive sleepiness for 1 year, but has become worse in the past 6 months

- She works at a casino from 10 pm to 6 am for 5 years

- Has a 30- to 35-minute commute and has been struggling to stay awake while driving home in the morning

- Bedtime: 9 am, falls asleep right away, but wakes up 2 -3 hours later and sleep is fitful until she gets out of bed at 330 pm to 4 pm.

Sleep/Wake Diary

↓ Into Bed ; ↑ Out of Bed

PM

Date	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11
12/9										↓	■	■	■	■			↑							
12/10										↓	■	■			■		↑							
12/11										↓	■	■	■		■	■		↑						
12/12										↓	■	■		■	■		↑							
12/13										↓		■	■	■	■	■		↑						
12/14	↓			■	■	■	■	■	■	■	↑				■	■								
12/15	↓		■	■			■	■	■	■		↑				■								
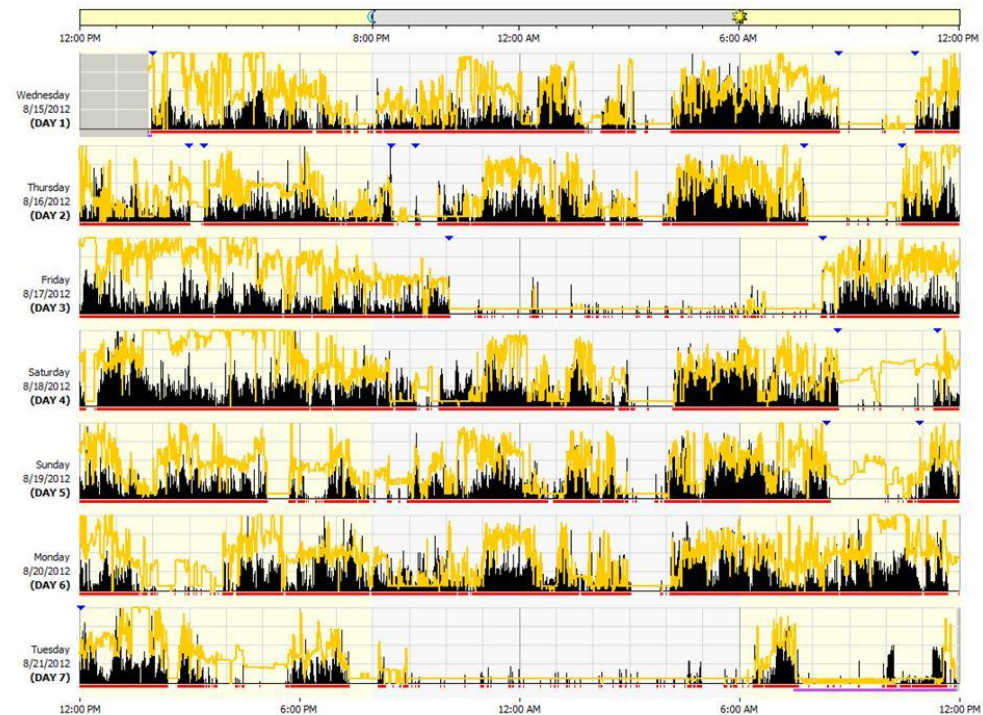
Circadian Medicine Clinic

Mission: To diagnose and treat circadian disorders and to promote circadian health as a key component of medicine.

Initial screening – CRSWD, shift workers, circadian misalignment in medicine

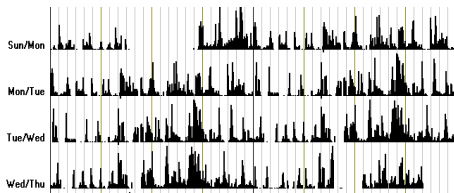**(Sleep log, feeding/activity questionnaires)**
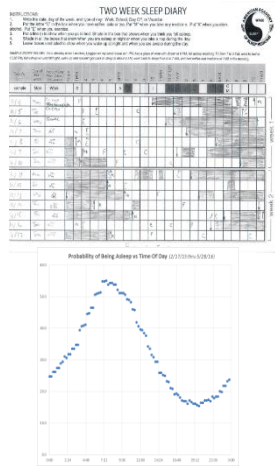
Clinical Evaluation

Telemedicine

– saliva, 24 hour urine

- Personalized circadian profile

Personalized PrecisionTreatment

What can we learn from patients?