

SLEEP, CIRCADIAN RHYTHMS, AND DELIRIUM: PHYSIOLOGIC AND CLINICAL IMPLICATIONS

FOCUS ON CLINICAL INVESTIGATION

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NIDUS
Network for Investigation of
Delirium: Unifying Scientists

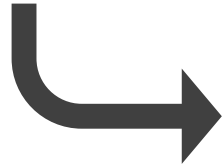
Dr. Knauert is a member of Serca LLC and has a patent pending for an integrated circadian health program in healthy adults. Not relevant to this talk.

Dr. Knauert is currently supported by the NHLBI (R01 HL163659). Past support includes the NHLBI (K23 HL138229, R03HL157009), the Academy of Sleep Medicine Foundation, and the Fund to Retain Clinical Scientists at Yale sponsored by the Doris Duke Charitable Foundation award #2015216, the Yale Center for Clinical Investigation and the National Center for Advancing Translational Science (KL2 TR000140).

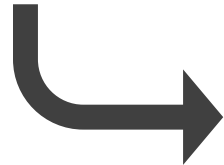


OUR OBJECTIVE? ... TO UNDERSTAND: HOW DID WE GET HERE? WHERE ARE WE GOING?

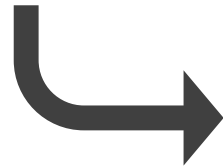
ICU Delirium



Sleep ... and (finally) Circadian disruption



Outcomes

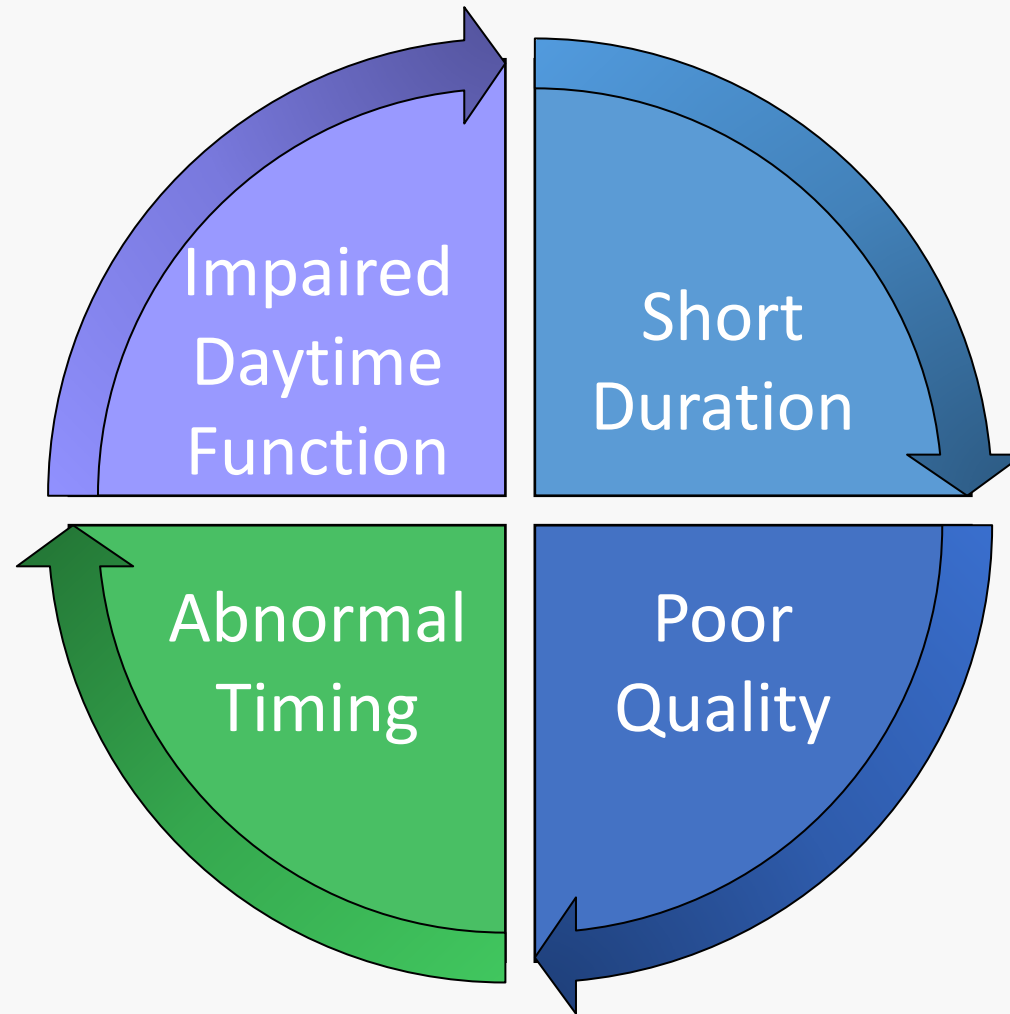


Treatment

DELIRIUM IN THE (MEDICAL) ICU IS COMMON AND CHALLENGING

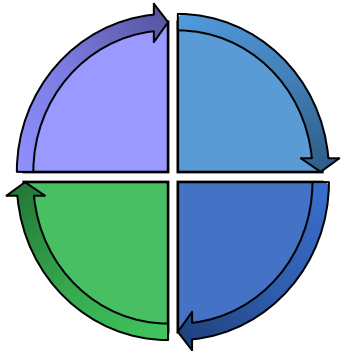
- **Risk factors:** sedatives, age, dementia, prior coma, pre-ICU emergency surgery/trauma, APACHE severity of illness scores, ASA score
- **Prevalence:** 50 to 80% on the medical ICU
- **Outcomes:** impact on cognition, hospital LOS, mortality
- **Treatment:** limited pharmacologic treatment; sleep and mobility bundles recommended

SLEEP IN THE ICU IS SEVERELY DISRUPTED



Cooper, Chest, 2000
Freedman, AJRCCM, 2001
Parthasarathy, AJRCCM, 2002
Gabor, AJRCCM, 2003
Knauert, Heart&Lung, 2014

ICU SLEEP DISRUPTION IS ASSOCIATED WITH POOR OUTCOMES



- Poor sleep is associated with delirium.
- Delirium is associated with poor sleep and decreased melatonin levels.
- Poor sleep is associated with an increased risk of death.

Harrell, J Clin Psych, 1987
Trompeo, Minerva Anes, 2011
Sun, J Int Med Res, 2021

Knauert, JCC, 2018

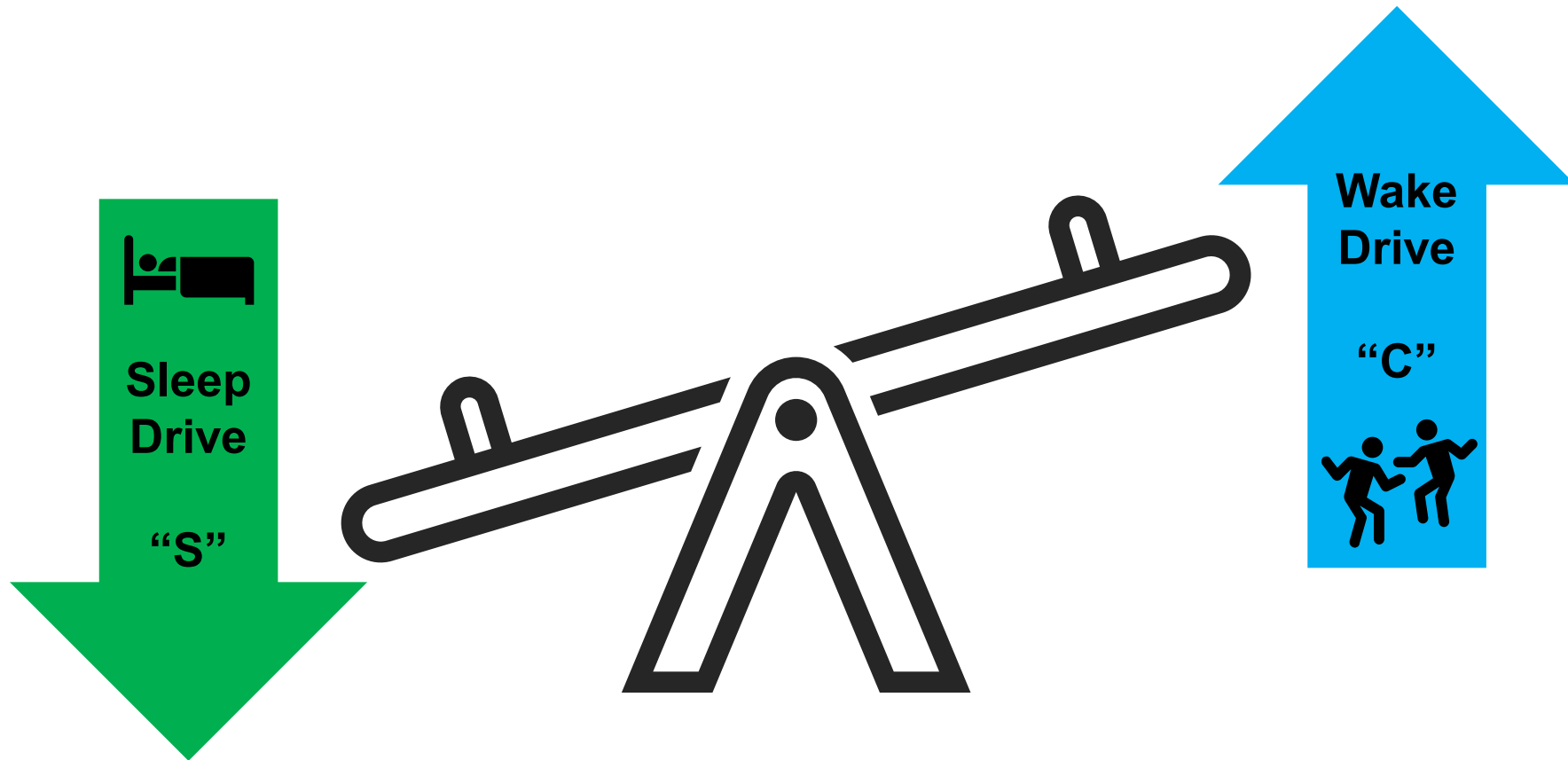


GETTING UNSTUCK FROM THE SLEEP OPPORTUNITY PERSPECTIVE

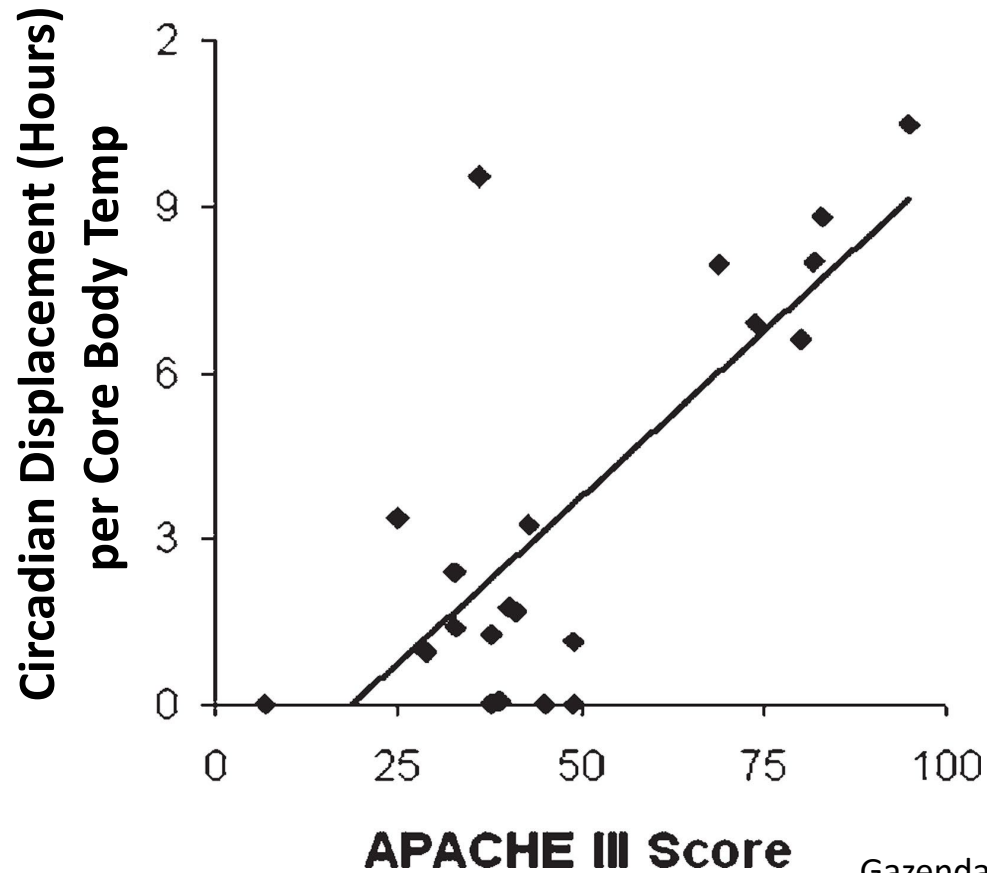
*Add environmental control
and/or cluster care to avoid
overnight interruptions.*

Necessary but not sufficient.

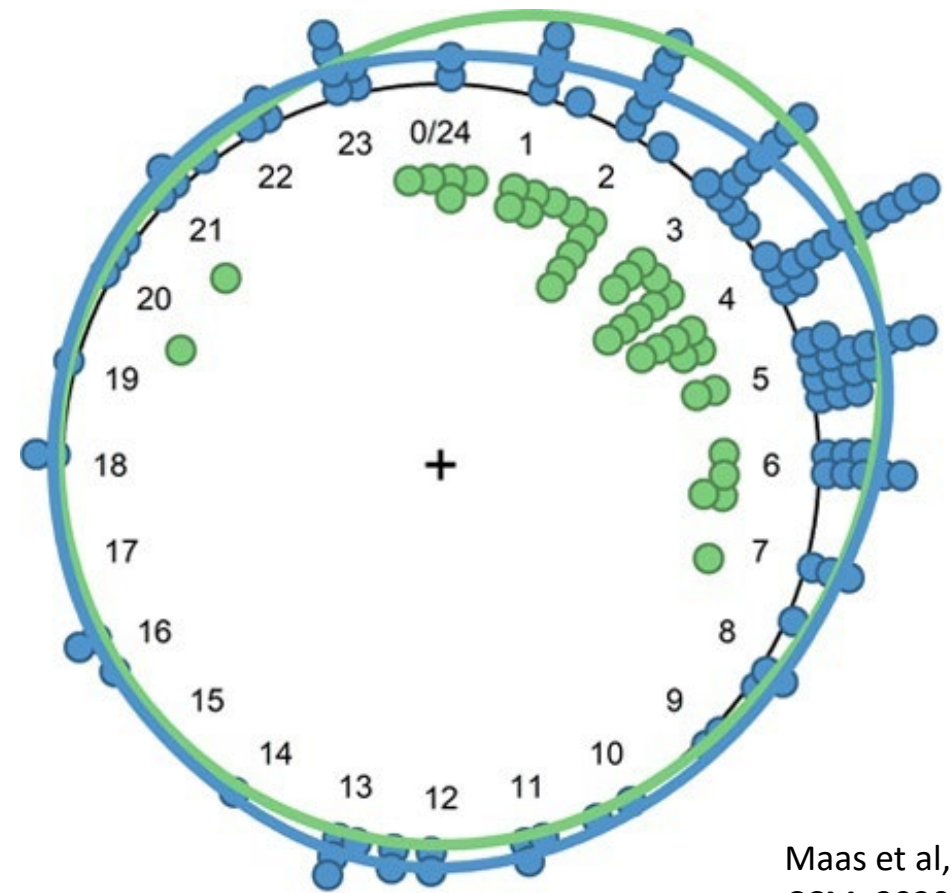
THE TIMING AND DURATION OF SLEEP IS CONTROLLED BY THE 2-PROCESS MODEL



CIRCADIAN RHYTHMS ARE (ALSO) ABNORMAL IN THE ICU



Gazendam et al,
Chest, 2013

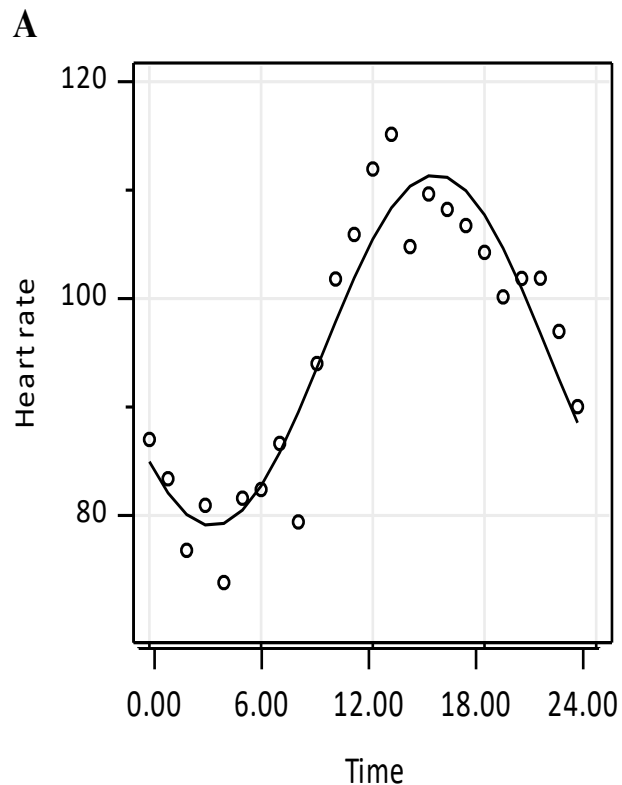


Serum Melatonin Acrophase
Critically Ill Patients (Blue) and Healthy Controls (Green)

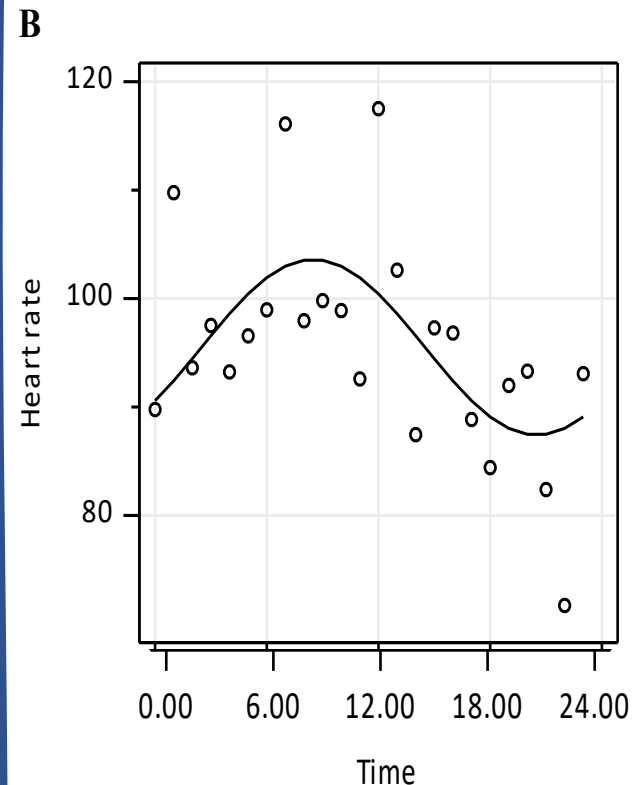
Maas et al,
CCM, 2020

USING CONTINUOUS HEARTRATE DATA FROM TELEMETRY TO ESTIMATE CIRCADIAN PHASE (DIURNAL VARIATION)

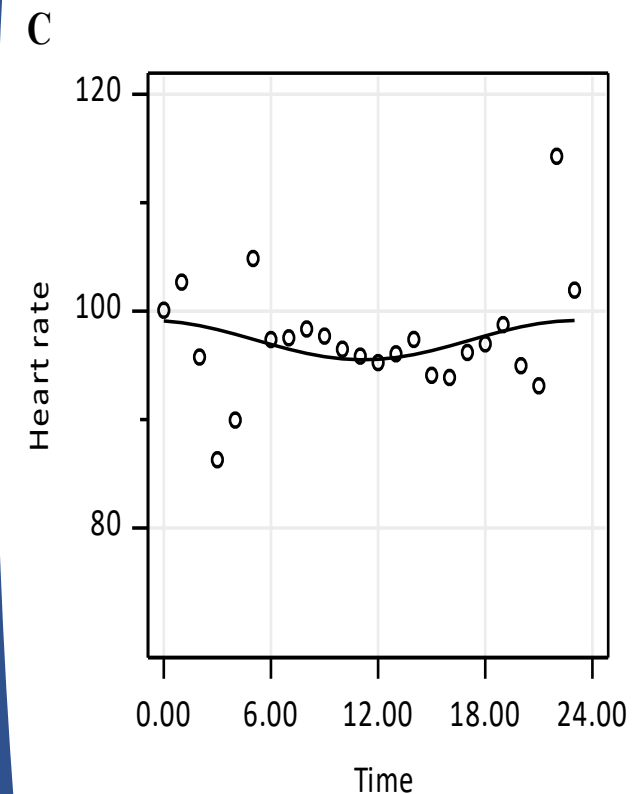
Patients with aligned diurnal variation (n=9)



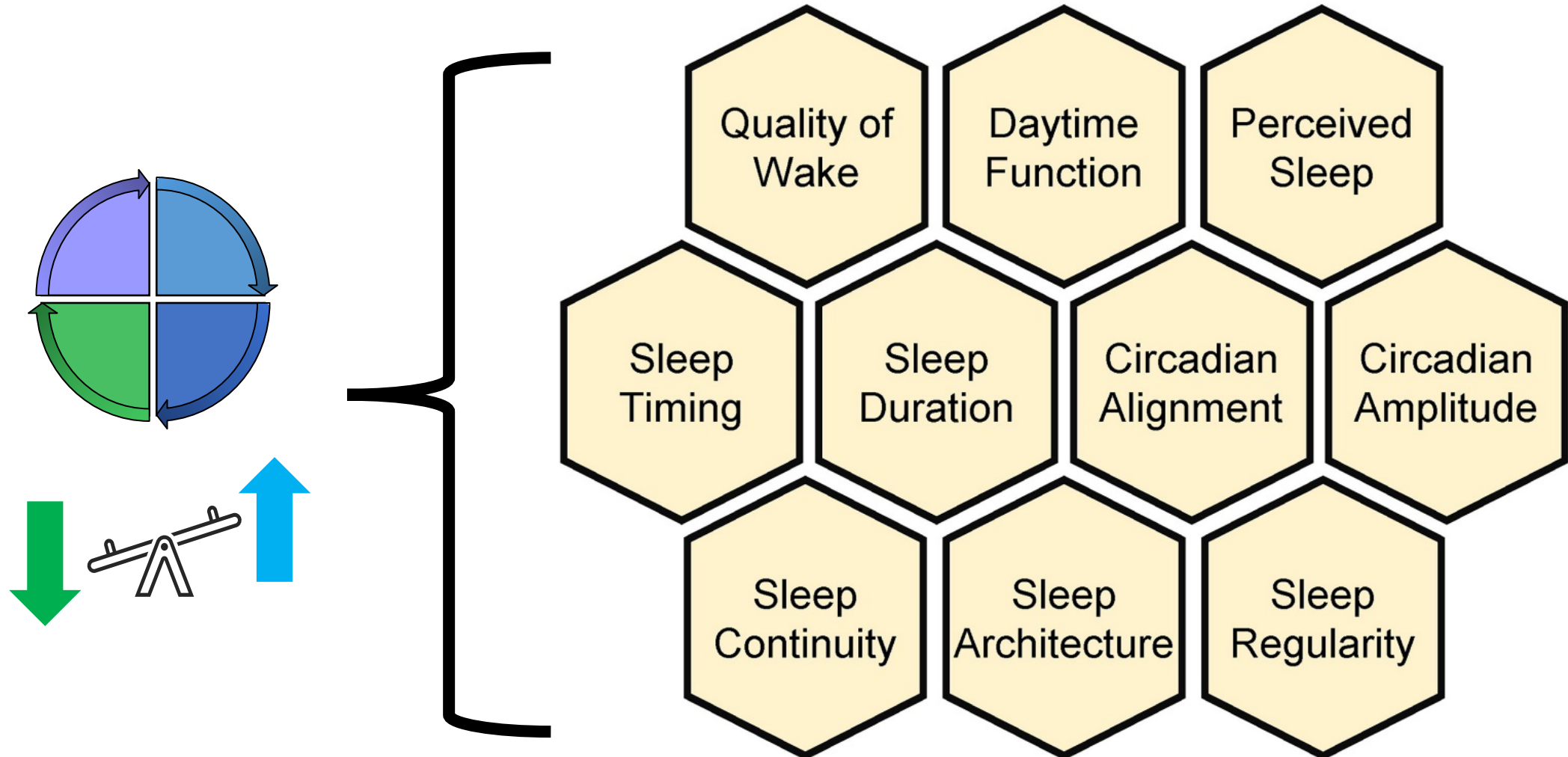
Patients with misaligned diurnal variation (n=39)



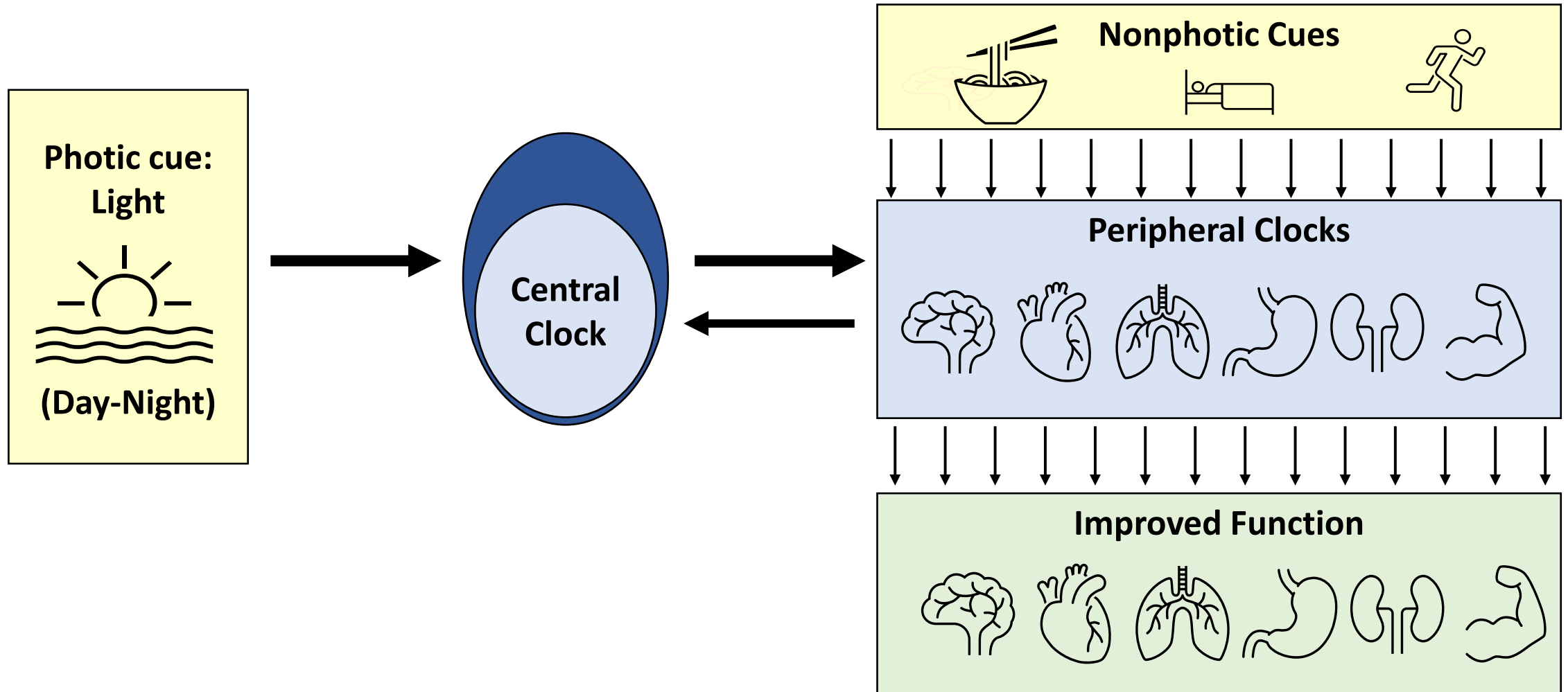
Patients without diurnal variation HR (n=8)

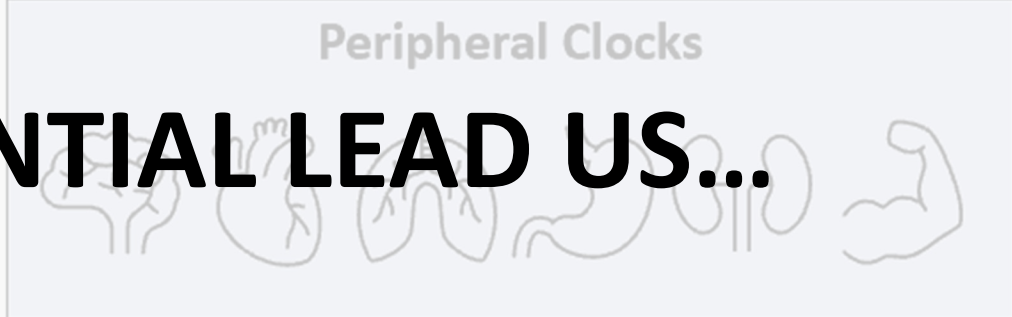
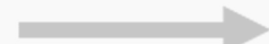
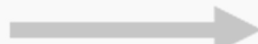
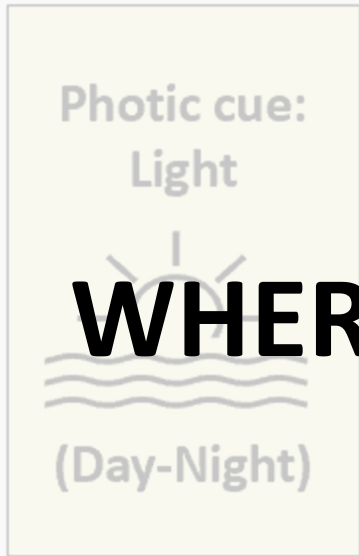


ICU SLEEP AND CIRCADIAN DISRUPTION HAS MANY DOMAINS



CIRCADIAN FRAMEWORK SUGGESTS KEY TARGETS FOR SLEEP PROMOTION & BEYOND





1



WHERE DOES THIS POTENTIAL LEAD US...

SLEEP BUNDLES LIKELY IMPROVE DELIRIUM OUTCOMES

20 studies of bundled care

- 6 delirium + sleep
- 14 sleep alone

Sleep measures

- 12 did not measure
- 7 subjective sleep scale (RCSQ)
- 1 study specific scale

Delirium measures

- 2 ICDSC
- 15 CAM ICU
- 3 other

Study design

- 18 before/after
- 2 interrupted time series

Outcomes

12 of 20 showed improvement in delirium measures

EYE MASKS AND EAR PLUGS MAY IMPROVE DELIRIUM OUTCOMES

5 studies of eye masks, ear plugs

- 4 both
- 1 ear plugs alone

Sleep measures

- 3 RCSQ
- 2 objective, subjective mix

Delirium measures

- 2 CAM ICU
- 1 NEECHAM
- 2 not described

Study design

- 5 RCTs

Outcomes

2 showed improvement in delirium; 2 showed improvement in sleep but no related change in delirium (1 with PSG, low overall delirium)

BRIGHT LIGHT THERAPY

???

DELIRIUM OUTCOMES

5 studies Light Studies

- mixed light prescriptions

Sleep and circadian measures

- 1 ISI, 4 none
- no circadian measures

Delirium measures

- All CAM ICU

Study design

- 1 retrospective cohort
- 2 prospective cohort
- 2 RCT

Outcomes

1 RCT showed improvement in delirium measures

MELATONIN ??? DELIRIUM OUTCOMES

8 studies melatonin rx

- varied dose and timing
- 4 MICU only, 4 mixed ICU

Sleep and circadian measures

- 1 PSG, 2 RCSQ, 5 none
- no circadian

Delirium measures

- 7 CAM ICU
- 1 ICDSC

Study design

- 4 double blind RCT
- 3 retrospective observational
- 1 prospective cohort

Outcomes

2 of 8 improvement in delirium; 1 of these only in MICU subgroup (intervention included ear plugs)

1 negative study 800+ patients in 12 ICUs, 4mg at 21:00, RCT

OTHER PHARMA ??? DELIRIUM OUTCOMES

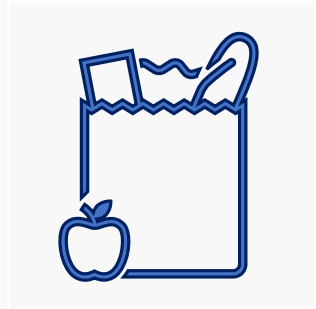
11 Pharma Studies

- 4 ramelteon (RCT)
- 4 dexmedetomidine (RCT, 1 post hoc of RCT)
- 3 suvorexant (RCT)

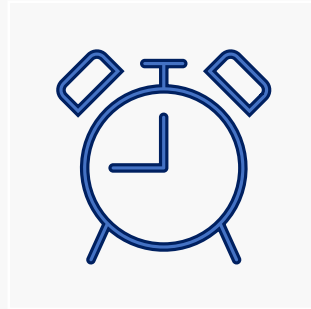
Outcomes

- ramelteon: 2 of 4 improved
- dexmedetomidine: 2 sleep better, delirium same; 2 sleep same, delirium better (sleep by questionnaire)
- suvorexant: 3 of 3 improved

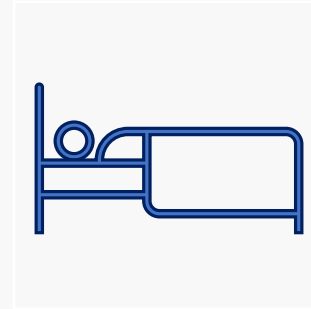
GAPS AND CHALLENGES



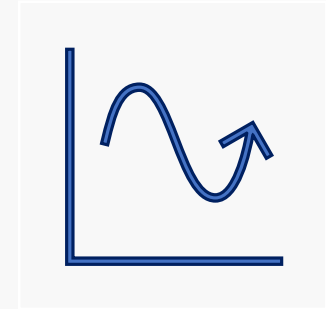
**MIXED
INTERVENTIONS**



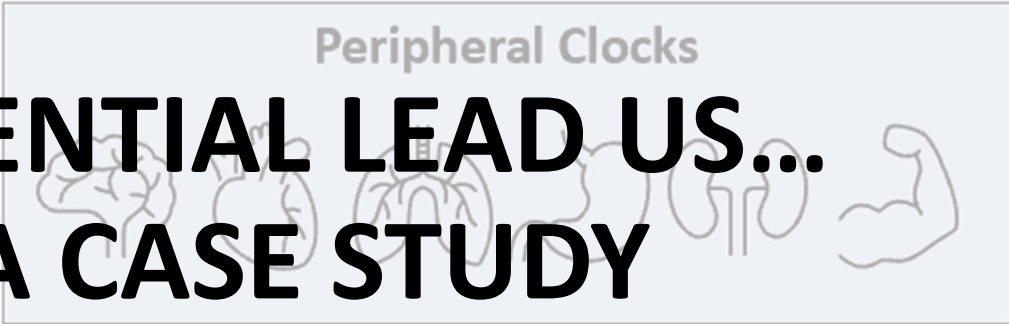
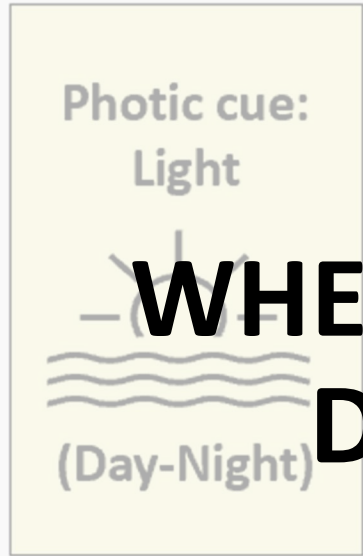
**MIS-TIMED OR
MIS-DOSED
INTERVENTIONS**



**CHALLENGING
SLEEP AND
CIRCADIAN
MEASUREMENT**



**VARIED OUTCOME
MEASURES**



**WHERE DOES THIS POTENTIAL LEAD US...
DAYTIME LIGHT AS A CASE STUDY**

1

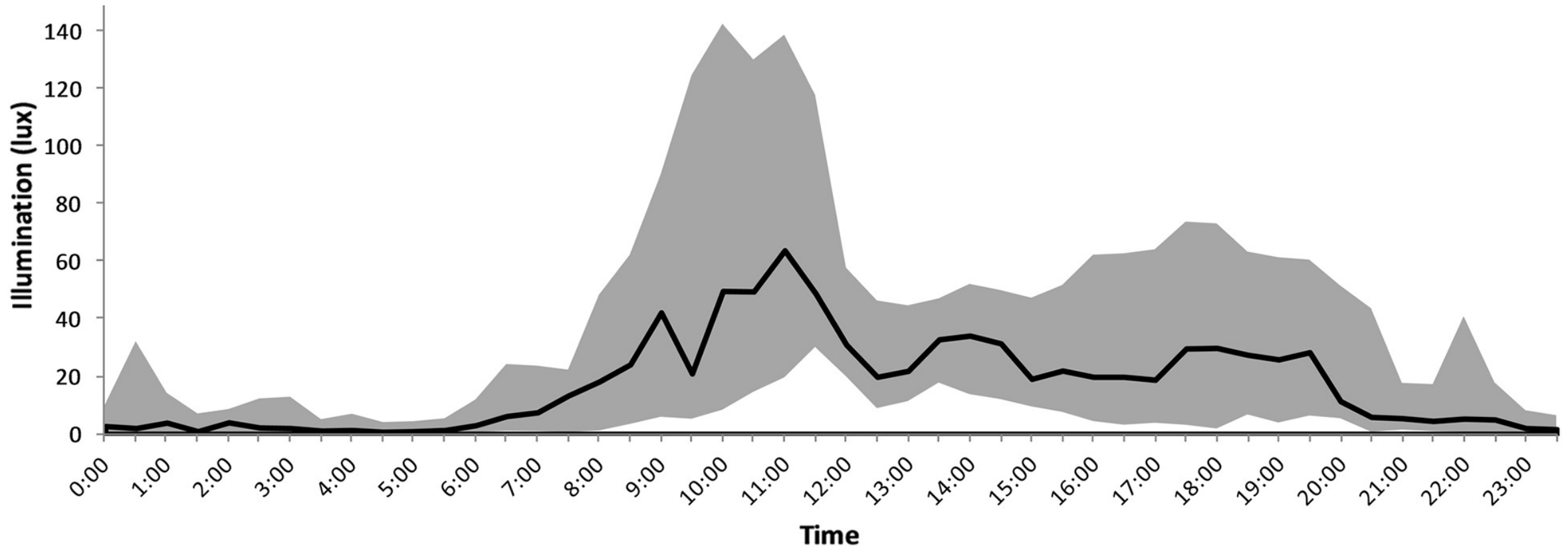


LIGHT

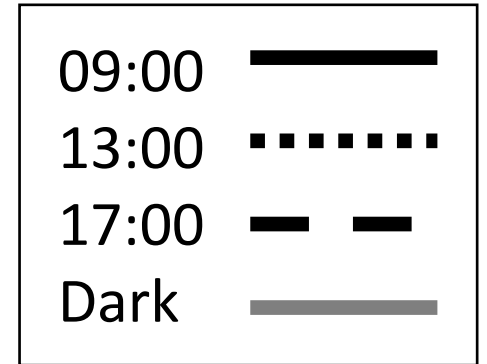
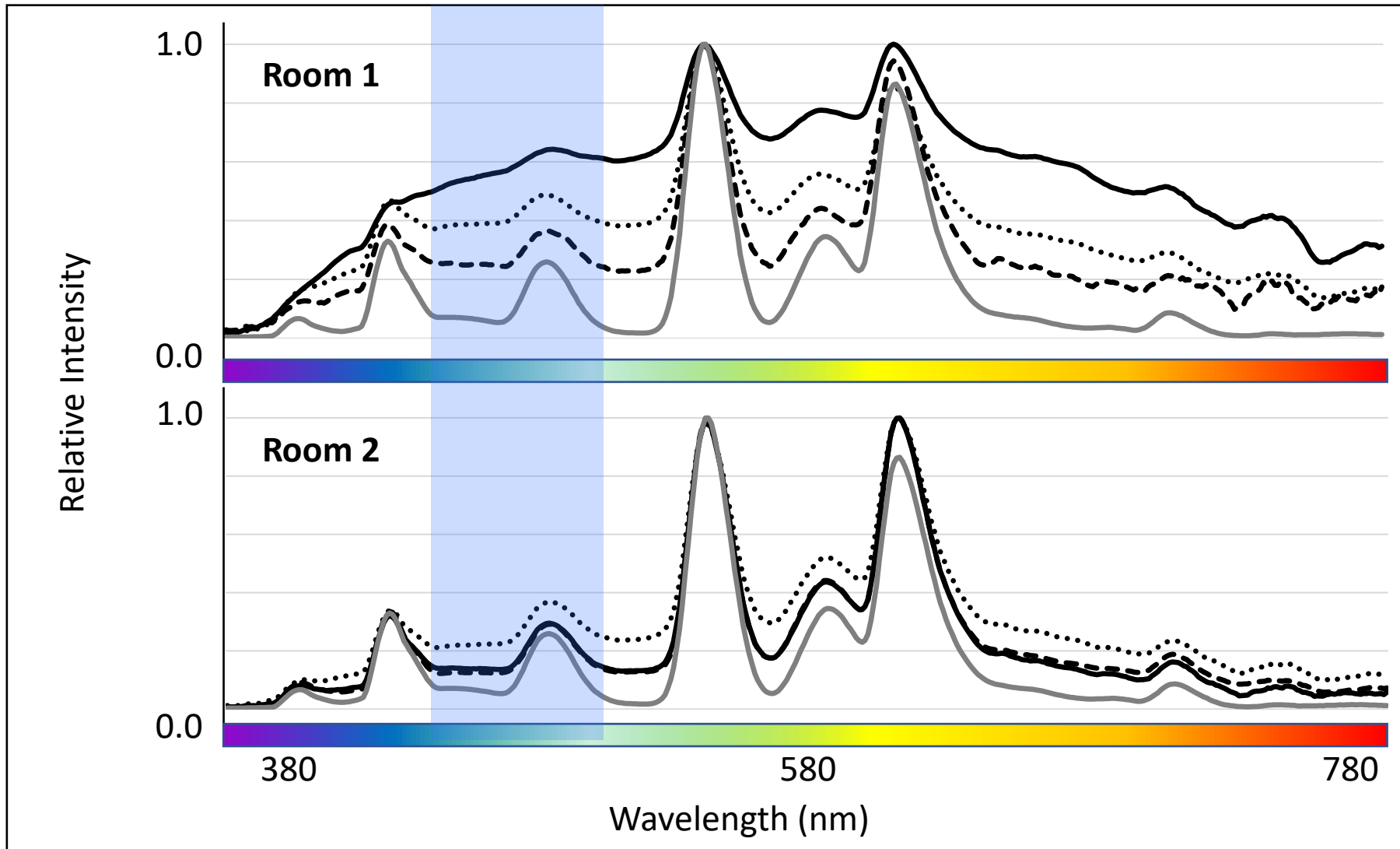
TIMING
DURATION
INTENSITY
SPECTRA
HISTORY

NON-CIRCADIANT LIGHT PATTERNS ARE PRESENT...

DIM DAYTIME LIGHT IS A KEY PROBLEM



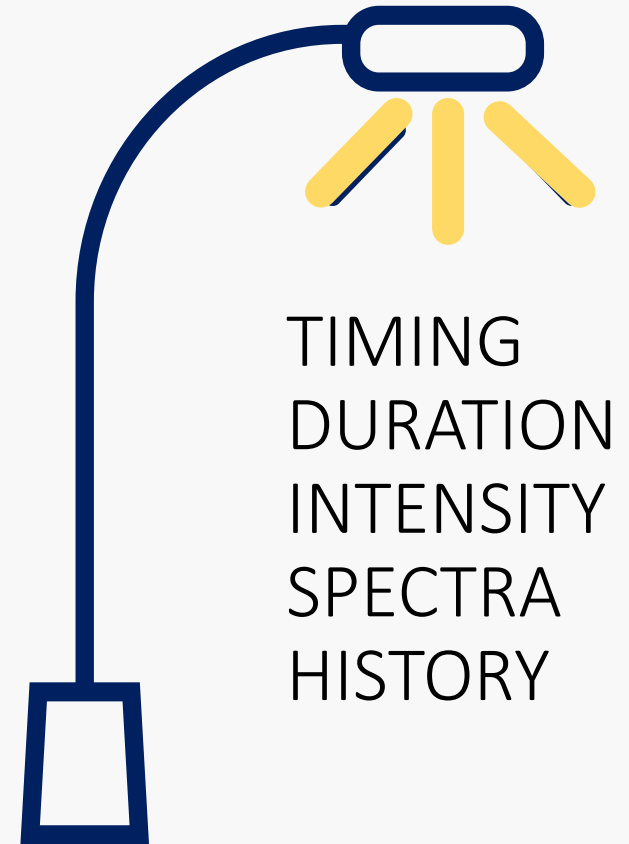
ICU LIGHT IS ARTIFICIAL

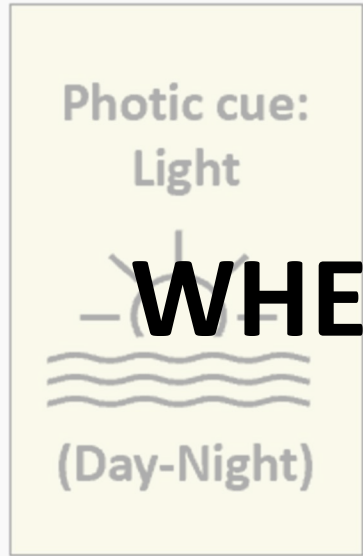


Knauert, unpublished data

CAN WE ARRIVE AT A BEST PRACTICE FOR LIGHT INTERVENTION

- Patients are likely delayed
- Daytime 4 or 8-hour block bright light
- 10,000 lux at source
- High blue light content, e.g., 5000 Kelvin
- Nighttime MINIMAL LIGHT
- Light and spectra monitoring





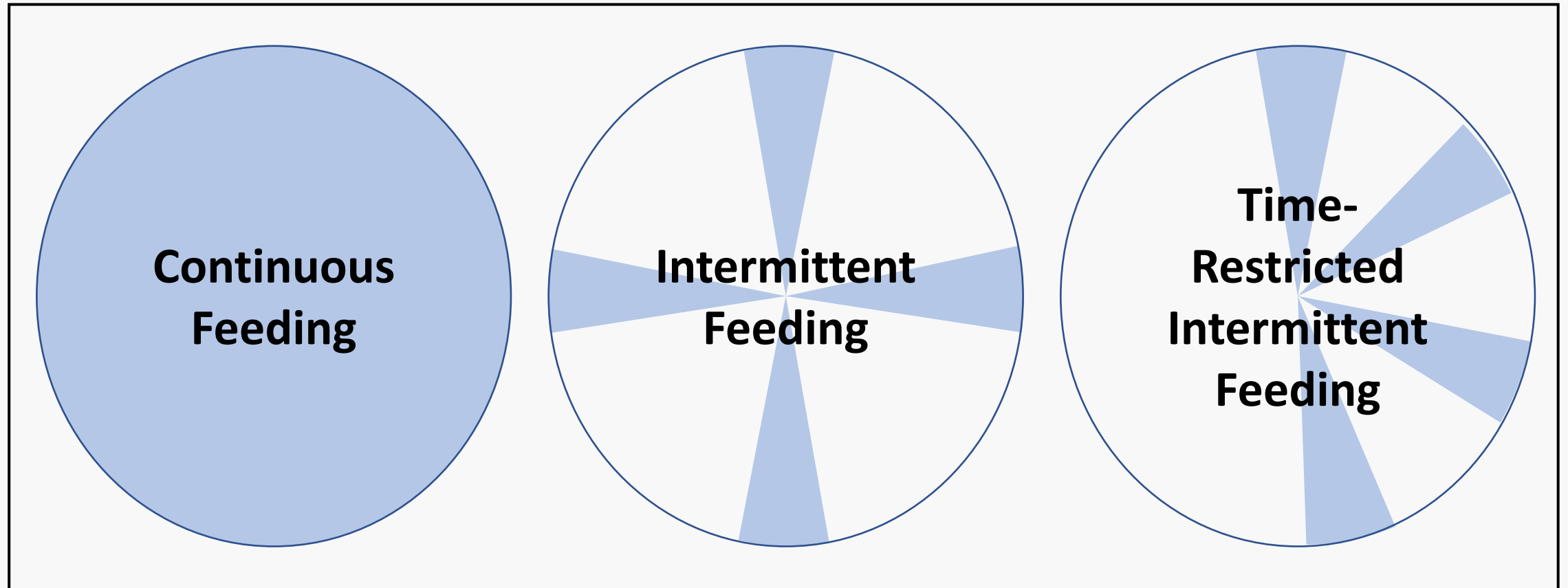
**WHERE DOES THIS POTENTIAL LEAD US...
OTHER ZEITGEBERS**

1

NON-PHOTIC CUES: SLEEP & EXERCISE/MOBILITY



NON-PHOTIC CUES: FEEDING TIMING



THE IMMEDIATE FUTURE OF ICU SLEEP AND CIRCADIAN RESEARCH



LOW HANGING FRUIT

TX: LIGHT, SLEEP,
FEEDING & MOBILITY

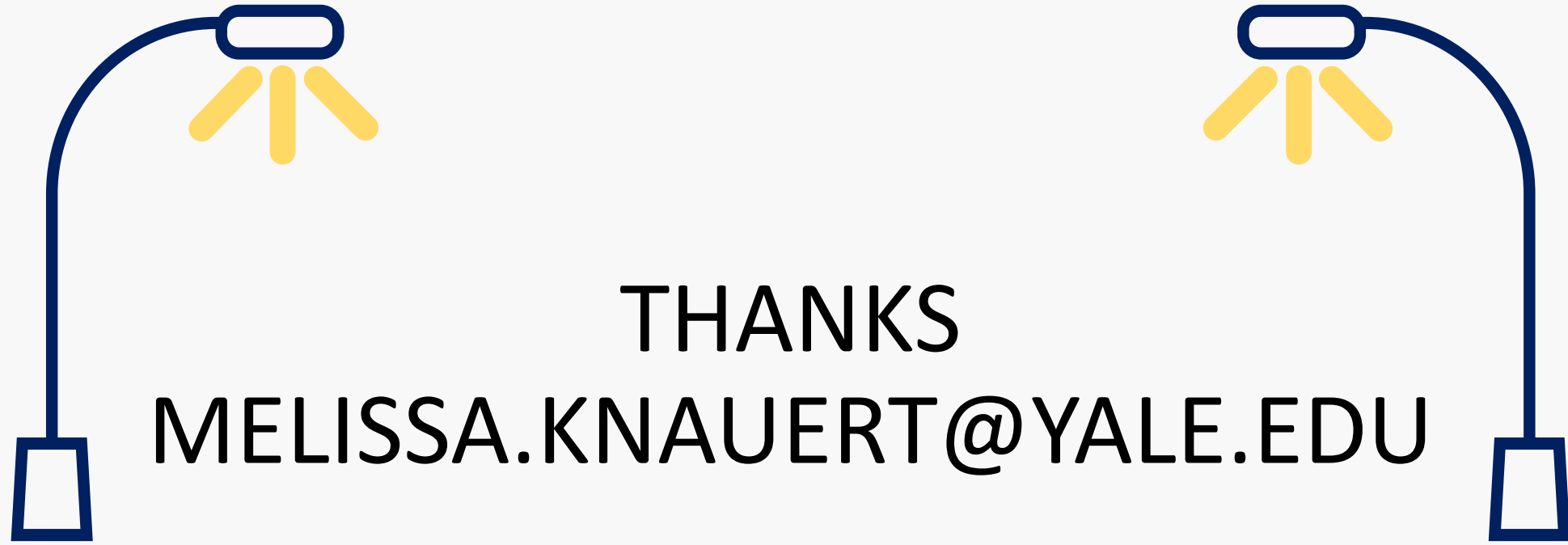


IMPROVE: **DELIRIUM**,
SLEEP, METABOLISM,
STRENGTH

MOONSHOT(S)



- LARGE SCALE &/OR
BEDSIDE MEASURES
- PERIPHERAL CLOCK
MEASURES
- PHARMACOTHERAPY



THANKS
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Knauert MP, Ayas NT et al. **Causes, Consequences, and Treatments of Sleep and Circadian Disruption in the ICU: An Official American Thoracic Society Research Statement.** *Am J Respir Crit Care Med.* 2023 Apr 1.

Klerman, EB, Brager, A, Carskadon, MA, et al. **Keeping an eye on circadian time in clinical research and medicine.** *Clin Transl Med.* 2022; 12:e1131.