

Addressing insomnia among patients receiving medication treatment for opioid use disorder

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Disclosure Information

- ☀ Presenter 1: Caitlin E. Martin

- ☀ No Disclosures

- ☀ Presenter 2: Joseph M. Dzierzewski

- ☀ Served on an Advisory Board for Eisai Pharmaceuticals. Not related to the content of this presentation.

- ☀ Presenter 3: Andrew S. Huhn

- ☀ Receives research funding from Indivior through his university and has consulted for Gilgamesh. These conflicts are not related to the content of this presentation.

- ☀ Presenter 4: Ashley Wilson

- ☀ No Disclosures

Learning Objectives

Upon completion, participants will be able to:

- ☀ Define insomnia and its diagnostic criteria as well as report on the current science underlying the complex bidirectional relationship between opioid use disorder (OUD) and insomnia
- ☀ List the components of cognitive behavioral therapy for insomnia and conduct brief counseling interventions with patients in OUD treatment, such as those related to sleep hygiene, sleep restriction and keeping a sleep diary
- ☀ Describe the evidence supporting the use of pharmacologic treatments for insomnia and recent findings regarding their efficacy in clinical samples of individuals receiving medication for opioid use disorder

What is insomnia?

- Difficulty initiating or maintaining sleep
 - Waking up too early with associated daytime consequences, occurring despite opportunity and circumstances for sleep
- Chronic condition
 - At least 3 times per week for 3 months
- Terminology
 - No longer separate subtypes into 'primary' or 'secondary'
 - International Classification of Sleep Disorders, 3rd edition

Why is insomnia important?

- ☀️ Prevalent in general population 5-15%
 - ☀️ Up to 50% of adults have insomnia symptoms
- Public health importance
 - Associated with cardiovascular disease, daytime fatigue, depression, suicide risk, functioning impairment, reduced quality of life, increased healthcare costs, work absences & lower work productivity (\$\$)

Insomnia disparities

- ✦ Age: Increasing insomnia symptoms with older age
- ✦ Sex: Higher persistence of insomnia in females than males through the lifecourse starting from puberty
 - ✦ Reproductive hormonal fluctuations bring additional sleep disturbances during pregnancy, postpartum and menopause
- ✦ Gender: Caregiving, work strain, social support & experiences of stressful life events are associated with insomnia
 - ✦ Common contributors to poor sleep identified in qualitative research in community-based samples

Insomnia disparities

☀ Social determinants of health

- ☀ Likely major drivers of racial and ethnic disparities documented across sleep parameters

☀ Neighborhood-level factors

- ☀ Rates of poverty, unemployment, air quality, noise, bright lights
- ☀ Differences largely follow historically segregated housing lines

☀ Systemic racism

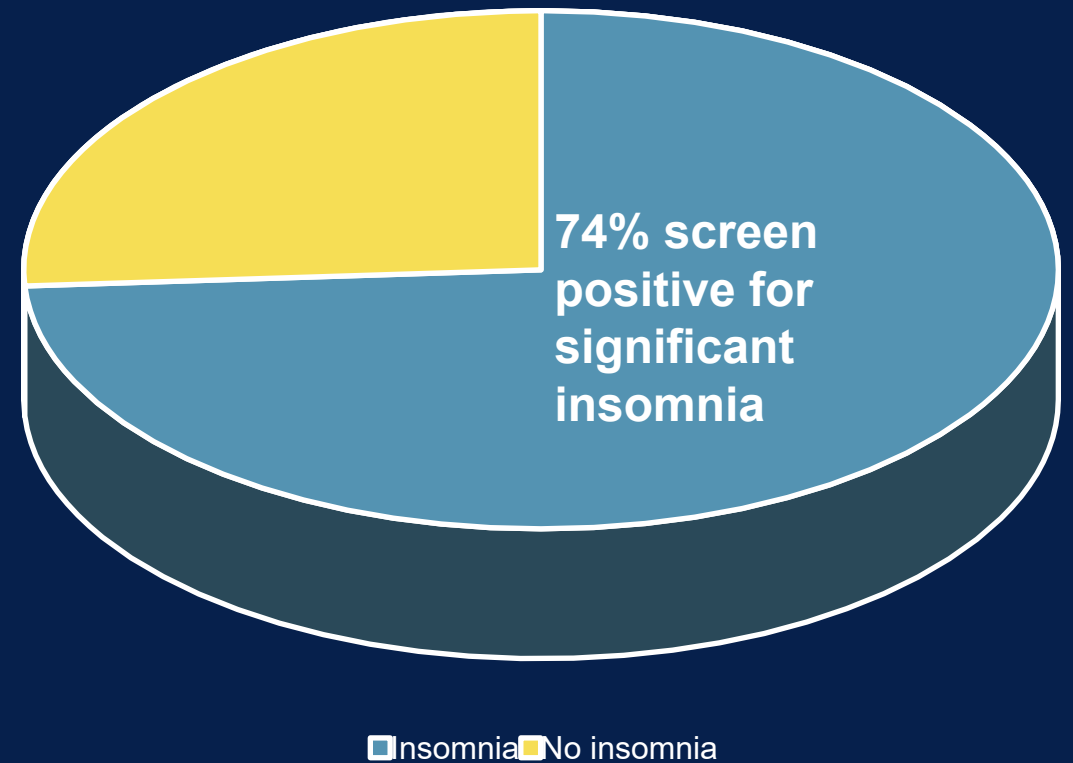
- ☀ Psychosocial trauma, discrimination associated with poor sleep health
- ☀ Racism-related vigilance correlates with insomnia symptoms



Insomnia among OUD patients

- ☀ Insomnia exists across the OUD treatment & recovery cascade
 - ☀ Opioid use & withdrawal disrupts sleep architecture
 - ☀ After cessation of non-prescribed substance use, insomnia symptoms can persist for years
- ☀ Insomnia is highly prevalent among patients receiving OUD medication treatment

Prevalence of insomnia among a buprenorphine treatment sample



Roehrs et al. Pharm, Biochem, Beh. 2021; Greenwald et al. Translational Research 2021; Groenwald et al. Sleep 2021; Huhn et al. Experimental Clin Psychopharm 2021; Dunn et al. Addict Beh 2018; Mukherjee et al. DAD 2021; Valentino and Volkow. NPP 2020; Martin CE. Et al, *unpublished data*

Insomnia among OUD patients

- ✦ Poor sleep is linked to increased pain sensitivity, stress, impulsivity, cravings, interference with learning
 - ✦ Chronic sleep deficiency -> modulates stress reactivity -> risks for substance use recurrence & treatment destabilization
- ✦ Treating insomnia could achieve additional benefits for OUD treatment & recovery
 - ✦ Insomnia is also an important priority to patients!

Insomnia as a patient-reported priority

“If I do get proper sleep, I don’t have cravings. So...sleep is very important. My cravings are not as bad.”

“Sleep is important...Bad decisions can be impulsively made after not sleeping properly...letting that darkness... that little voice that can get inside you saying ‘Oh, you deserve a day to party,’ you know”

“If you’re not getting sleep, then you’re not gonna be able to handle those triggers as well, like if you were to run into somebody on the street that you used to use with or something like that. If you’re not sleeping well and you’re tired you might not be as like strong I guess to, you know, turn down the offer to [use] or whatever.”

“If you don’t get enough sleep, then you up thinking about all kind of negative things that can cause you to want to relapse. Or you can be negative talking about yourself and we’re our worst enemies. I know I’m my worst enemy. I can talk real bad about myself and it’ll cause me to want to just do stupid stuff, like use.”



Addressing insomnia in the clinic

- ☀ Step 1: Assessment and diagnosis
- ☀ Step 2: Evaluation of patient's prior experiences & goals
- ☀ Step 3: Development of an individualized treatment plan
 - ☀ Initial intervention: CBT-I (Cognitive Behavioral Therapy for Insomnia)
 - ☀ Consideration of medications using a shared decision making approach

Step 1: Insomnia assessment

- ☀️ Assess patient history for insomnia diagnostic criteria:
 - ☀️ Difficulty initiating +/- maintaining sleep +/- waking up too early WITH associated daytime consequences
 - ☀️ Occurring despite adequate opportunity for sleep
 - ☀️ At least 3x/week for at least 3 months
- ☀️ Use validated tool (patient self-completes)
 - ☀️ Daily sleep diary (≥ 7 days)
 - ☀️ Insomnia Symptom Questionnaire (13 items)
 - ☀️ Insomnia Severity index (10 items)

Example: Insomnia Severity Index

For each question, please CIRCLE the number that best describes your answer.

Please rate the *CURRENT* (i.e. *LAST 2 WEEKS*) *SEVERITY* of your insomnia problem(s).

Insomnia Problem	None	Mild	Moderate	Severe	Very Severe
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problems waking up too early	0	1	2	3	4

4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?

Very Satisfied Satisfied Moderately Satisfied Dissatisfied Very Dissatisfied
0 1 2 3 4

5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?

Not at all
Noticeable A Little Somewhat Much Very Much Noticeable
0 1 2 3 4

6. How WORRIED/DISTRESSED are you about your current sleep problem?

Not at all
Worried A Little Somewhat Much Very Much Worried
0 1 2 3 4

7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?

Not at all
Interfering A Little Somewhat Much Very Much Interfering
0 1 2 3 4

☀️ Score range: 0-28

☀️ 0-7: No clinically significant insomnia

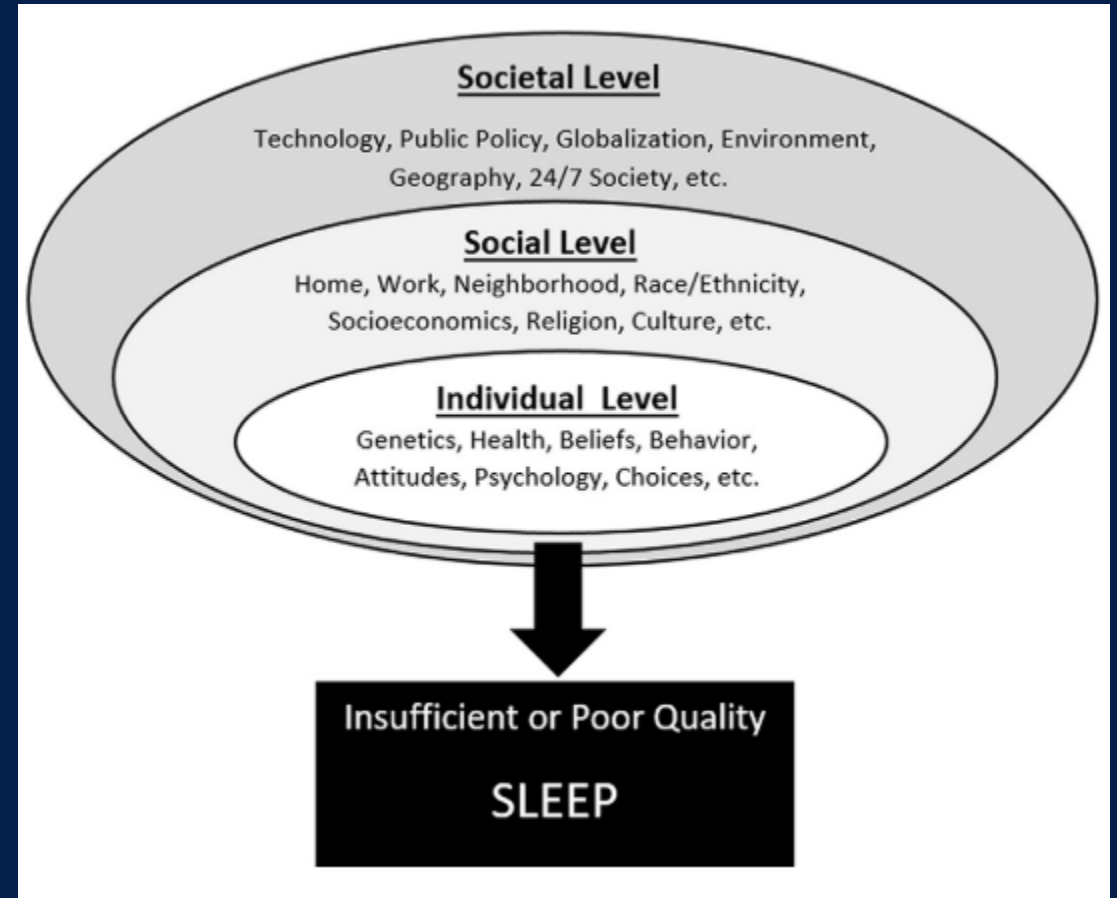
☀️ 8-14: Sub-threshold insomnia

☀️ 15-21: Moderate insomnia

☀️ 22-28: Severe insomnia

Step 2: Evaluate patient's goals

- ☀️ Prior experiences with treatments
 - ☀️ Sleep hygiene
 - ☀️ Behavioral therapies
 - ☀️ Medications
- ☀️ Barriers to and facilitators for treatment options
 - ☀️ Access to virtual vs. in person therapies
 - ☀️ Willingness to take a daily medication



Example: Patient-reported preferences

- ☀️ *“I feel like I need to retrain my brain on how to sleep like a normal human being that isn’t on the go, hustling dope 24/7. Because that’s the one area [sleep] that I never really focused on since I’ve gotten back to a normal life at home. Because I’m go-go-go-go constantly.”*
- ☀️ *“I would be willing to try [a sleep medication] because I would definitely like to be sleeping better. It also depends on what it is...I still have to be able to wake up if my daughter is crying or if something happens.”*
- ☀️ *“I have had good experiences with counseling and working with someone to resolve problems instead of medication. So, I would hope that would work with sleep too. Being in recovery, I try to not take as many medications as possible. Try to keep it just to my suboxone.”*

**STEP 1: Insomnia
Diagnosis**

Assessment of
insomnia
symptoms

**STEP 2: Evaluate
treatment history**

Evaluate patient goals &
preferences

**STEP 3: Develop
individualized
insomnia treatment
plan**

1. Optimize treatments for physical & psychiatric comorbidities
2. Optimize sleep environment
3. Modify sleep-interfering medications

Initiate CBT-I

Inadequate CBT-I
treatment response

Adequate CBT-I
treatment response

Pharmacotherapy
shared decision-making

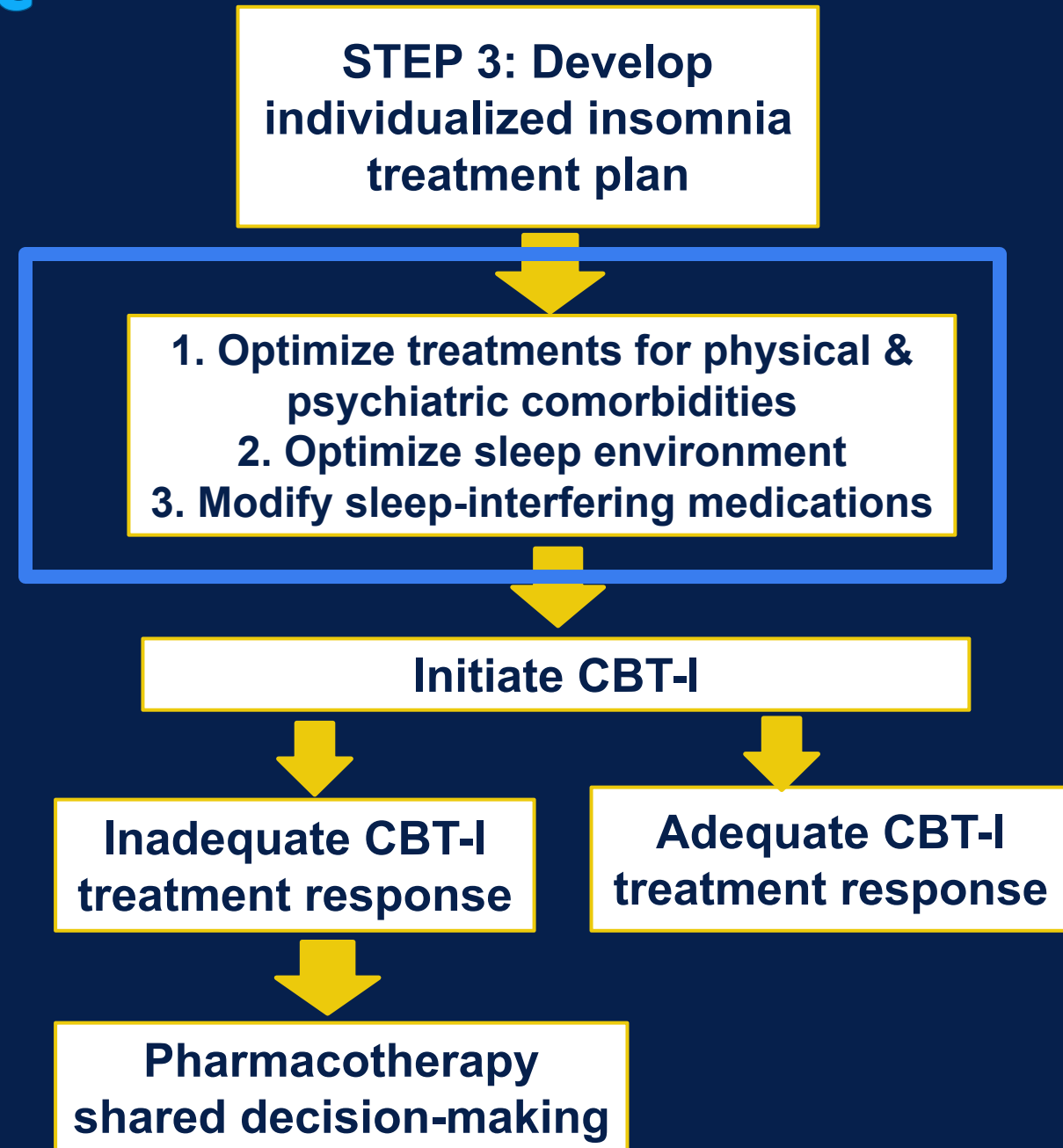
Unwillingness to
engage in CBT-I
or
Significant
barriers to CBT-I
access

**Step 3: Develop
individualized
care plan**



Non-pharmacologic interventions

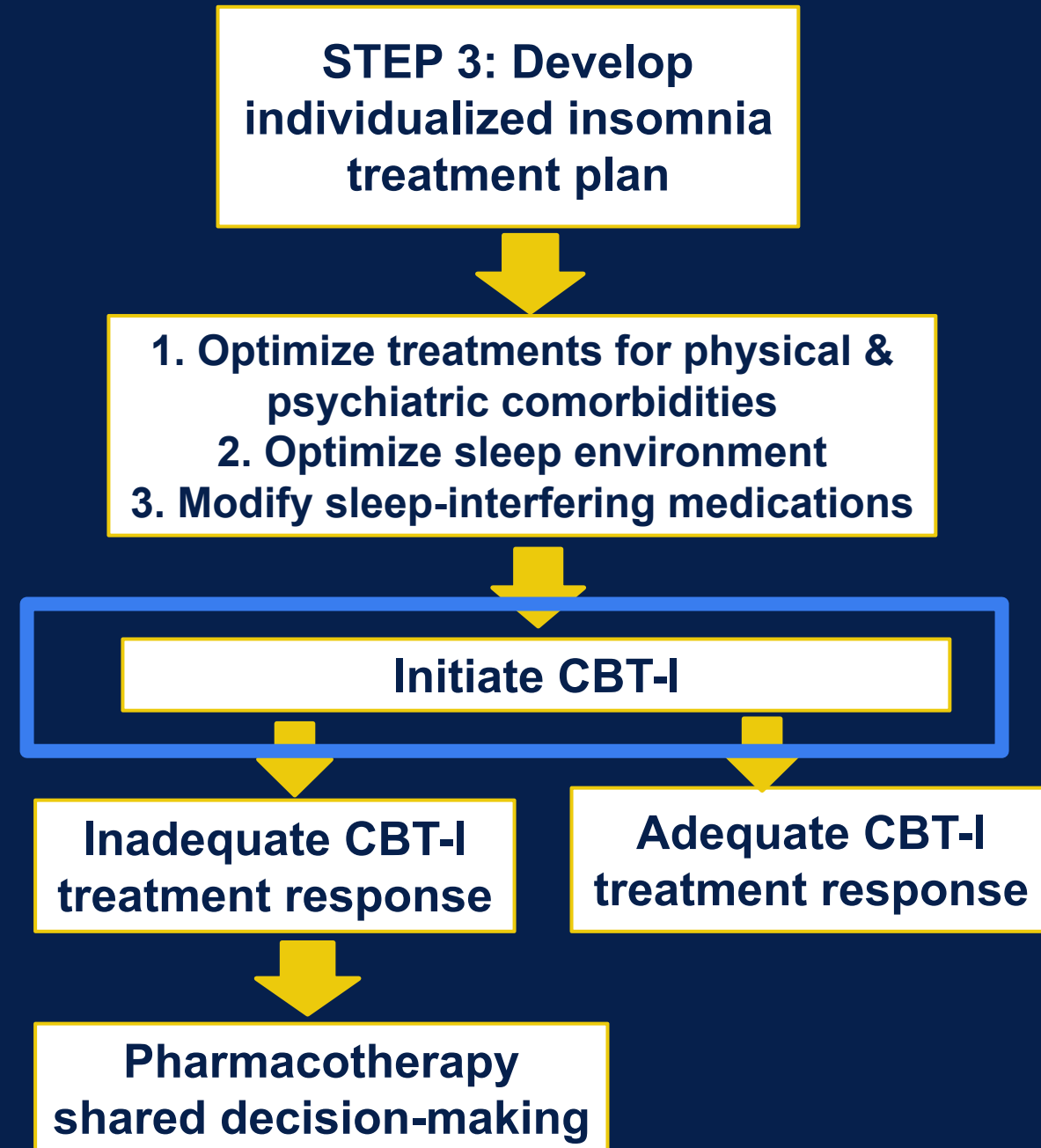
- ☀️ Optimize pharmacologic and non-pharmacologic treatment plans for comorbidities
 - ☀️ Pain conditions
 - ☀️ Psychiatric diagnoses
 - ☀️ Non-prescribed substance use
- ☀️ “~~Sleep hygiene~~” → Sleep behaviors
 - ☀️ Quiet, dark, cool temperature
 - ☀️ Avoid screen time, caffeine, alcohol, food before bedtime
 - ☀️ Exercise!



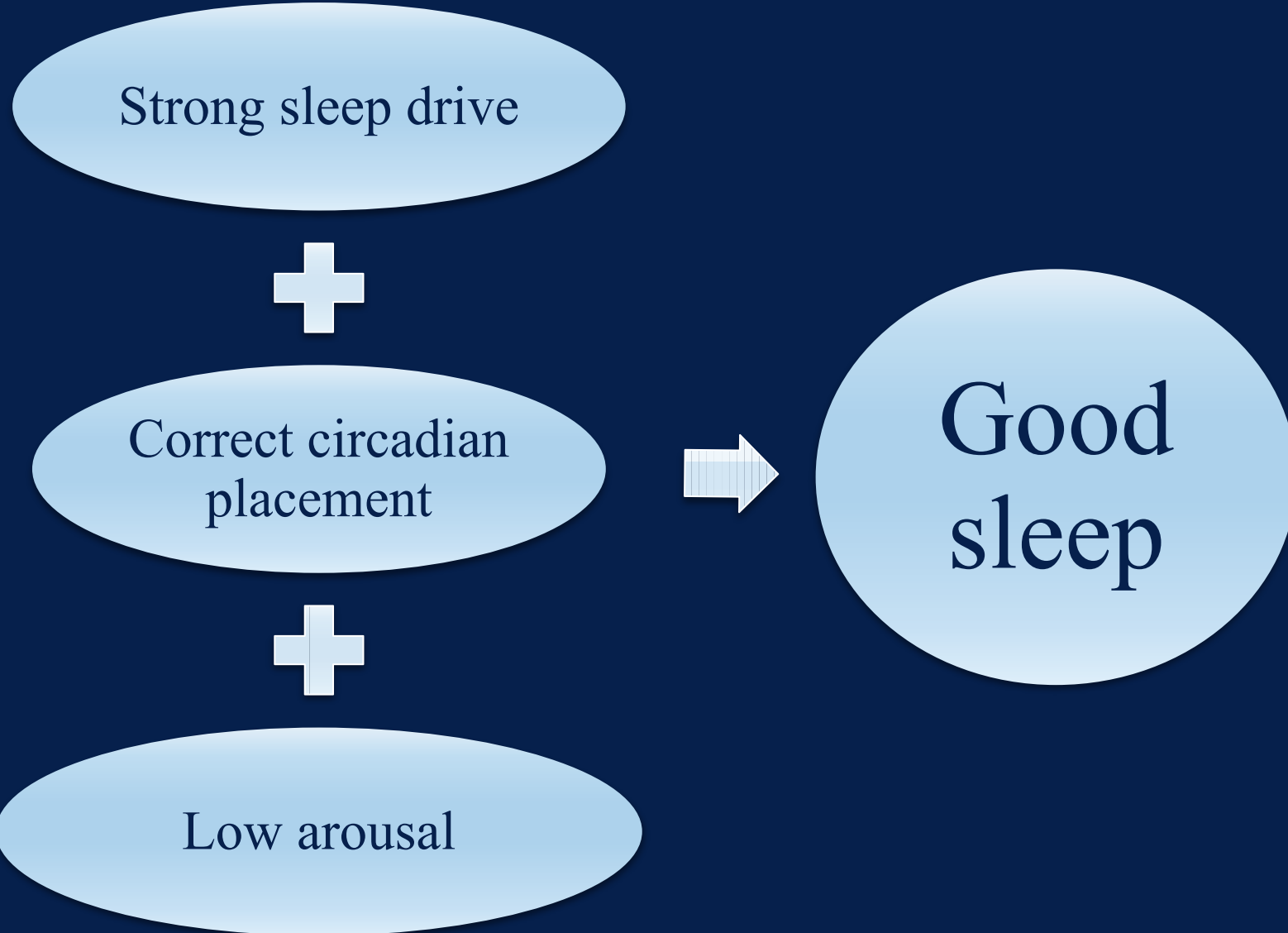
CBT-I

- ☀ Recommended first-line treatment
- ☀ Robust evidence indicating effectiveness for sleep parameters and secondary outcomes (depression, pain).
- ☀ Delivery formats
 - ☀ In-person, Telehealth
 - ☀ Self-paced via internet browser or mobile apps
- ☀ **Yet only 1 small trial in OUD (methadone) patients (n=22)**

Soleimani et al. IJMS 2015; Wu et al. JAMA Internal Med. 20115.



A basic overview:



CBT-I and sleep regulation

- The GOAL of CBT-I is to use the processes that regulate sleep to facilitate natural, healthy sleep
 - Explain treatment rationale
 - Work with the Sleep Drive and Circadian Alerting System
- Use strategies to reduce arousal that can over-ride natural sleep regulation
 - Reduce anxiety and alertness near bedtime
 - Attend to what the patient does during the nighttime when awake
 - Explore beliefs and attitudes about sleep

Sleep diaries

- Daily logs used to track sleep habits and sleep quality
- Information used to inform treatment of insomnia
- ESSENTIAL TOOL USED IN SLEEP RESTRICTION AND COGNITIVE-BEHAVIORAL THERAPY FOR INSOMNIA
- Use a metaphor like a thermometer or checking blood pressure to help patient to understand the purpose/importance of data monitoring



Carney et al. Sleep 2012

Complete each morning:

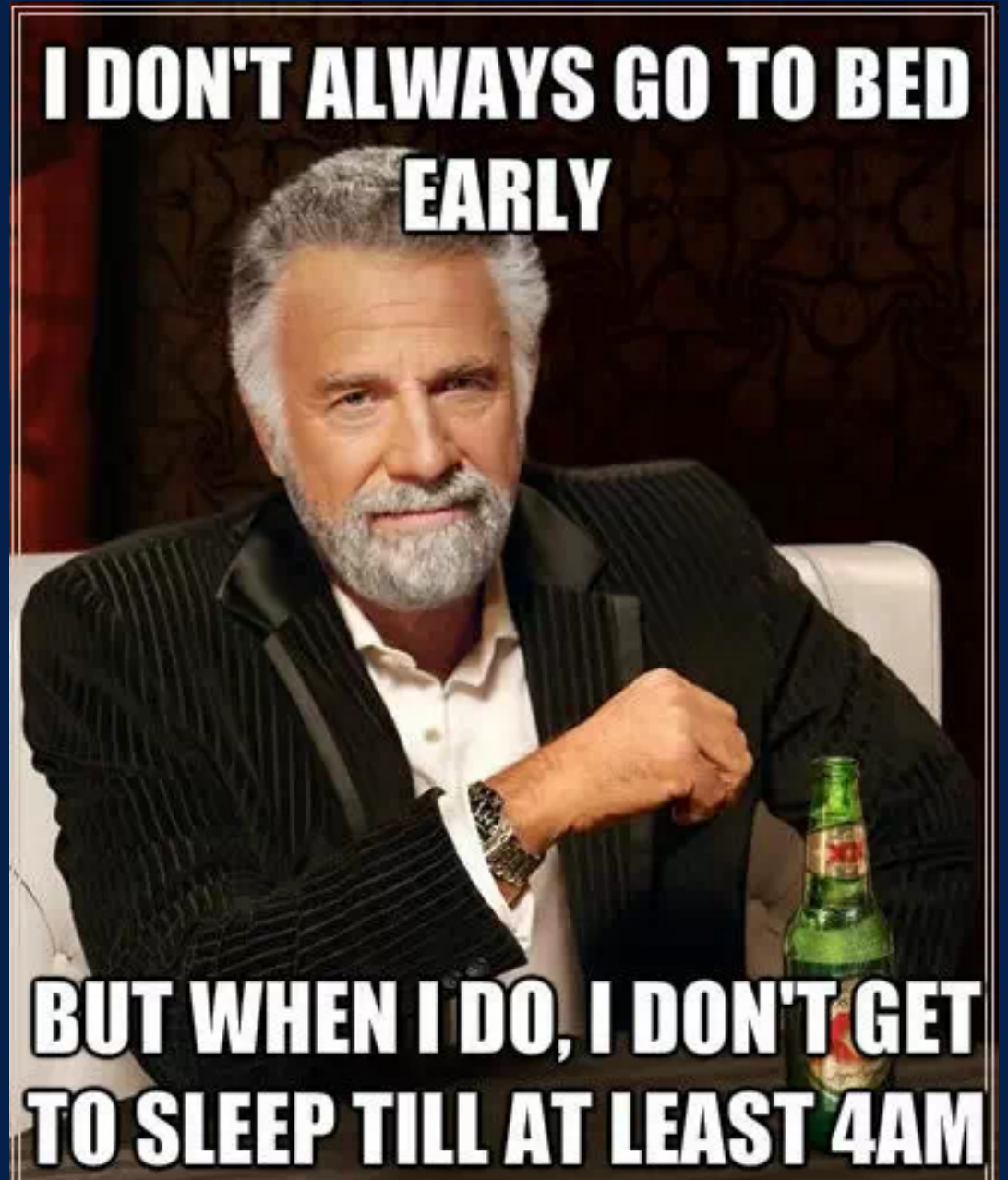
Date	04/03						
How much time did you nap/doze yesterday?	0 min						
What time did you go to bed last night intending to sleep?	10:30 pm						
How long did it take you to fall asleep?	10 min						
How many times did you wake up during the night?	2						
How much time were you awake, in total?	80 min						
What time did you wake up in the morning?	7:30 am						
How long did you lay in bed before rising?	5 mins						
How would you rate your sleep quality? (0 poor – 10 excellent)	7						

Example: 8 hours in bed every night

Date	04/03	04/04	04/05	04/06	04/07	04/08	04/09
How much time did you nap/doze yesterday?	0 min	0 min	0 min	0 min	0 min	0 min	0 min
What time did you go to bed last night intending to sleep?	11:00 pm	11:30 pm	11:05 pm	10:35 pm	9:55 pm	12:15 am	10:15 pm
How long did it take you to fall asleep?	25	20	40	60	55	15	95
How many times did you wake up during the night?	2	2	1	1	2	3	2
How much time were you awake, in total?	20	25	15	35	20	45	60
What time did you wake up in the morning?	7:00am	6:20am	6 am	7:00 am	7:00 am	9:30 am	9:45 am
How long did you lay in bed before rising?	15	60	60	25	15	80	120
How would you rate your sleep quality (0-10)	6	5	5	6	4	7	2

>10 hrs >12 hrs

Sleep Restriction



Sleep Restriction

- Rationale:
 - Most patients with insomnia spend too much time in bed
 - While this is often a strategy to increase sleep time, it leads to sleep fragmentation and perpetuates insomnia over time
- General strategy:
 - Measure time in bed and total sleep time with sleep diary
 - Limit time in bed to match time asleep
 - Expand slowly until the patient is getting the right amount of sleep

Why use sleep restriction?

- Powerful intervention:
 1. Works with the Sleep Drive
 2. Works with the Circadian System
 3. Targets many perpetuating factors for insomnia

Step 1: Determine baseline sleep stats

- Determine the following sleep statistics:
 - Total Sleep Time (i.e., sleep duration)
 - Time in Bed (i.e., sleep opportunity)
 - Sleep Onset Latency (i.e., time to fall asleep)
 - Wake after Sleep Onset (i.e., time awake during the night)
 - Terminal Wakefulness (i.e., early morning awakenings)
 - **Sleep Efficiency (i.e., % time in bed actually asleep)**
- **Sleep diary is ESSENTIAL to this process**

Step 2: Establish wake-up time

- Based on diary and patient's life demands
- To be maintained SEVEN days a week
- Be realistic

Step 3: Match time in bed to sleep time

- Consider the following:
 - Patient spending 10.5 hours in bed a night
 - Patient sleeping only 6.5 hours in bed a night
 - Recommendation = spending 6.5 hours in bed per night
- Never recommend less than 5 hours a night
- Useful analogy: rolling pizza dough



Step 4: Prescribe sleep window

- Use desired wake-up time
- Work backwards
- Set bedtime
- No sleep permitted outside of this window
- NO NAPS
- To be maintained everyday
- Check on feasibility and adjust as needed

CBT-I Case Introduction (Mrs. B)

- ☀️ 37 year old female patient stable on methadone 100 mg for 4 years, last use of non-prescribed substances 2 years ago
- ☀️ Difficulty falling asleep for over a year, leading to daytime sleepiness interfering with job
- ☀️ Has been optimizing sleep hygiene and stimulus control
- ☀️ Instructed to complete a sleep diary x 1 week, comes in for follow-up to your clinic

Mrs. B comes in for follow-up in 1 week...

☀️ Three options to adjust sleep window:

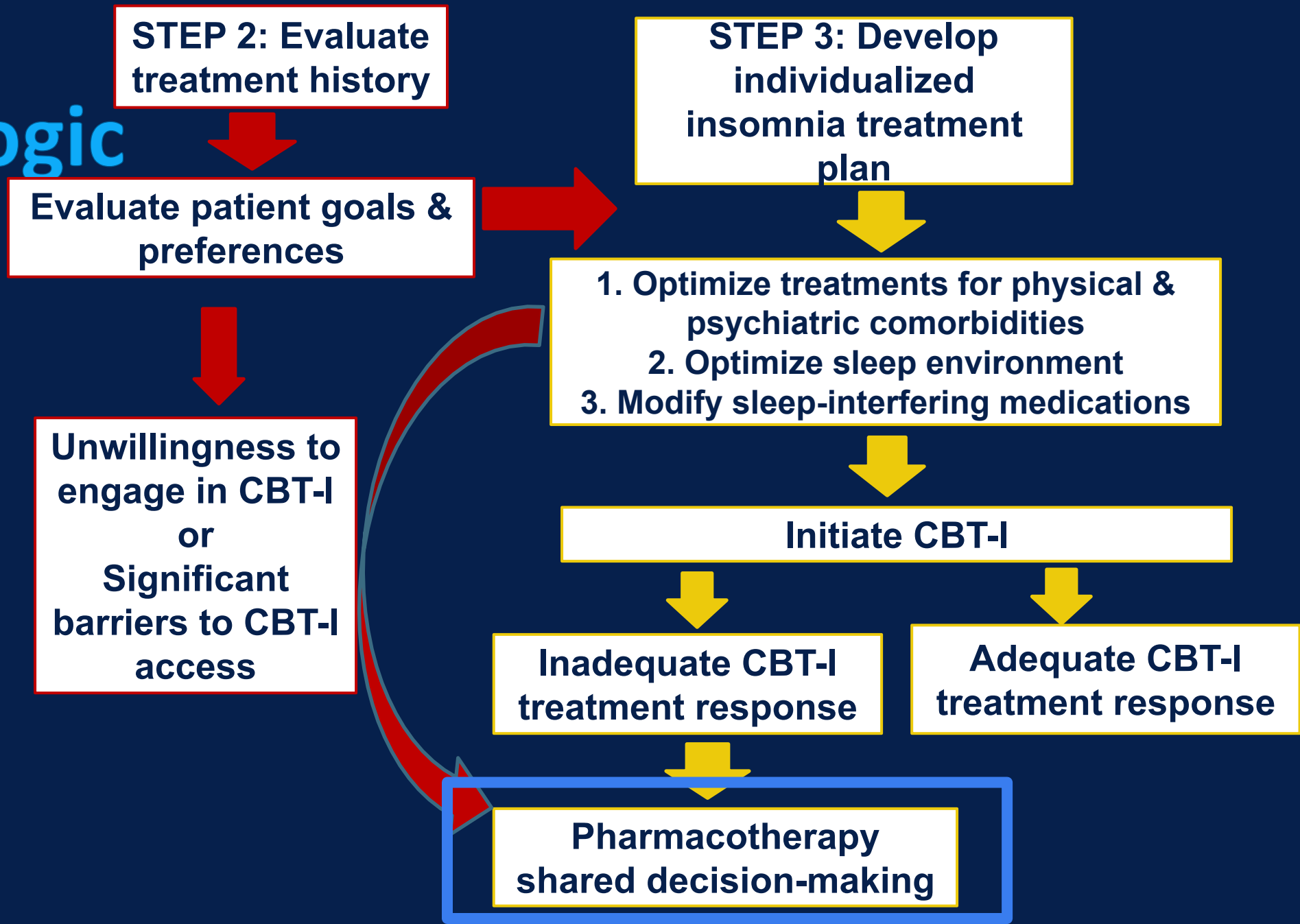
- ☀️ 1. Increase sleep window
- ☀️ 2. Reduce sleep window
- ☀️ 3. Do nothing, keep sleep window the same
- ☀️ 4. Start over, recalculate sleep window

National Sleep Foundation's Best Slept Self[®] Recommendations



theNSF.org for more information

Pharmacologic treatment options



Insomnia Medications

Pharmacotherapy
shared decision-making



Decision made for
medication trial



Sleep Onset Insomnia



Sleep Maintenance
Insomnia



Benzodiazepine-like drugs: Eszopiclone & Zolpidem
Antidepressants: Doxepin, Mirtazapine, Trazodone
Orexin receptor antagonists: Suvorexant
Benzodiazepines: Temazepam



Melatonin agonists: Melatonin
Supplements, Ramelteon
Benzodiazepine-like drugs:
Eszopiclone, Zaleplon & Zolpidem
Benzodiazepines: Temazepam &
Triazolam

Which of these medications have had a clinical trial among MOUD patients?

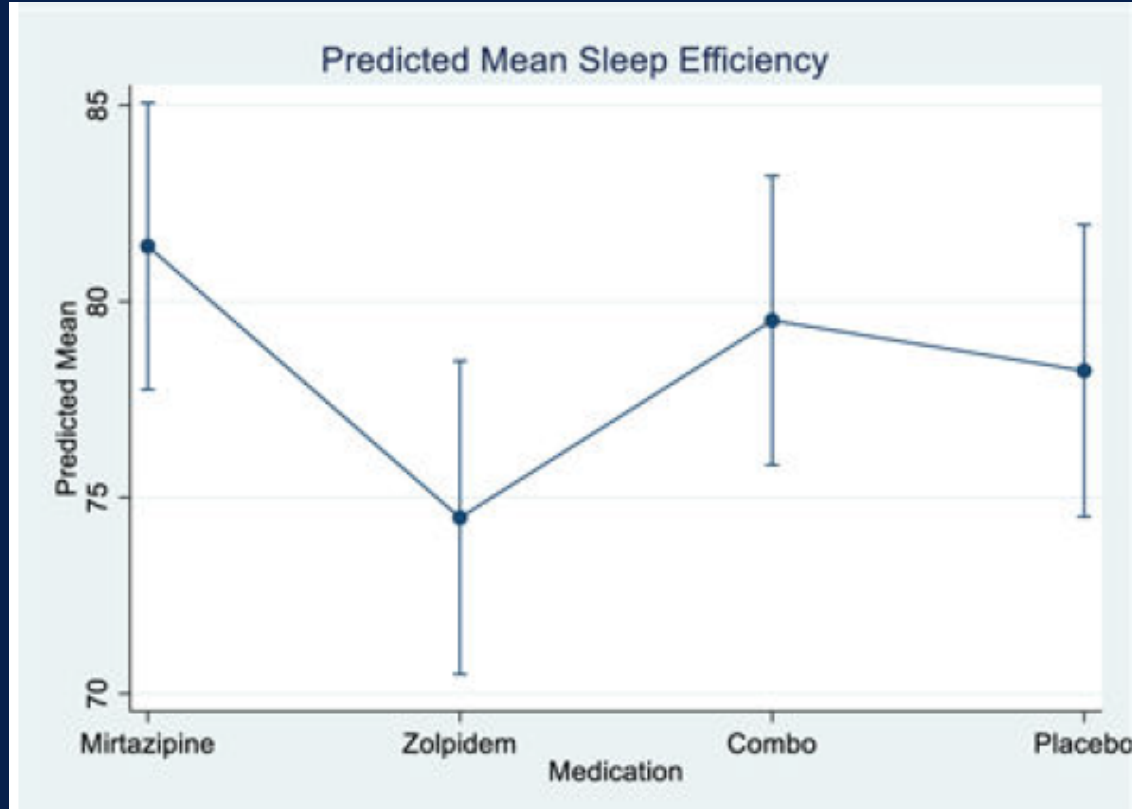
- ☀ Randomized, double blind crossover trial of methadone patients with insomnia (n=10)
- ☀ Study med or placebo taken over 4 one-week periods over 8-weeks with 1-week 'off' between meds
 - ☀ Zolpidem CR 12.5
 - ☀ Mirtazapine 30 mg
 - ☀ Zolpidem 10 mg + Mirtazapine 30 mg
 - ☀ Placebo

Sleep Onset Insomnia



Melatonin agonists: Ramelteon
Benzodiazepine receptor agonists: Eszopiclone, Zaleplon & **Zolpidem**
Benzodiazepines: Temazepam & Triazolam

Zolpidem & Mirtazapine (Stein 2020)



- ★ Primary outcomes: sleep parameters by wrist actigraphy + home sleep diaries
- ★ Compared to placebo:
 - ★ Mirtazapine INCREASED sleep time by 23 minutes
 - ★ Zolpidem DECREASED sleep time by 16 minutes
 - ★ Combination of Mirtazapine + Zolpidem increased sleep time by 17 minutes

Which of these medications have had a clinical trial among MOUD patients?

- ☀ Double-blind, randomized, placebo-controlled trial (n=38) of patients with OUD and active non-prescribed opioid use
- ☀ Study medication or placebo administered over 8 days during a buprenorphine taper on an inpatient treatment unit
 - ☀ Suvorexant 20 mg
 - ☀ Suvorexant 40 mg

Sleep Maintenance
Insomnia



Benzodiazepine receptor agonists:

Eszopiclone & **Zolpidem**

Heterocyclics: Doxepin

Orexin receptor antagonists:

Suvorexant

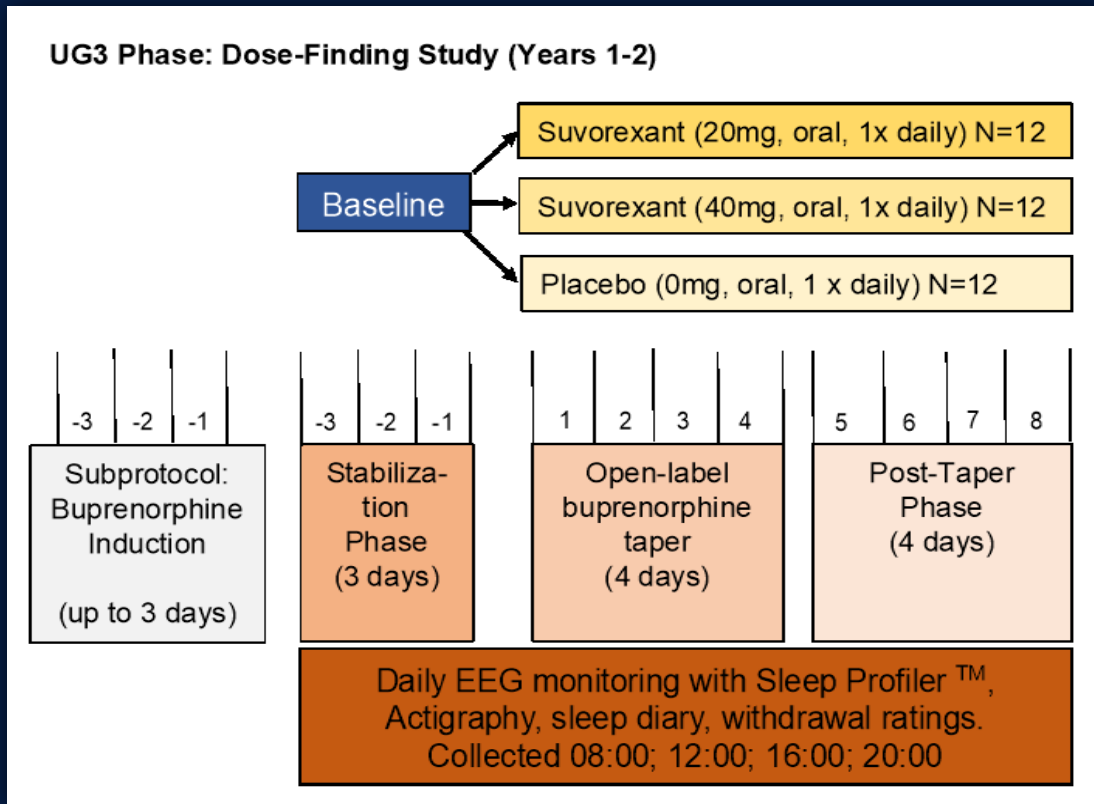
Benzodiazepines: Temazepam

Suvorexant (Huhn 2022)

☀ Power Analysis: Minimum N=36 to detect strong effect (.7)

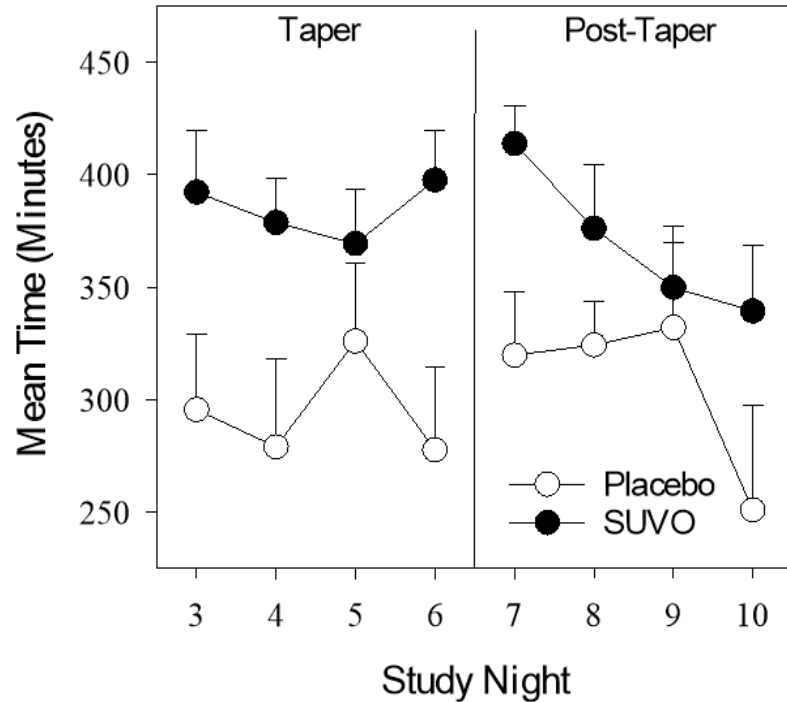
☀ Con-Meds

- acetaminophen
- Ibuprofen
- milk of magnesia
- loperamide
- simethicone

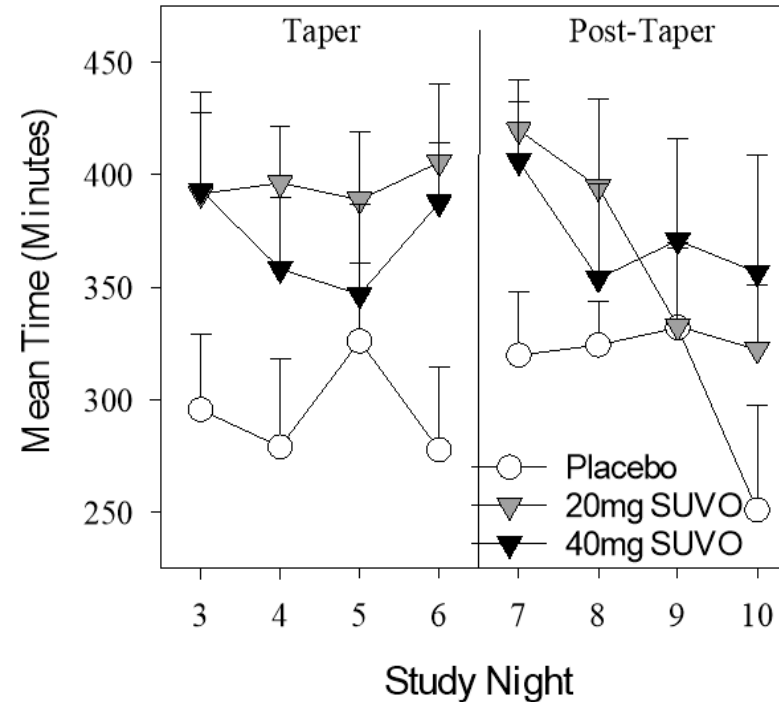


Objective Sleep Outcomes

ITT Analyses: Placebo N=12; SUVO 20mg N=14; SUVO 40mg N=12



Two-group analysis
 Taper: $F=7.29$, $p=.010$
 Post-taper: $F=4.95$, $p=.033$

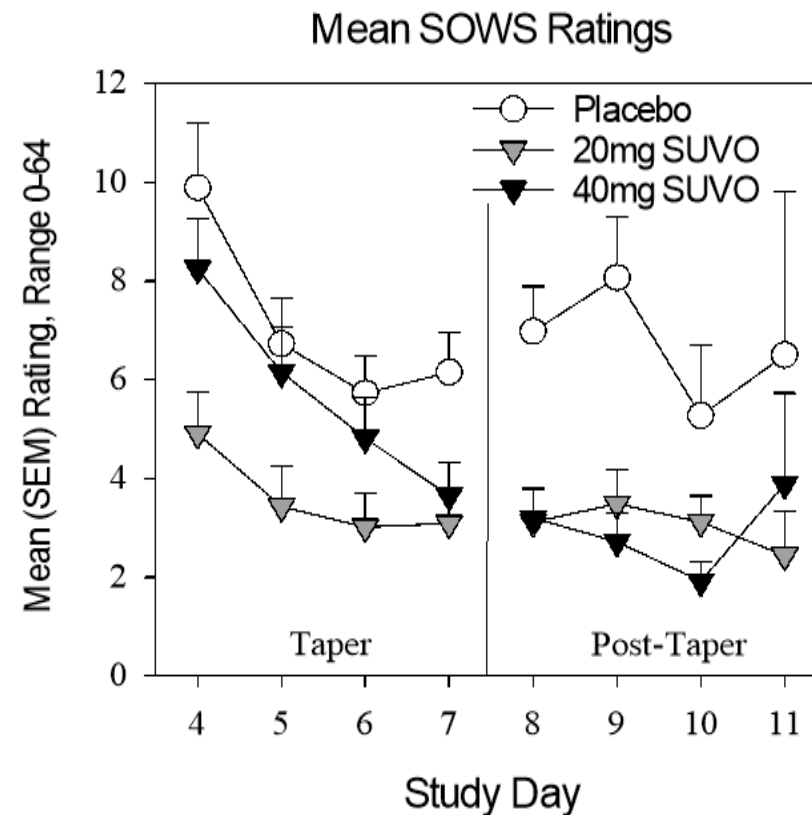
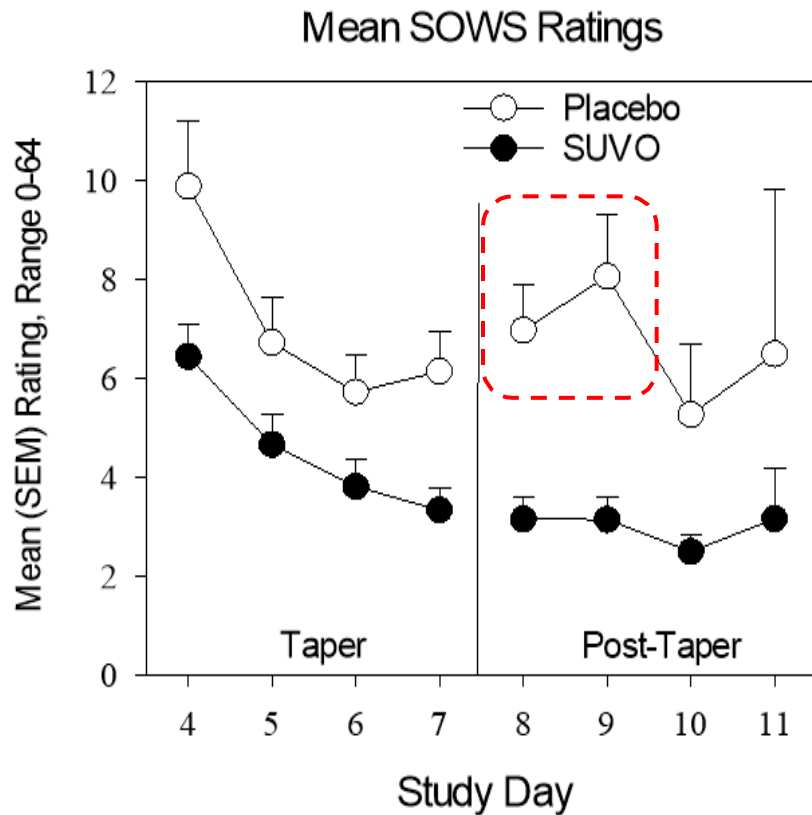


Three-group analysis
 Taper: $F=3.81$, $p=.032$
 Post-taper: $F=2.43$, $p=.105$

Huhn et al. Suvorexant ameliorated sleep disturbance, opioid withdrawal, and craving during a buprenorphine taper. *Science Translational Medicine*. 2022.

Opioid Withdrawal Outcomes

ITT Analyses: Placebo N=12; SUVO 20mg N=14; SUV40mg N=12



Huhn et al. Suvorexant ameliorated sleep disturbance, opioid withdrawal, and craving during a buprenorphine taper. *Science Translational Medicine*. 2022.

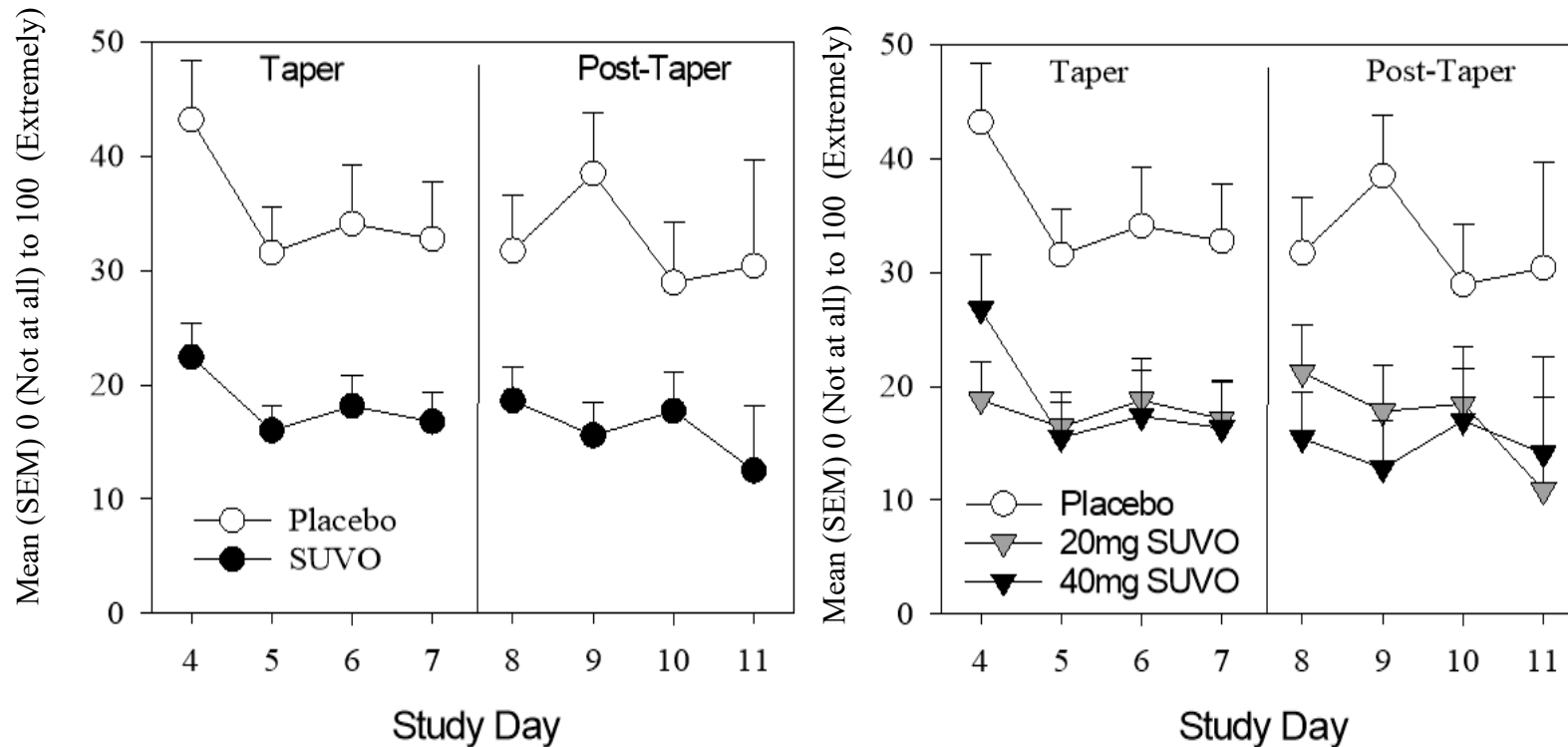
Two-group analysis
 Taper: $F=2.03$, $p=.163$
 Post-taper: $F=5.71$, $p=.023$

Three-group analysis
 Taper: $F=1.58$, $p=.221$
 Post-taper: $F=2.77$, $p=.078$



Opioid Craving Outcomes

ITT Analyses: Placebo N=12; SUVO 20mg N=14; SUV40mg N=12



Huhn et al. Suvorexant ameliorated sleep disturbance, opioid withdrawal, and craving during a buprenorphine taper. *Science Translational Medicine*. 2022.

Two-group analysis
 Taper: $F=4.30$, $p=.045$
 Post-taper: $F=2.88$, $p=.099$

Three-group analysis
 Taper: $F=2.12$, $p=.135$
 Post-taper: $F=1.44$, $p=.252$



Insomnia Medications NOT Recommended by AASM

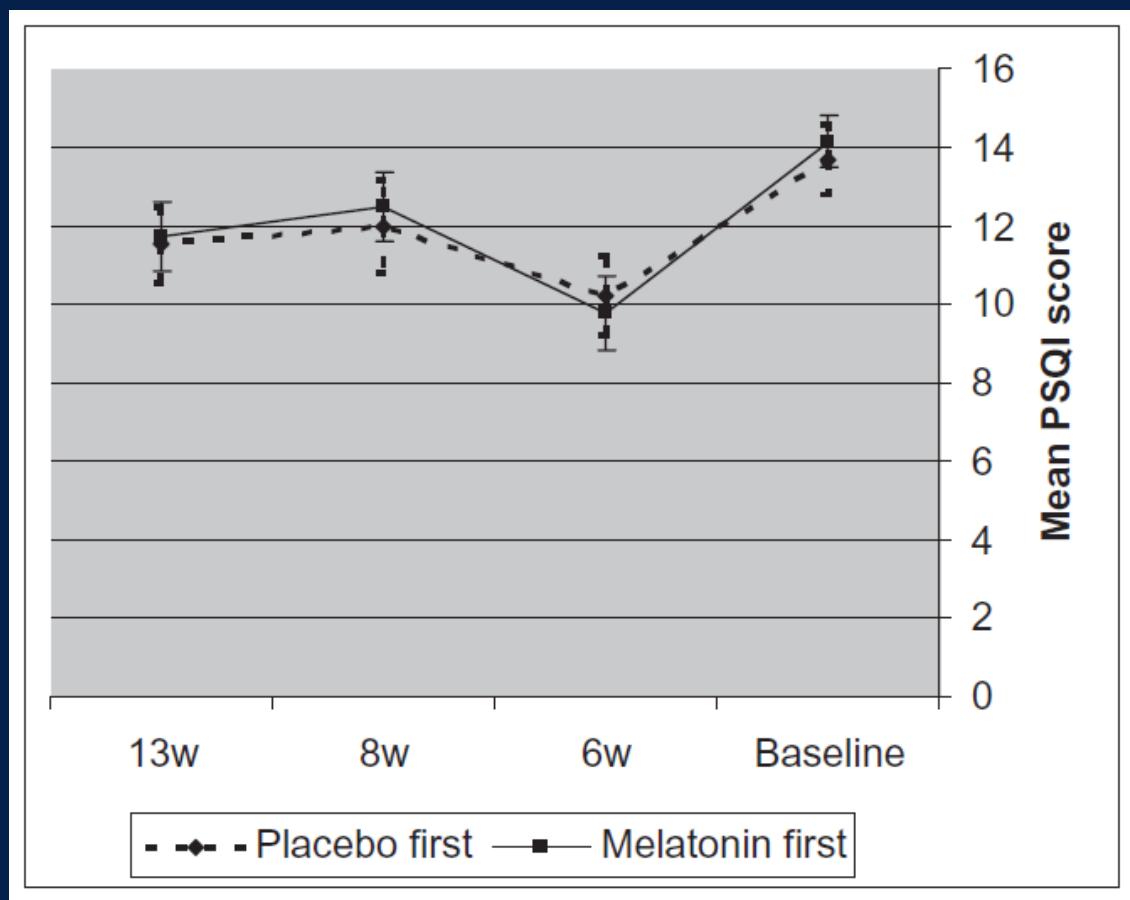
Diphenhydramine	<p>Sleep latency: Mean reduction was 8 min greater, compared to placebo (95% CI: 2 min increase to 17 min reduction); Total sleep time: Mean improvement was 12 min longer, compared to placebo (95% CI: 13 min reduction to 38 min improvement); Quality of sleep*: No improvement^a in quality of sleep, compared to placebo; Side effects: See Recommendation 11, "Harms"</p> <p><i>This recommendation is based on trials of 50 mg doses of diphenhydramine.</i></p>
Melatonin	<p>Sleep latency: Mean reduction was 9 min greater, compared to placebo (95% CI: 2 to 15 min reduction); Quality of sleep*: Small^a improvement in quality of sleep, compared to placebo; Side effects: See Recommendation 12, "Harms"</p> <p><i>This recommendation is based on trials of 2 mg doses of melatonin.</i></p>
Tiagabine	<p>Total sleep time: Mean improvement was 17 min longer, compared to placebo (95% CI: 7 min reduction to 15 min improvement); Wake after sleep onset: Mean reduction was 1–9 min greater, compared to placebo (95% CI: 6 min increase to 25 min reduction); Quality of sleep*: No-to-Small^a improvement in quality of sleep, compared to placebo; Side effects: See Recommendation 10, "Harms"</p> <p><i>This recommendation is based on trials of 4 mg doses of tiagabine.</i></p>
Trazodone	<p>Sleep latency*: Mean reduction was 10 min greater, compared to placebo (95% CI: 9 to 11 min reduction); Wake after sleep onset: Mean reduction was 8 min greater, compared to placebo (95% CI: 7 to 9 min reduction); Quality of sleep*: No improvement^d in quality of sleep, compared to placebo; Side effects: See Recommendation 9, "Harms"</p> <p><i>This recommendation is based on trials of 50 mg doses of trazodone.</i></p>
L-tryptophan	<p>Sleep latency: Not reported; Wake after sleep onset*: Mean reduction was 10 min greater, compared to placebo (95% CI: 4 to 15 min reduction); Quality of sleep*: Small^e improvement in quality of sleep, compared to placebo; Side effects: see Recommendation 13, "Harms"</p> <p><i>This recommendation is based on trials of 250 mg doses of tryptophan.</i></p>
Valerian	<p>Sleep latency: Mean reduction was 9 min greater, compared to placebo (95% CI: 0 to 18 min reduction); Quality of sleep*: Not reported; Side effects: See Recommendation 14, "Harms"</p> <p><i>This recommendation is based on trials of variable dosages of valerian and valerian-hops combination.</i></p>

Trazodone (Stein 2012)

	Mean (SD)			t (p =)
	Total (n = 137)	Placebo (n = 68)	Trazodone (n = 69)	
Global PSQI Score	12.9 (3.0)	12.8 (3.0)	13.1 (3.1)	-0.60 (.55)
PSG Parameters	(n = 131)	(n = 63)	(n = 68)	
Sleep Period Time	428 (127)	420 (139)	435 (116)	-0.66 (.51)
Total Sleep Time	341 (125)	325 (137)	355 (113)	-1.34 (.18)
Sleep Efficiency	83.0 (11.6)	82.6 (11.6)	83.2 (11.7)	-0.30 (.76)
% Stage 1 Sleep	2.6 (3.0)	2.9 (3.9)	2.4 (1.6)	1.05 (.30)
% Stage 2 Sleep	66.5 (11.7)	66.2 (12.0)	66.8 (11.5)	-0.26 (.80)
% Slow Wave	13.0 (9.1)	13.9 (9.9)	12.3 (8.3)	1.00 (.32)
% REM	17.8 (8.9)	17.0 (9.3)	18.6 (8.6)	-1.02 (.31)
% Time Awake	17.1 (11.6)	17.4 (11.6)	16.8 (11.7)	0.30 (.76)
Arousal Index	9.4 (9.4)	9.1 (10.5)	9.6 (8.4)	-0.27 (.79)
Apnea Index	2.7 (8.8)	3.4 (11.0)	2.0 (6.2)	0.85 (.40)

- ☀ Methadone patients with insomnia randomized to Trazodone 50 mg or Placebo (n=137)
- ☀ 3 months of study drug
- ☀ Self-titration allowed up to 150 mg Trazodone
- ☀ No significant improvements in sleep parameters nor non-prescribed substance use
- ☀ Subjective sleep time increased 45 minutes (Trazodone) vs. 10 minutes (placebo)

Melatonin



- ☀ Ghaderi 2018: male methadone patients (Iran)
 - ☀ 10 mg Melatonin (n=26) & Placebo (n=28) x 12 weeks
 - ☀ Pittsburgh Sleep Quality Index (PSQI) significantly improved in Melatonin group ($p < 0.001$)
- ☀ Peles 2007: methadone patients (n=61) undergoing benzodiazepine taper x 6 weeks (Israel)
 - ☀ Melatonin 5 mg vs. placebo
 - ☀ Most sleep improvements were related to benzo discontinuation (likely not due to Melatonin itself)

Final Takeaways

- ☀️ Insomnia is one of the most prevalent comorbidities among people receiving medication treatment for OUD
- ☀️ Targeting insomnia during OUD treatment holds great promise to improve recovery outcomes
- ☀️ Initiating treatment with CBT-I is the standard of care
- ☀️ Pharmacologic options recommended by AASM exist yet have been very understudied in OUD populations

Q&A



References

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