The Importance of Assessing Sleep Disturbance in Clinical Trials for Opioid Use Disorder

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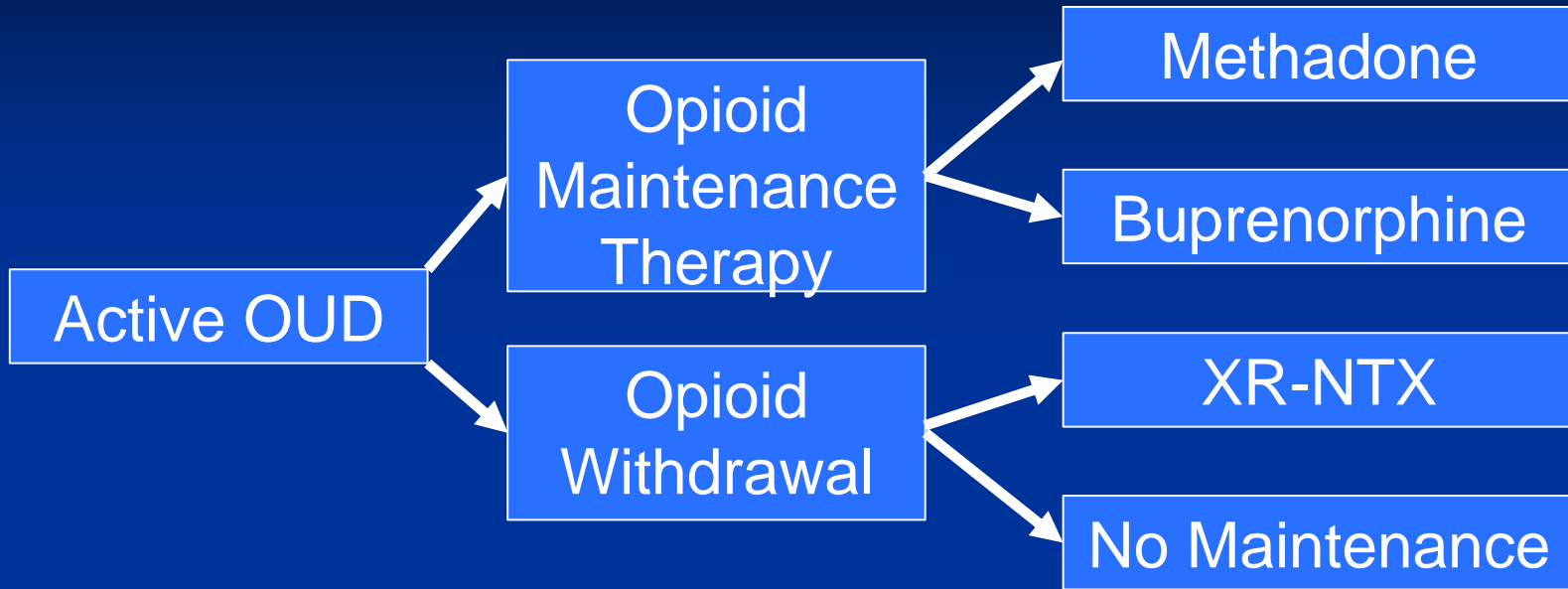
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Outline

- Current OUD treatment options
- Sleep outcomes and clinical trial design
- Incorporating sleep measures into OUD clinical trials
- The role of sleep and stress in OUD treatment outcomes
- Non-opioid receptor targets for sleep disturbance
  - Orexin
  - Serotonin
  - Others
- Ongoing studies

Choose your own adventure!

Treatment Trajectory

Active OUD

- Opioid Maintenance Therapy
  - Methadone
  - Buprenorphine
- Opioid Withdrawal
  - XR-NTX
  - No Maintenance

Levels of Care

| Residential/ Hospital	Sober Living Environment	Outpatient	12-step or no ongoing care

January 2, 2020

We don't know much about how different treatment options impact biological systems that affect treatment outcomes

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Relationship between sleep and the HPA-axis

Increased stress is associated with sleep disturbances.

Sleep disturbances can be a result of OR contribute to HPA-axis dysregulation.

Figure 1
Circadian Release of Cortisol
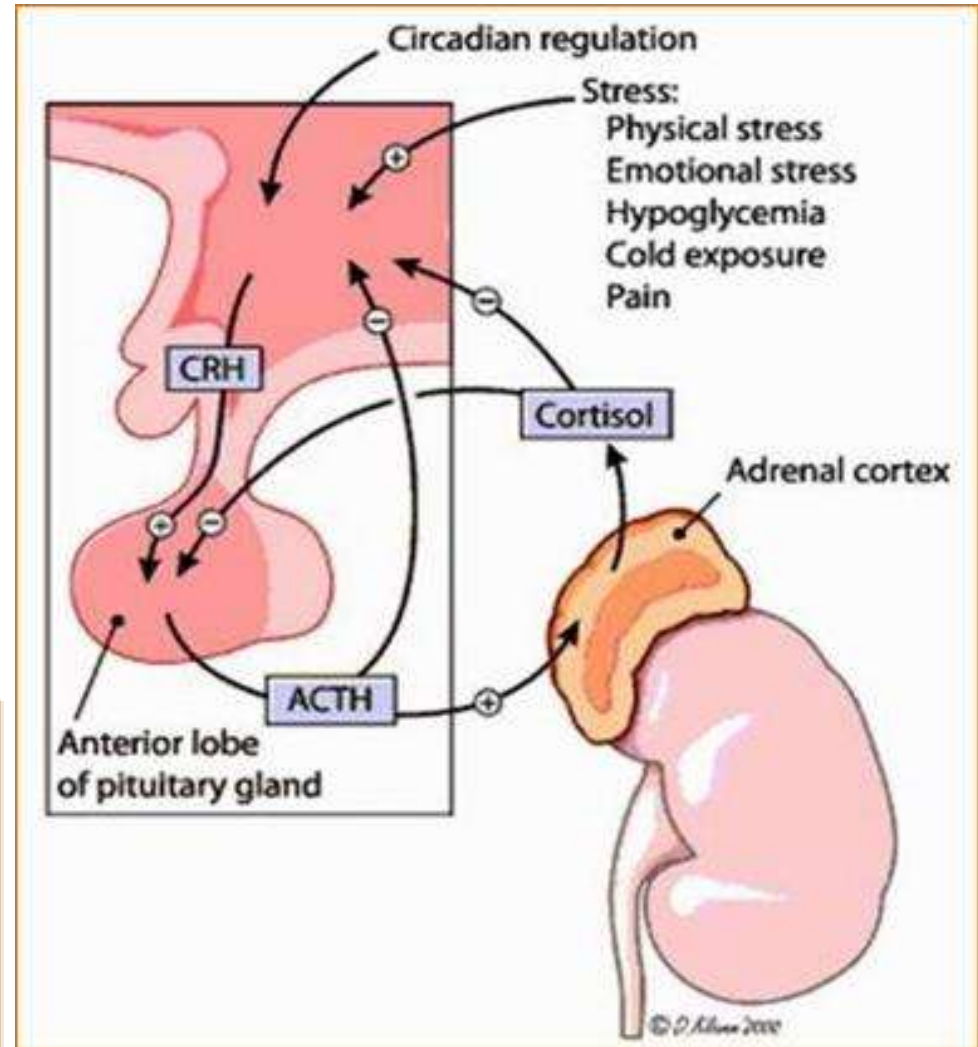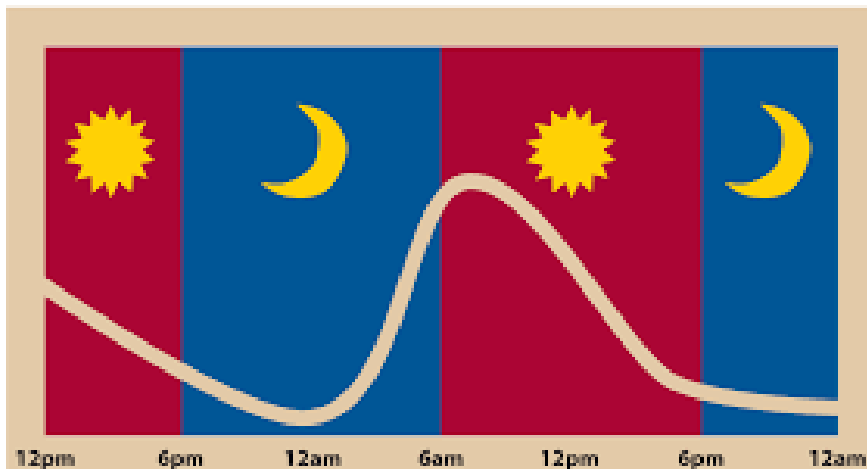
Opioid Use and Sleep/Stress

Acute Opioid Use

- Reduces subjective reports of stress
- Reduces HPA-axis signaling
- Disrupts sleep architecture

Chronic Opioid Use

- Increases stress reactivity
- Alters HPA-axis function
- Persistent sleep disturbance

There are very few studies on sleep quantity and quality in recovery from opioid use disorder.

Treatment Intake Survey at Ashley Addiction Treatment (N=354)

- Sleep disturbance is associated with past 30-day opioid use (p=0.028) and feelings of depression, anxiety, and anger (p<0.001).

OUD Patients at Treatment Admissions (past 30-day outcomes)

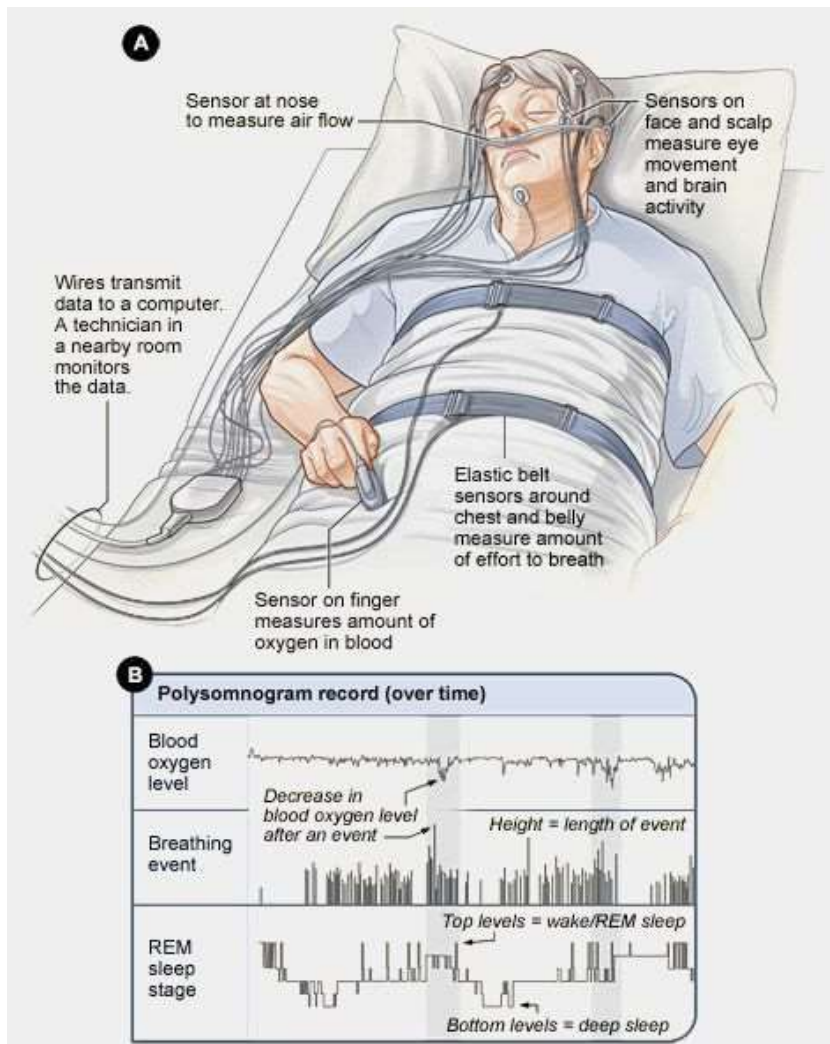Legend: 0 days · 1-3 days · 4-8 days · 9-15 days · 16-30 days
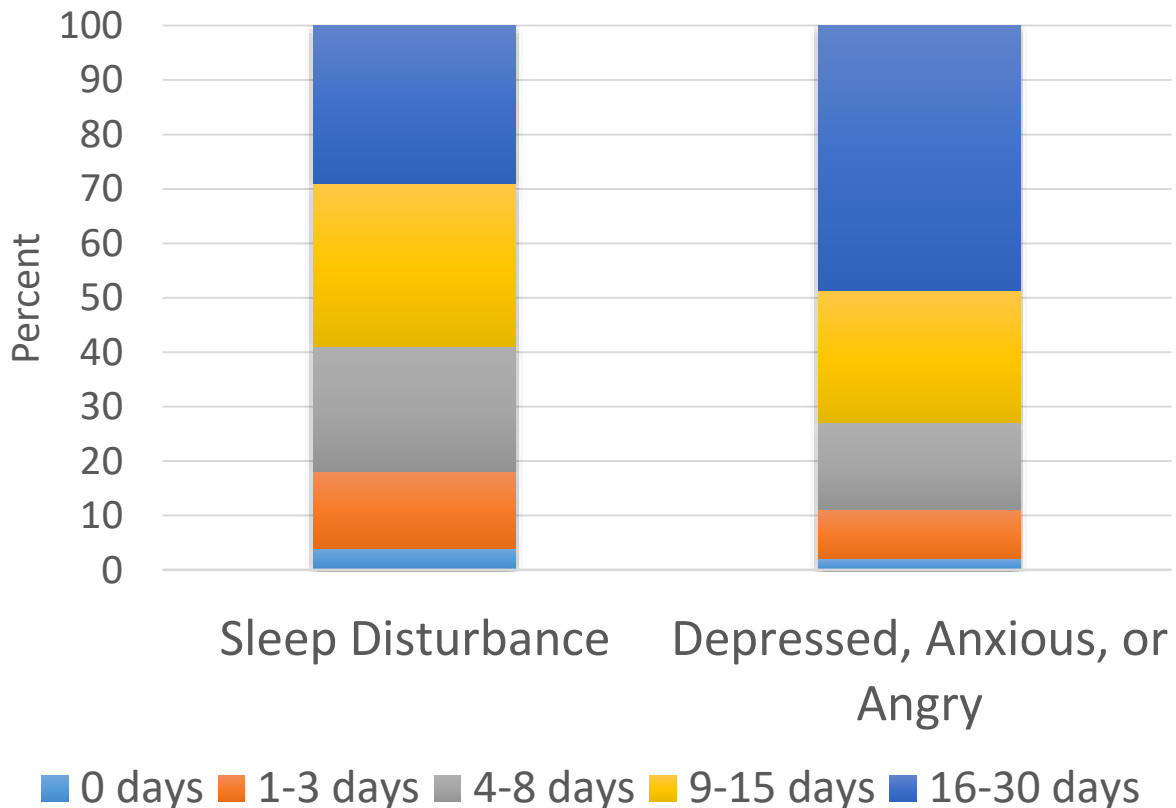
Outcomes for Sleep Studies

- Total sleep time (TST)
- Sleep onset latency
- Wake after sleep onset (WASO)
- Sleep efficiency
- Sleep midpoint
- Sleep architecture
  - Time in each phase
  - Time in "deep sleep"
- Sleep Apnea
  - Apnea-Hypopnea Index (AHI)
  - Obstructive versus central
- Restfulness
- Daytime sleepiness

Methods for measuring sleep in clinical trials of OUD patients

- Polysomnography (PSG)
- Sleep Profiler
- Actrigraphy
- Other wearable technology
- Ecological momentary assessment (EMA)
- Sleep diary
- Retrospective questionnaires

Methods for measuring sleep in clinical trials of OUD patients

A

Sensor at nose to measure air flow

Sensors on face and scalp measure eye movement and brain activity

Wires transmit data to a computer. A technician in a nearby room monitors the data.

Elastic belt sensors around chest and belly measure amount of effort to breath

Sensor on finger measures amount of oxygen in blood

B Polysomnogram record (over time)

Blood oxygen level

Decrease in blood oxygen level after an event

Height = length of event

Breathing event

REM sleep stage

Top levels = wake/REM sleep

Bottom levels = deep sleep

Polysomnography (PSG): The gold standard in assessing sleep. PSG studies are typically 1 night but could be multiple nights.

sciencesource.com

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Methods for measuring sleep in clinical trials of OUD patients

- Sleep Profiler^{TM} is an ambulatory system that can be used at home; outcomes include sleep architecture.

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Methods for measuring sleep in clinical trials of OUD patients

- Actrigraphy can be used as a secondary measure of sleep by tracking movement, room lighting, etc.

fitbit.com

apple.com

bmedical.com.au

actigraphcorp.com

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Methods for measuring sleep in clinical trials of OUD patients

- Sleep diaries can be used as stand alone self-reports of sleep quantity and quality. Also used in conjunction with objective measures of sleep.

Day	Time in bed	Time fell asleep	Night time awakenings	Time awake	Total time asleep	Sleep quality (0-10)
Monday						
Tuesday						
Wednesday						

Methods for measuring sleep in clinical trials of OUD patients

- Ecological momentary assessments can be used to deliver morning sleep diaries or other brief sleep assessments.

- EMA can also be used to understand the relationship between sleep and mood, or diurnal fluctuations in stress, etc.

Methods for measuring sleep in clinical trials of OUD patients

- Other wearable technologies include the Oura Ring, which measures pulse, movement, and temperature, and the Watchpat, which measures Peripheral Arterial Tone (PAT).

ouraring.com

Methods for measuring sleep in clinical trials of OUD patients

- Retrospective questionnaires are included in almost every sleep study.
- Pittsburgh Sleep Quality Index (PSQI) is most common.

Clinical trial design for sleep medications

- Dose finding vs placebo
- Active vs placebo
- Active versus active

Other considerations

- Time duration of study
- Environment (homelessness, etc.)
- Allow self-titration?
- Abuse liability
- Relationship to stress
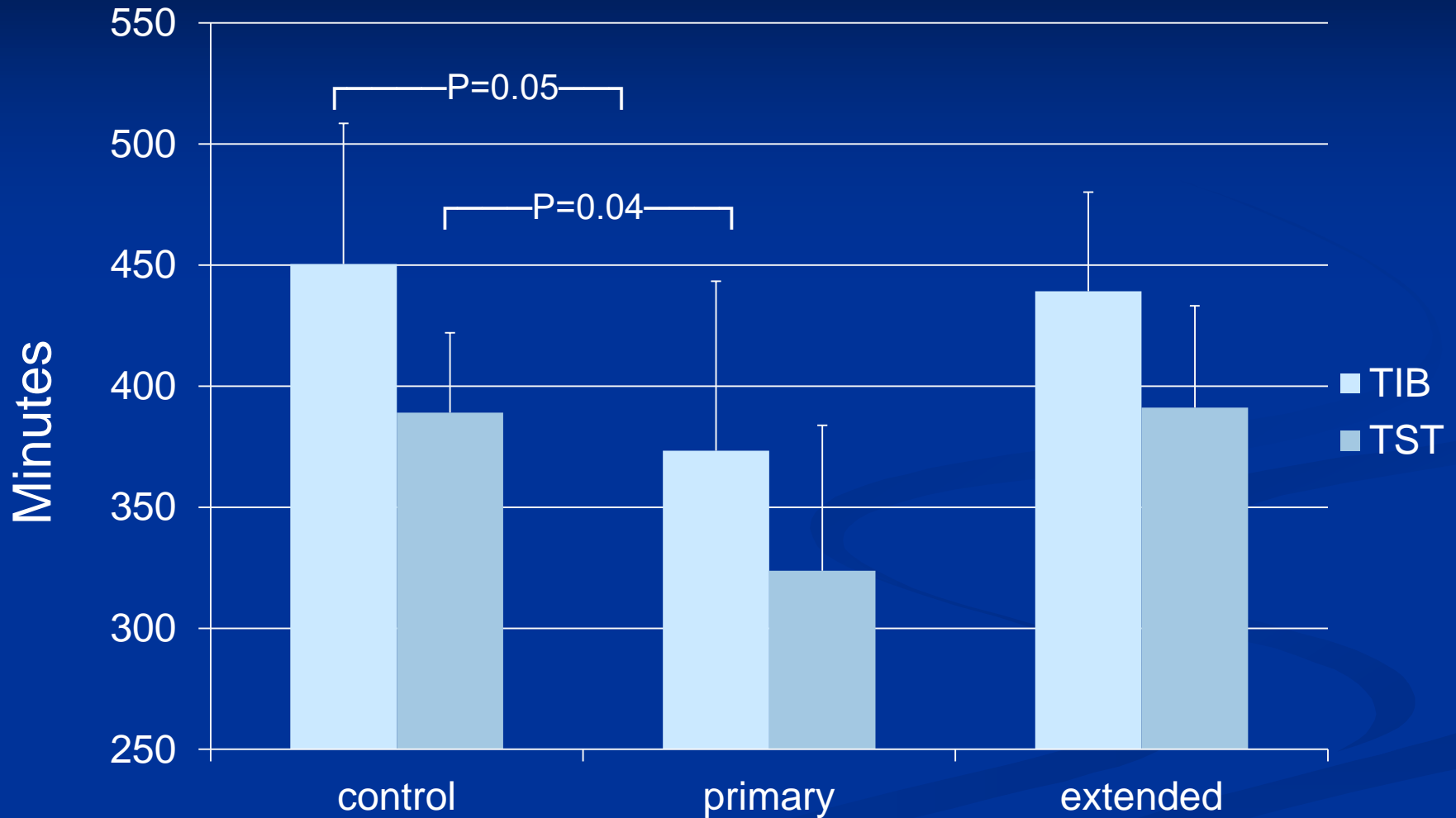- Relationship to relapse

RESEARCH

Caron Treatment Center

- 12 step based recovery

- "Primary Care" patients stay for 28 days

- "Extended Care" patients stay for an additional 90 days

- Treatments include:

  - Medical

  - Specialty groups

  - Spiritual

  - Family counseling

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Pilot Sleep Study at Caron

Time in Bed (TIB) & Total Sleep Time (TST) (N=21)

Bunce et al., (2012)

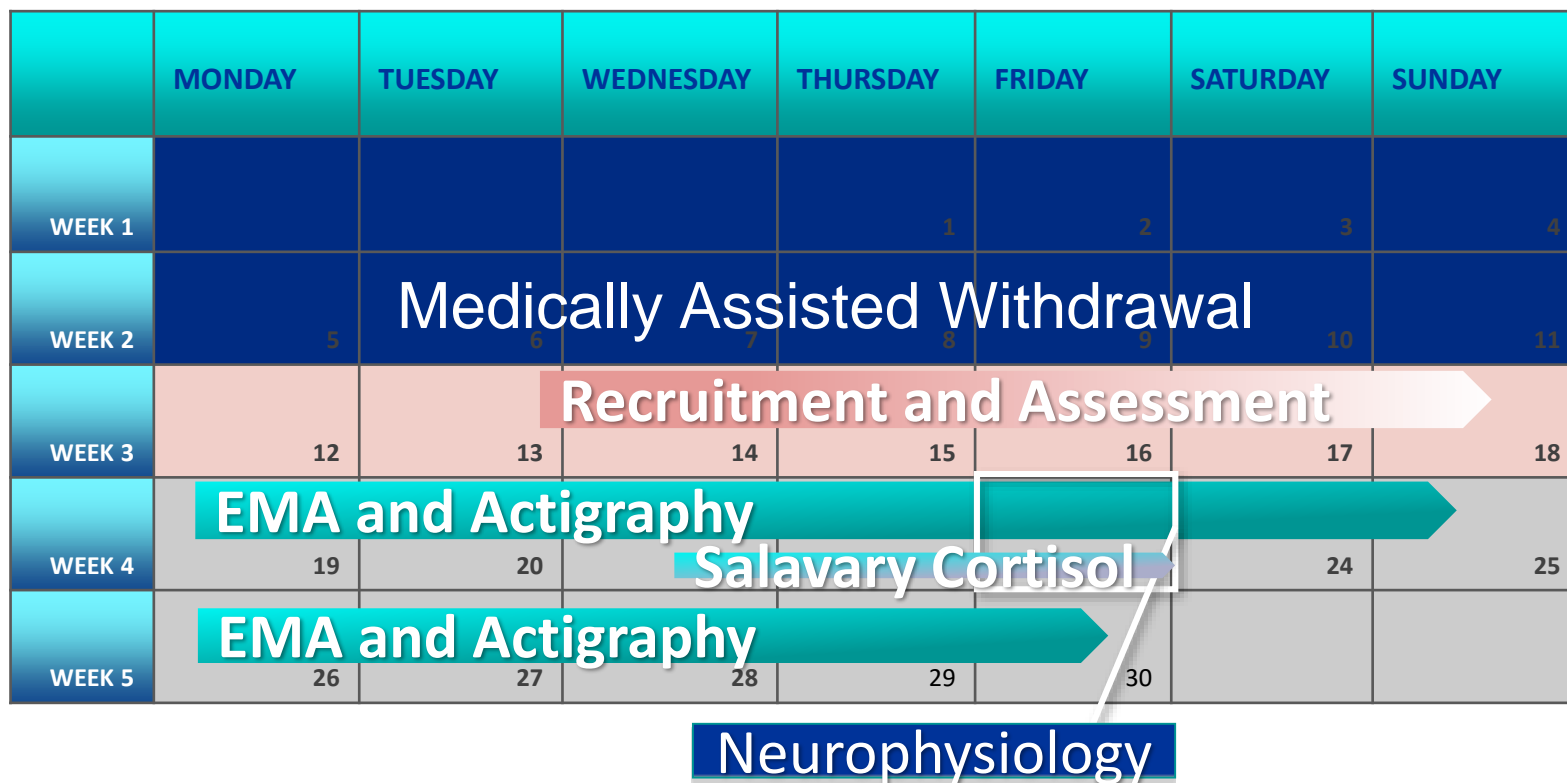JOHNS HOPKINS
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Prescription Opioid Use Disorder Study

- **117 participants recruited:**

  - **77 patients in "primary care" e.g. 1 month residential treatment.**

  - **22 patients in "extended care" e.g. 2-4 months residential treatment (9 patients with 3 data bursts).**

  - **40 age and gender matched controls.**

- **Longitudinal design:**

  - **Following patients through the treatment process and <u>follow-up for 90-days after discharge.</u>**

*Pilot Study: Drs. Bunce, Bixler, Meyer, Cleveland and Jon Harris*

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Data Burst Example

	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY	SUNDAY
WEEK 1				1	2	3	4
WEEK 2	5	6	7	8	9	10	11
WEEK 3	12	13	14	15	16	17	18
WEEK 4	19	20				24	25
WEEK 5	26	27	28	29	30		

Medically Assisted Withdrawal

Recruitment and Assessment

EMA and Actigraphy

Salavary Cortisol

EMA and Actigraphy

Neurophysiology

Variables Collected Daily:
- Ecological Momentary Assessment (EMA) – 4x daily
- Sleep Actigraphy
- Salivary Cortisol (5x daily, Days 3,4,5)

Data Burst Schedule

1st Data Burst: days 15-27 of primary care
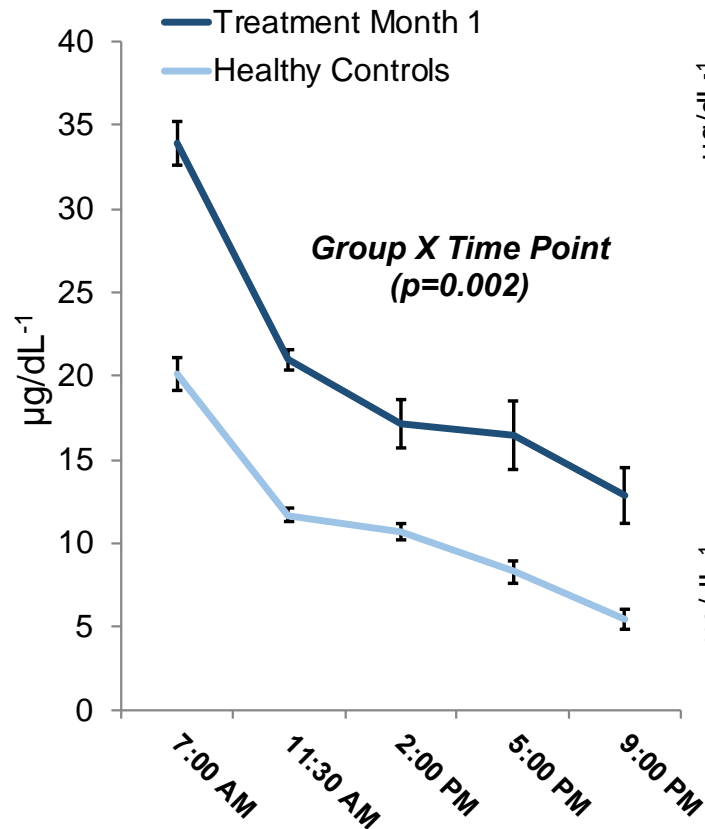
3rd Data Burst: days 15-27 of final month of extended care
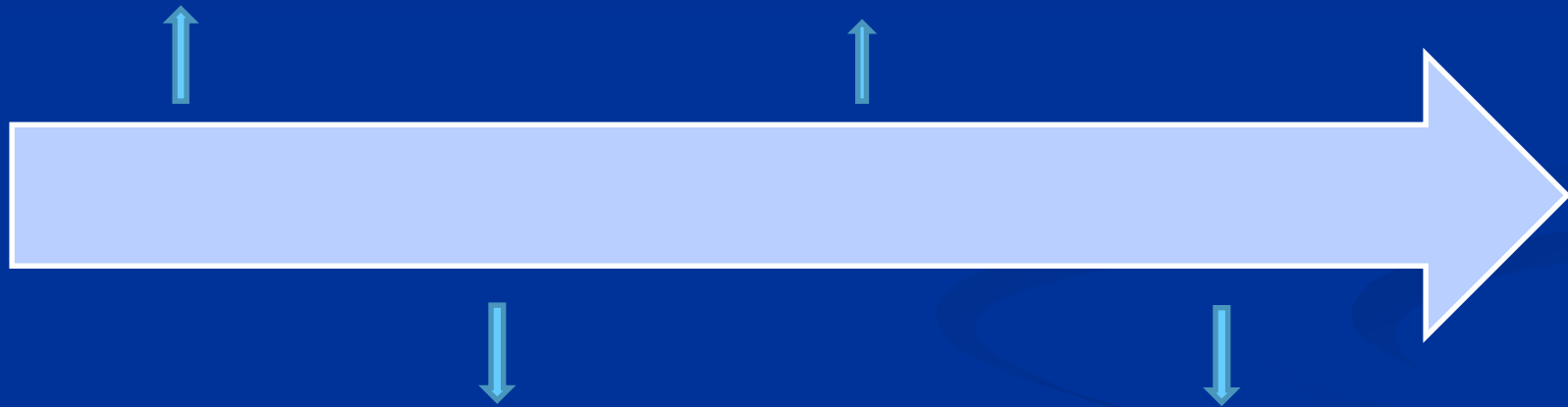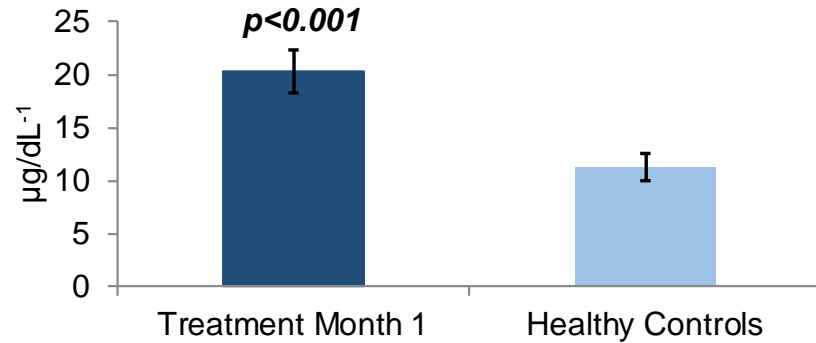
2nd Data Burst: days 15-27 of extended care

Follow up: 90 days post-residential treatment (weekly phone calls; hair collection)

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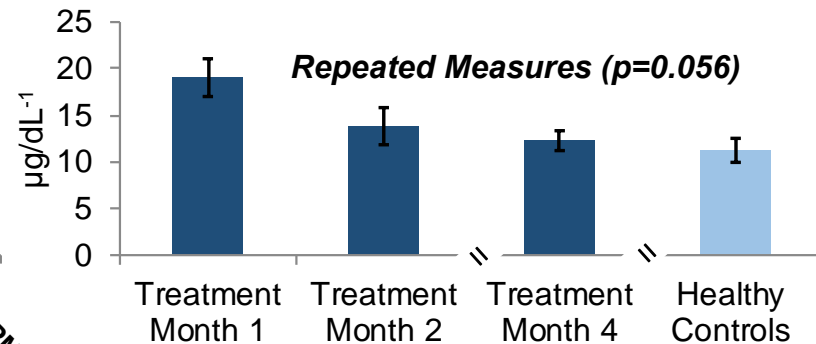# Evidence for re-regulation of the HPA-axis in early recovery from OUD (N=96)

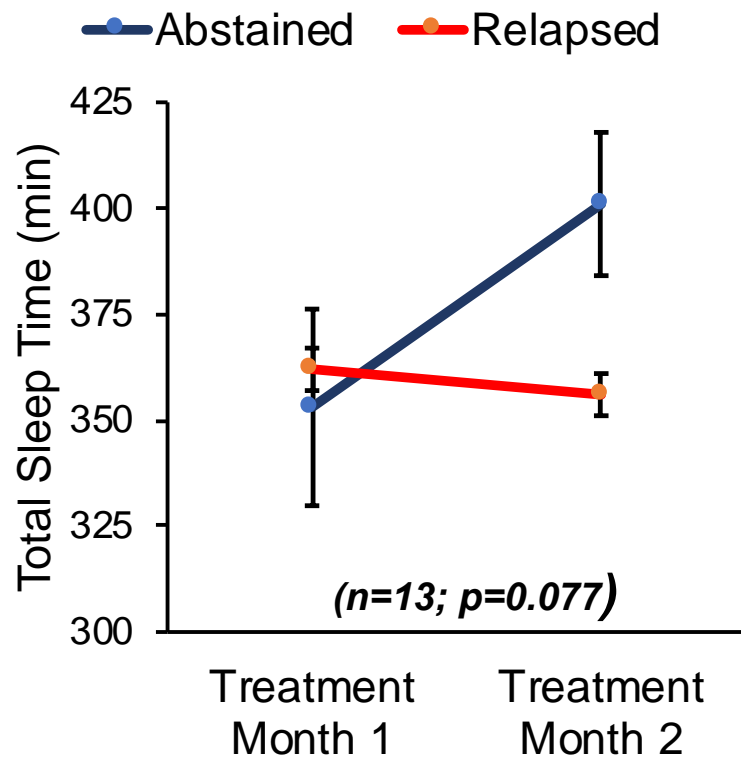
Cortisol Throughout Day

Treatment Month 1
Healthy Controls

Group X Time Point (p=0.002)

μg/dL⁻¹

7:00 AM, 11:30 AM, 2:00 PM, 5:00 PM, 9:00 PM

Mean Daily Cortisol

p<0.001

μg/dL⁻¹

Treatment Month 1   Healthy Controls

Mean Cortisol Over Time in Patient Subset (n=7)

Repeated Measures (p=0.056)

μg/dL⁻¹

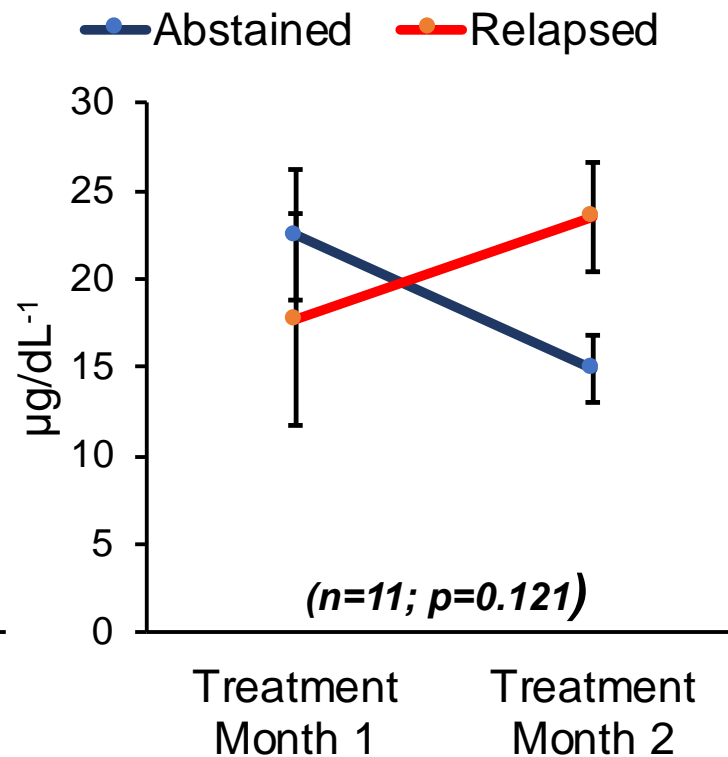Treatment Month 1   Treatment Month 2   Treatment Month 4   Healthy Controls

Re-regulation of sleep and stress predict treatment outcomes

Mean Daily Sleep and Relapse to Opioids

Abstained — Relapsed

Total Sleep Time (min)

425, 400, 375, 350, 325, 300

(n=13; p=0.077)

Treatment Month 1 — Treatment Month 2

Mean Daily Cortisol and Relapse to Opioids

Abstained — Relapsed

$\mu g/dL^{-1}$

30, 25, 20, 15, 10, 5, 0

(n=11; p=0.121)

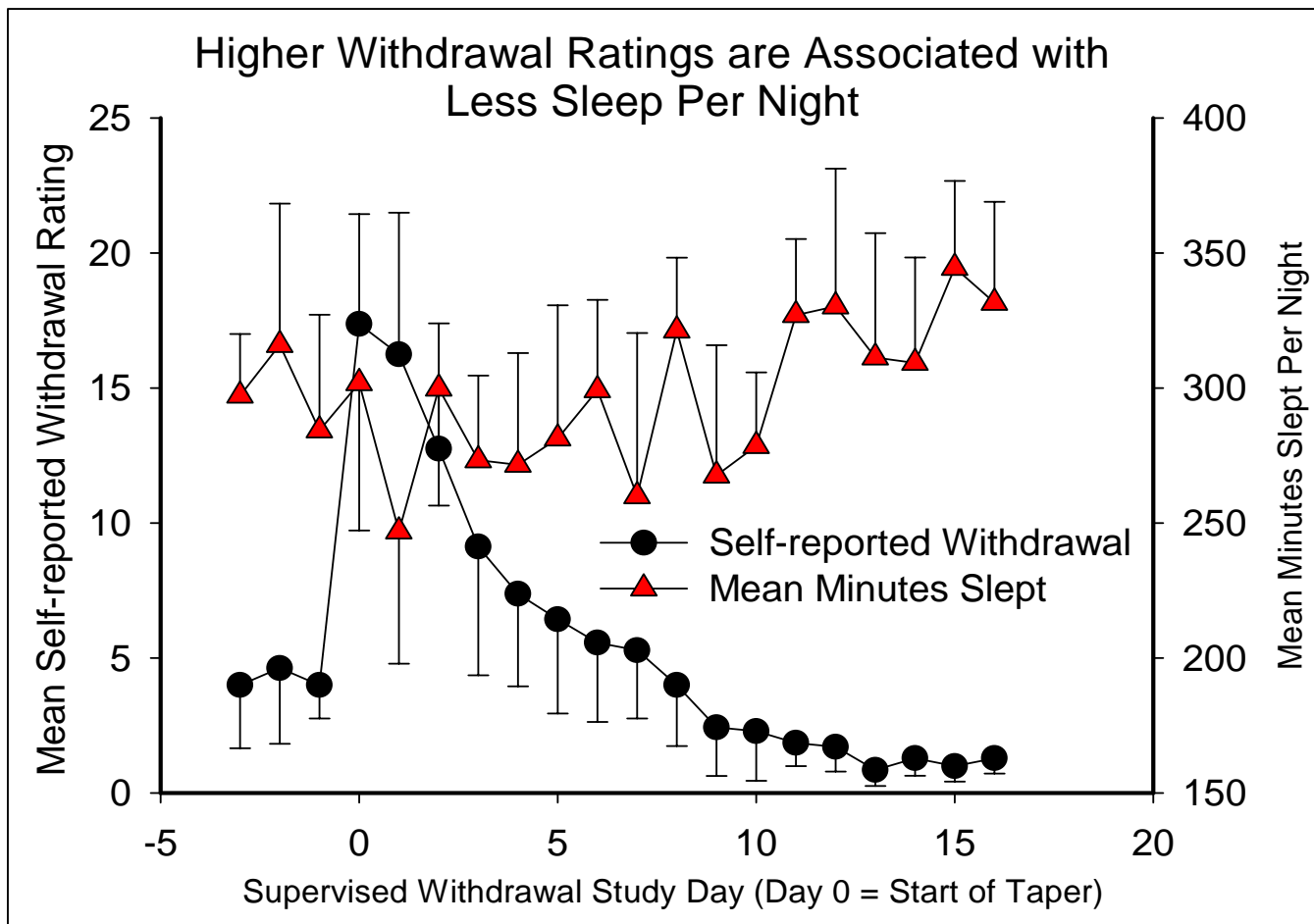Treatment Month 1 — Treatment Month 2

Sleep, positive affect, and opioid craving

- **Ecological momentary assessment study (4x daily; N=66)**

- **Greater levels of craving were observed on days when participants reported lower than usual sleep quality (p=0.003).**

- **Thirty-one percent of the overall association between sleep quality and craving was explained by anhedonia, i.e. poor sleep quality was associated with low positive affect, which was, in turn, associated with greater craving.**
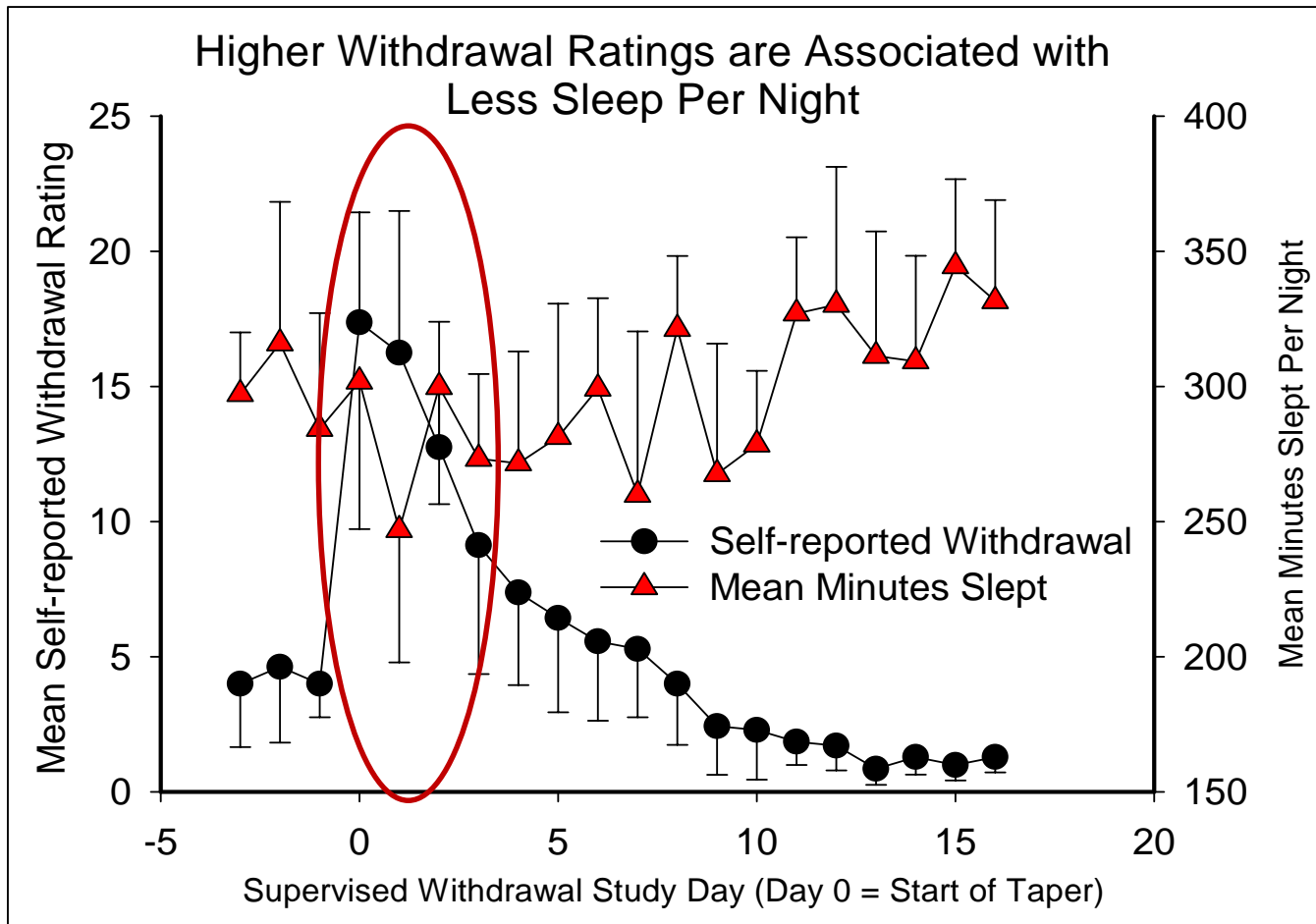

Lydon et al., 2017

Sleep Disturbance Drives Negative Treatment Outcomes during Opioid Withdrawal

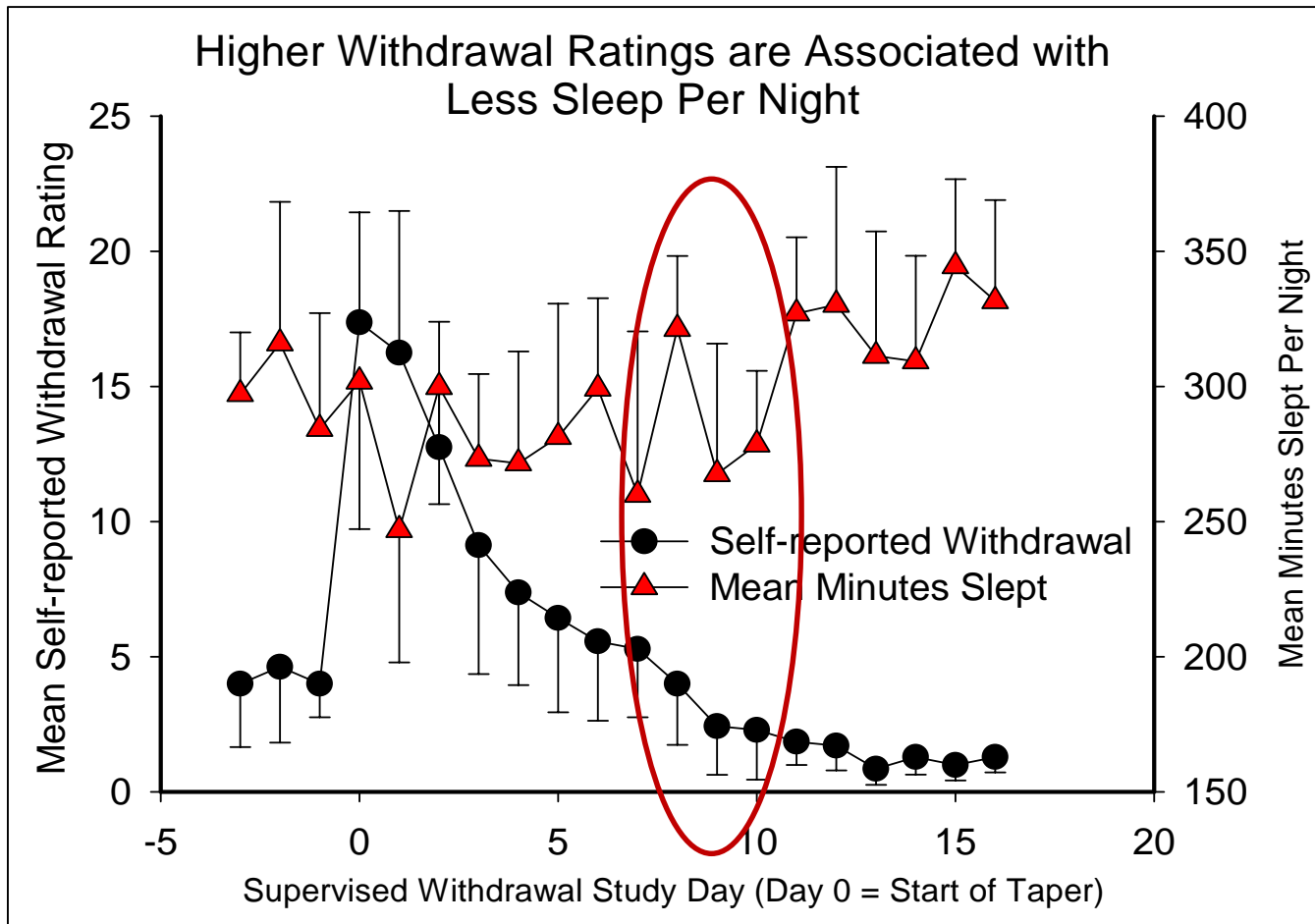# Relationship between sleep disturbance and opioid withdrawal (N=8)

Relationship between sleep disturbance and opioid withdrawal

Higher Withdrawal Ratings are Associated with Less Sleep Per Night

- Self-reported Withdrawal
- Mean Minutes Slept

Mean Self-reported Withdrawal Rating

Mean Minutes Slept Per Night

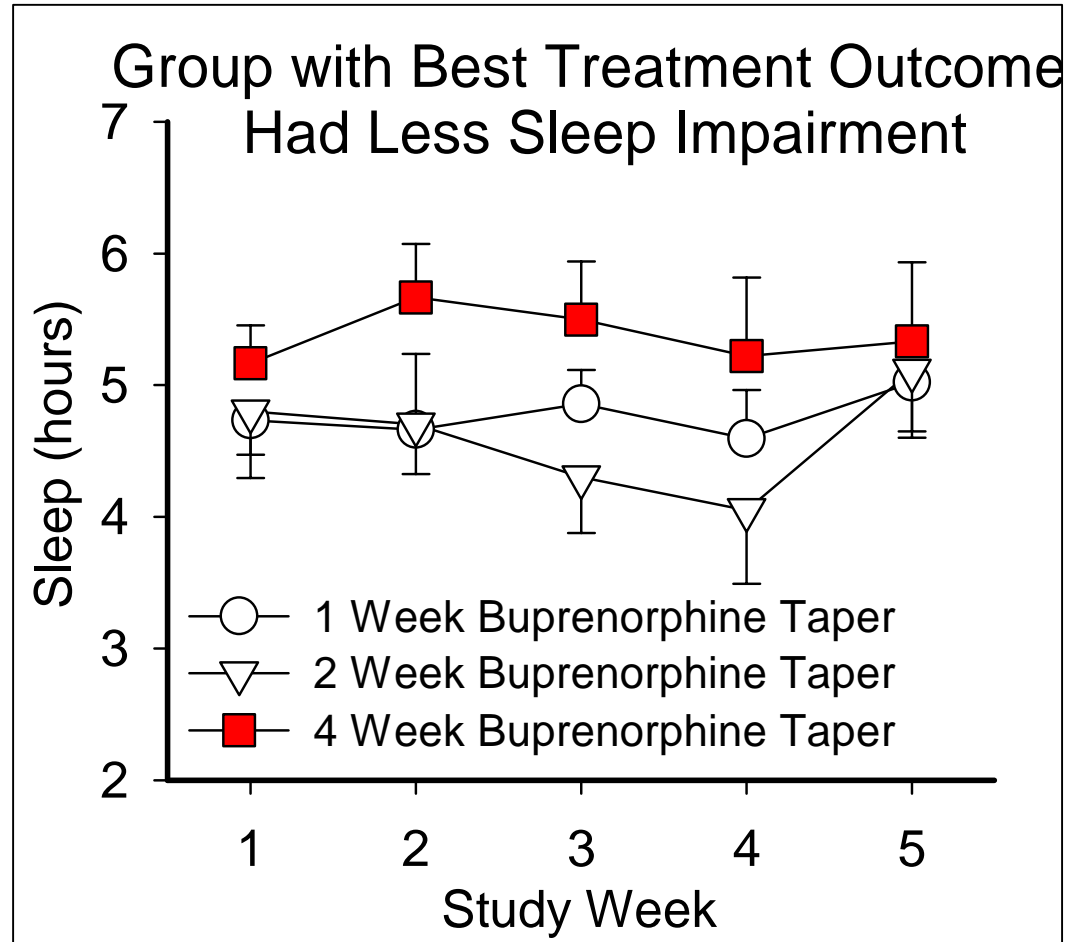Supervised Withdrawal Study Day (Day 0 = Start of Taper)

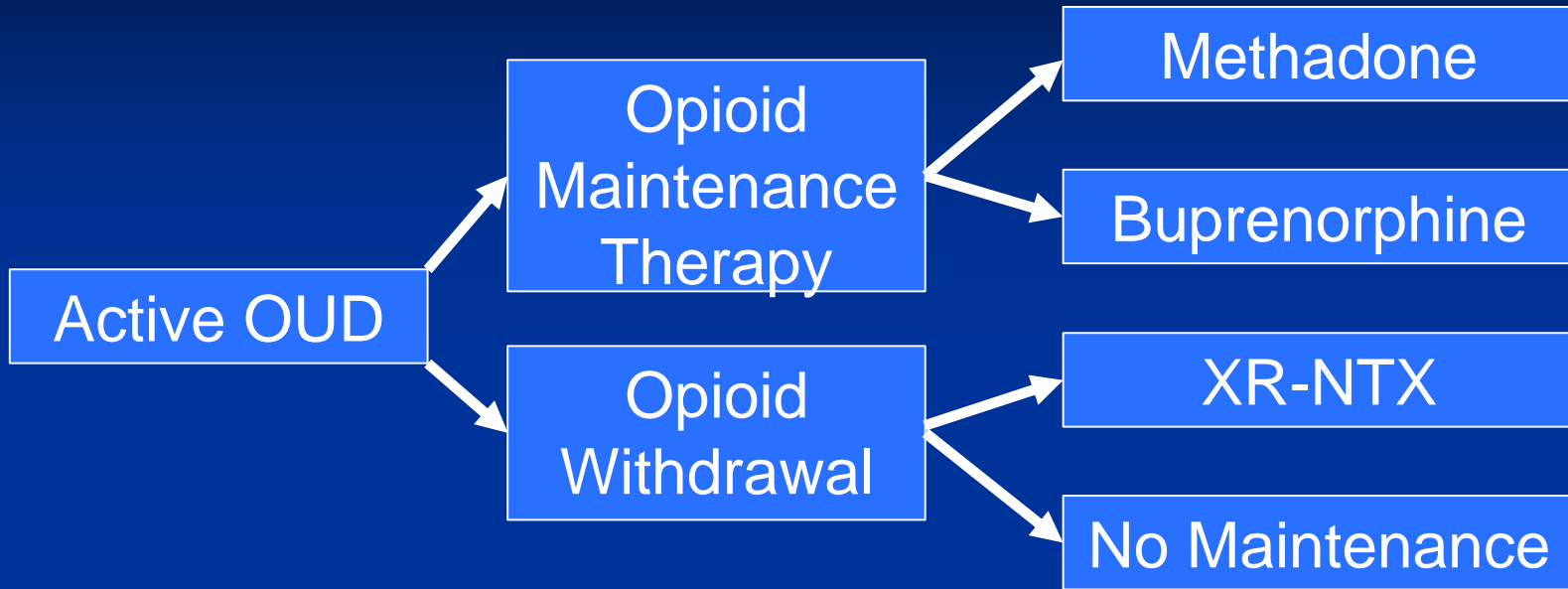# Relationship between sleep disturbance and opioid withdrawal

Sleep and opioid withdrawal treatment outcomes

Sub-study from a trial on opioid taper length and treatment outcomes (Sigmon and Dunn; N=28)

Group with Best Treatment Outcome Had Less Sleep Impairment

Sleep (hours)

○— 1 Week Buprenorphine Taper
▽— 2 Week Buprenorphine Taper
■— 4 Week Buprenorphine Taper

Study Week

Treatment Trajectory

```
Active OUD ──┬──▶ Opioid Maintenance Therapy ──┬──▶ Methadone
             │                                  └──▶ Buprenorphine
             └──▶ Opioid Withdrawal ──┬──▶ XR-NTX
                                      └──▶ No Maintenance
```

Levels of Care

Residential/ Hospital	Sober Living Environment	Outpatient	12-step or no ongoing care

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Commonly used sleep aids in OUD patients

- Benzodiazepines or benzo-like drugs (zolpidem) are often NOT used in this population due to abuse liability
- Common sleep aids include:
  - Melatonin
  - Hydroxyzine
  - Trazodone
  - Mirtazapine (Remeron®)

NEUROTRANSMITTER SYSTEMS TO TARGET IN TRIALS TO IMPROVE SLEEP IN OUD PATIENTS

NIDA's 10 most wanted

Orexin-1 or 1/2 antagonists or NAMs
Kappa opioid antagonists or NAMs
GABA-B agonists or PAMs
Muscarinic M5 antagonists or NAMs
AMPA antagonists, NAMs or PAMs
NOP/ORL agonists, antagonists, NAMs or PAMs
mGluR2/3 agonists or PAMs
Ghrelin antagonists or NAMs
Dopamine D3 partial agonists, PAMs, antagonists or NAMs
Cannabinoid CB-1 antagonists or NAMs

PAM positive allosteric modulator, *NAM* negative allosteric modulator, *AMPA* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, *GABA* γ-aminobutyric acid, *NOP* nociceptin opioid peptide receptor, *ORL* opioid receptor like, *mGluR* metabotropic glutamate receptor, *5HT* 5-hydroxytryptamine, *MOP* mu opioid protein
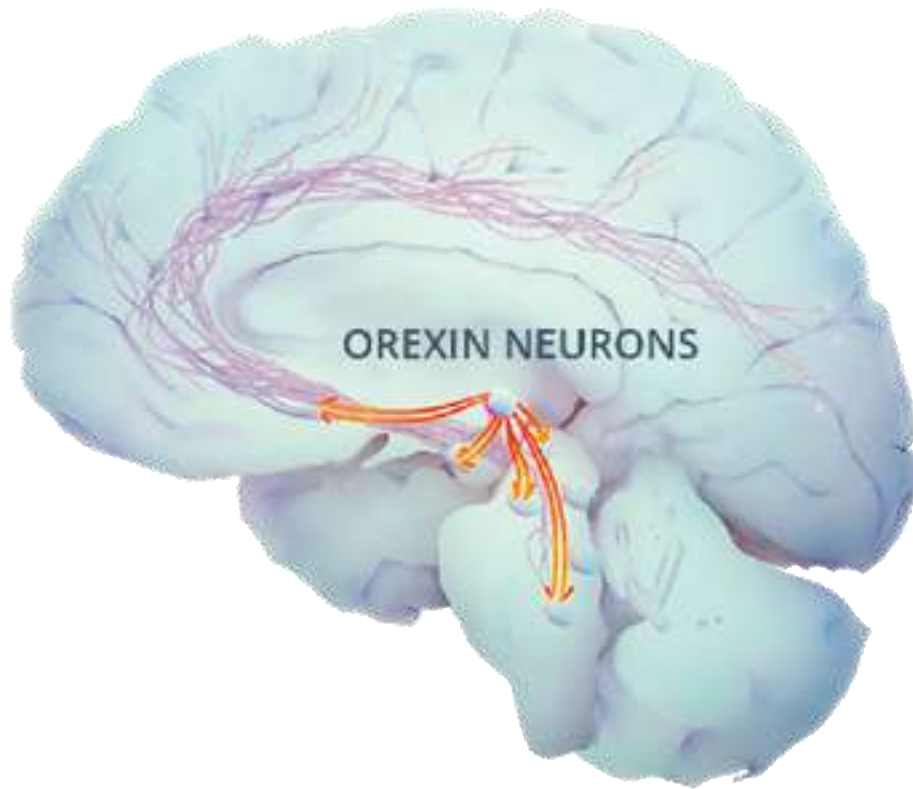
Other mechanisms of interest:

5HT2C agonists or PAMs, with or without 5HT2A antagonist/NAM activity

Biased Mu Opioid agonists or PAMs

NOP/MOP bifunctional agonists or PAMs
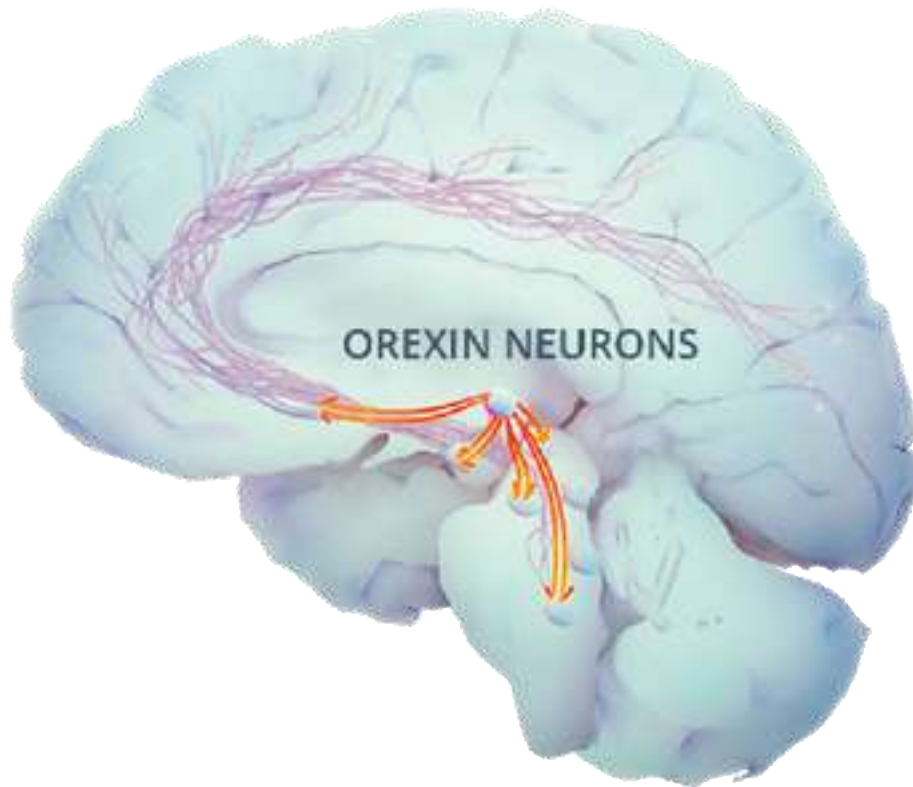
Respiratory stimulants (including nicotinic agonists)

Orexin Neurotransmitter System

OREXIN NEURONS

There are only 10,000 - 20,000 orexin-producing neurons in the human brain, located predominantly in the perifornical area and lateral hypothalamus.
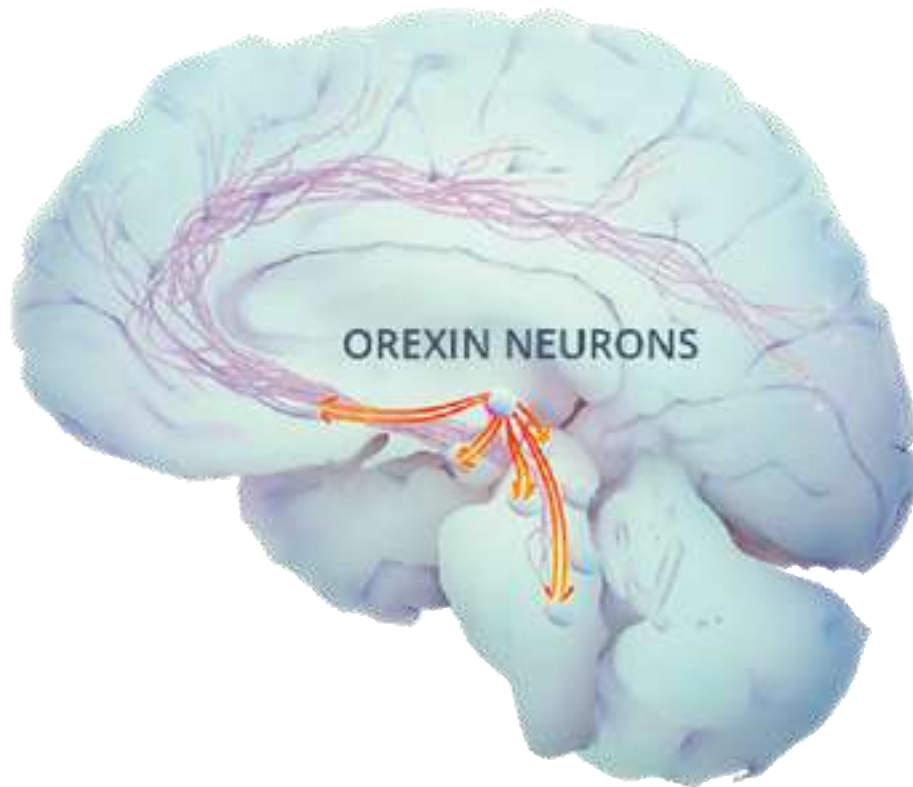
Orexin Neurotransmitter System

OREXIN NEURONS

Orexin signaling regulates wakefulness, food, drink (and consequently drug) consumption, and mood.

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Orexin Neurotransmitter System
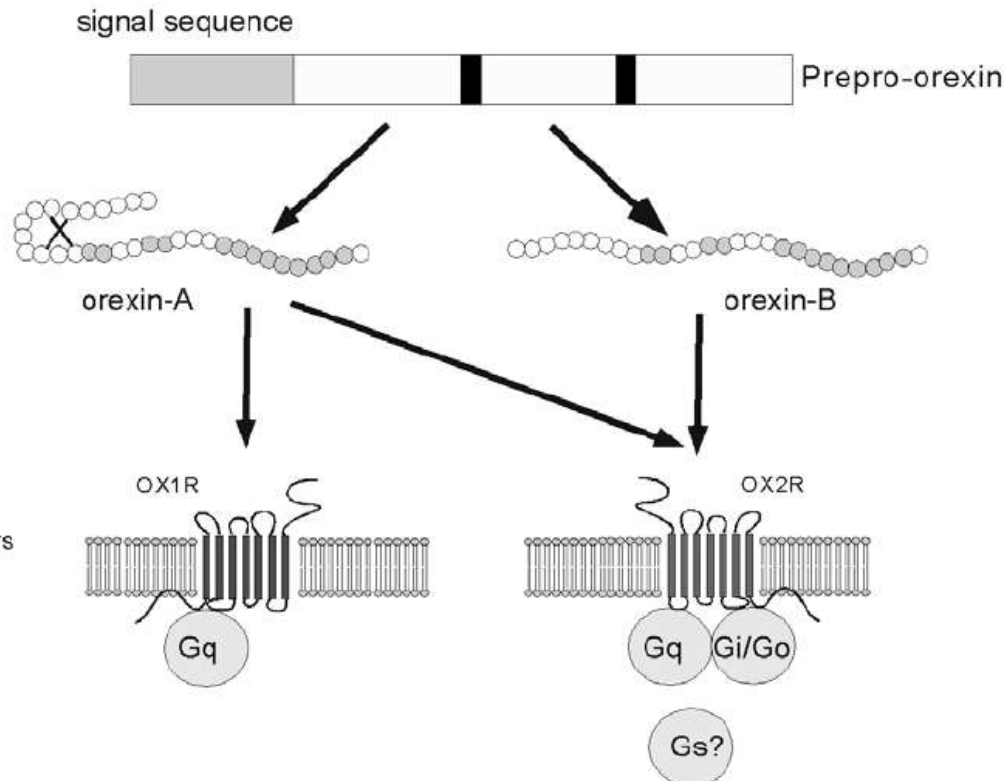
OREXIN NEURONS

Orexin signaling follows a circadian rhythm.

Within the sleep cycle, decreased orexin signaling is essential for the onset of REM sleep.
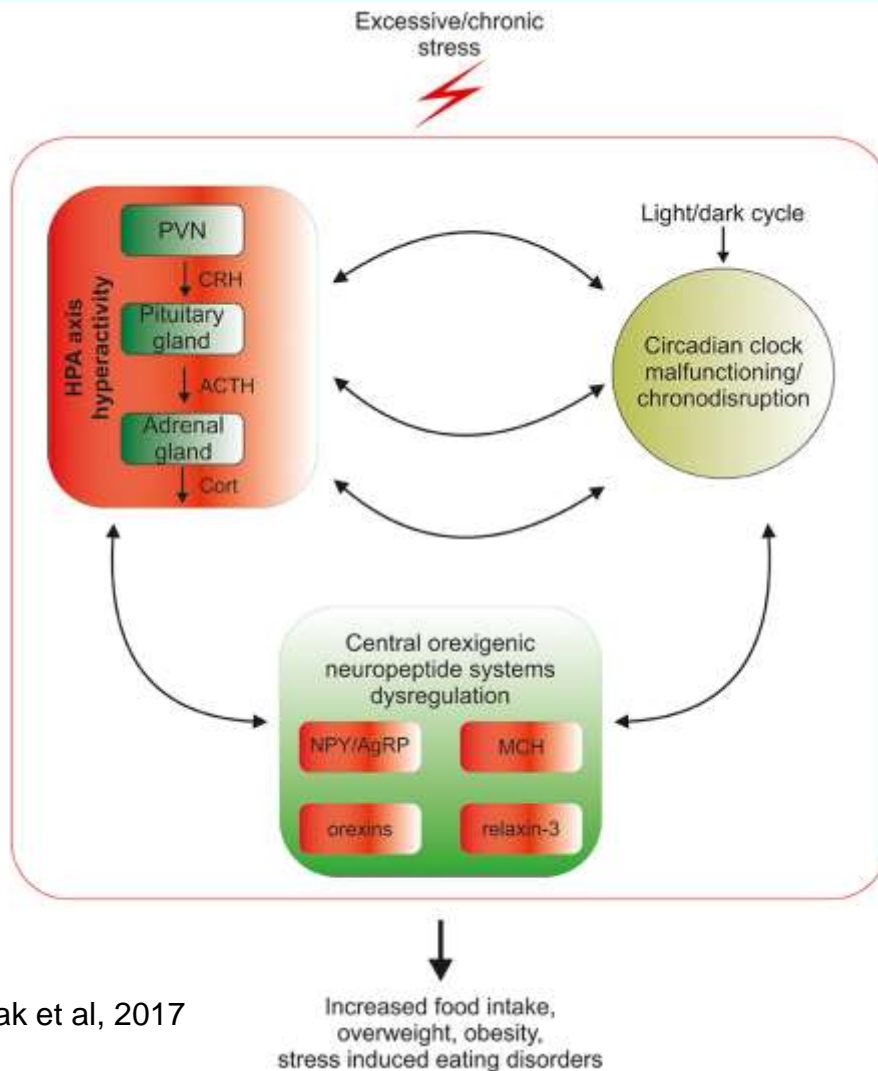
Orexin Neurotransmitter System

OX1R has more influence on consumption behaviors.

OX2R has more influence on wakefulness.

Sakurai, 2009

# Orexin System and HPA-axis

Blasiak et al, 2017

Complex and reciprocal relationship between the orexin system and the HPA-axis.

Orexin Neurotransmitter System and Opioid Use Disorder

- Several preclinical studies have implicated the orexin system in the progression and maintenance of OUD.

- Orexin signaling contributes to:
  - Opioid tolerance
  - Drug-cue induced reinstatement
  - Opioid withdrawal

- The only published study on the orexin system in humans is a recent post-mortem study showing that long-term heroin users have ~50% more orexinergic neurons in the hypothalamus than healthy controls (Thannickal et al., 2018).

Other Neurotransmitter System Targets for OUD and Sleep

- <u>Serotonin</u> is involved in the sleep-wake cycle and symptoms related to OUD (mood, withdrawal).
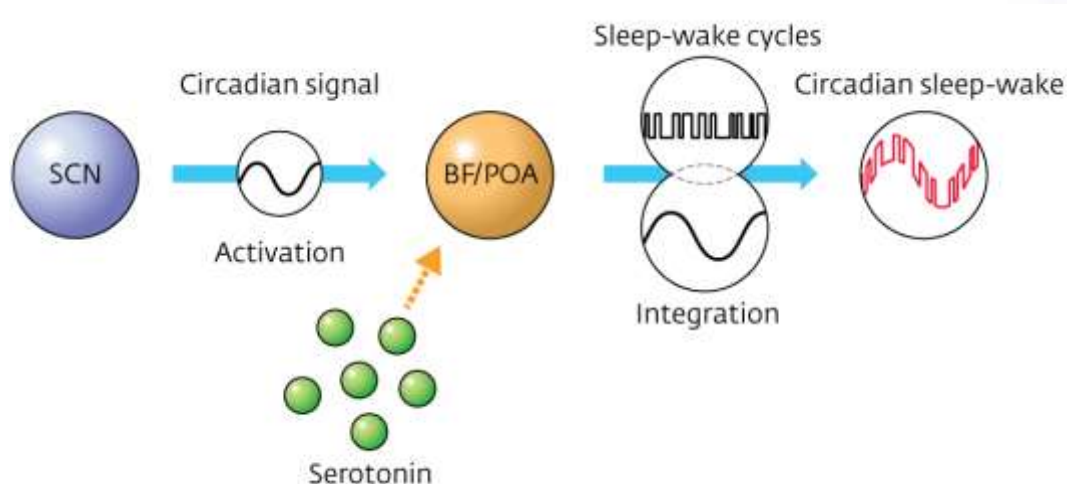
Miyamoto et al., 2012

Other Neurotransmitter System Targets for OUD and Sleep

- The only clinical trial clinical trial on trazodone (in methadone patients) reported mostly negative results (Stein et al., 2012)

- Higher dosing?

- Different MOUD?

- Tricyclics (Doxepin; Silenor®)?

- Antipsychotics (Quetiapine; Seroquel®)

Other Neurotransmitter System Targets for OUD and Sleep

- <u>Melatonin</u> is a hormone that regulates the sleep-wake cycle.
- Medications:
  - Melatonin supplement?
  - Ramelteon?

Other behavioral strategies

- Cognitive behavioral therapy for insomnia (CBTi) has effective in several studies.

ONGOING SLEEP STUDIES IN PERSONS WITH OUD

Ongoing study on sleep and opioid withdrawal

- Determine whether suvorexant reduces sleep disturbance and withdrawal symptoms during supervised opioid withdrawal.

- Examine the effect of suvorexant on opioid craving, stress, and treatment retention.

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Ongoing study on sleep and opioid recovery

- Determine whether suvorexant reduces sleep disturbance in persons on methadone or extended-release naltrexone.

- Examine the effect of suvorexant on opioid craving, stress, relapse, and treatment retention.

We covered a lot!

- Throughout the course of OUD, sleep and stress systems are altered.
    - This exacerbates OUD
- Sleep disturbance is a major issue during opioid withdrawal.
- Sleep assessments could be easily incorporated into OUD clinical trials.
- Sleep should be a focus of future trials to improve OUD outcomes.

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