Addressing Insomnia in Patients with Opiate Use Disorder

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Disclosure

- Nothing to disclose
- Family & Addiction Certified
- Special interest: Chronically sleep deprived

Learning Objectives

- Define Insomnia, describe epidemiology, and health implications.

- Better understand the complex relationship between opiate use disorder (OUD) and insomnia.

- List components of cognitive behavioral therapy and be able to conduct the basics of brief interventions.

- Describe evidence of pharmacologic treatments

What is insomnia?   DSM V....

- Impairment of the initiation, duration, or quality of sleep
  - Despite adequate opportunity for sleep
  - Results in daytime impairment
- Chronic condition
  - At least 3 times/week for 3 months
- No longer 'primary' or secondary'
  - DSM V, International Classification of Sleep Disorders, 3rd Edition

Seow LSE, Verma SK, Mok YM, Kumar S, Chang S, Satghare P, Hombali A, Vaingankar J, Chong SA, Subramaniam M. Evaluating DSM-5 insomnia disorder and the treatment of sleep problems in a psychiatric population. *J Clin Sleep Med*. 2018;14(2):237–244.

Sleep norms

▶ Most adults need 6-8 hours per night

▶ Less sleep as we age

▶ Most can function without optimal sleep

Thensf.org
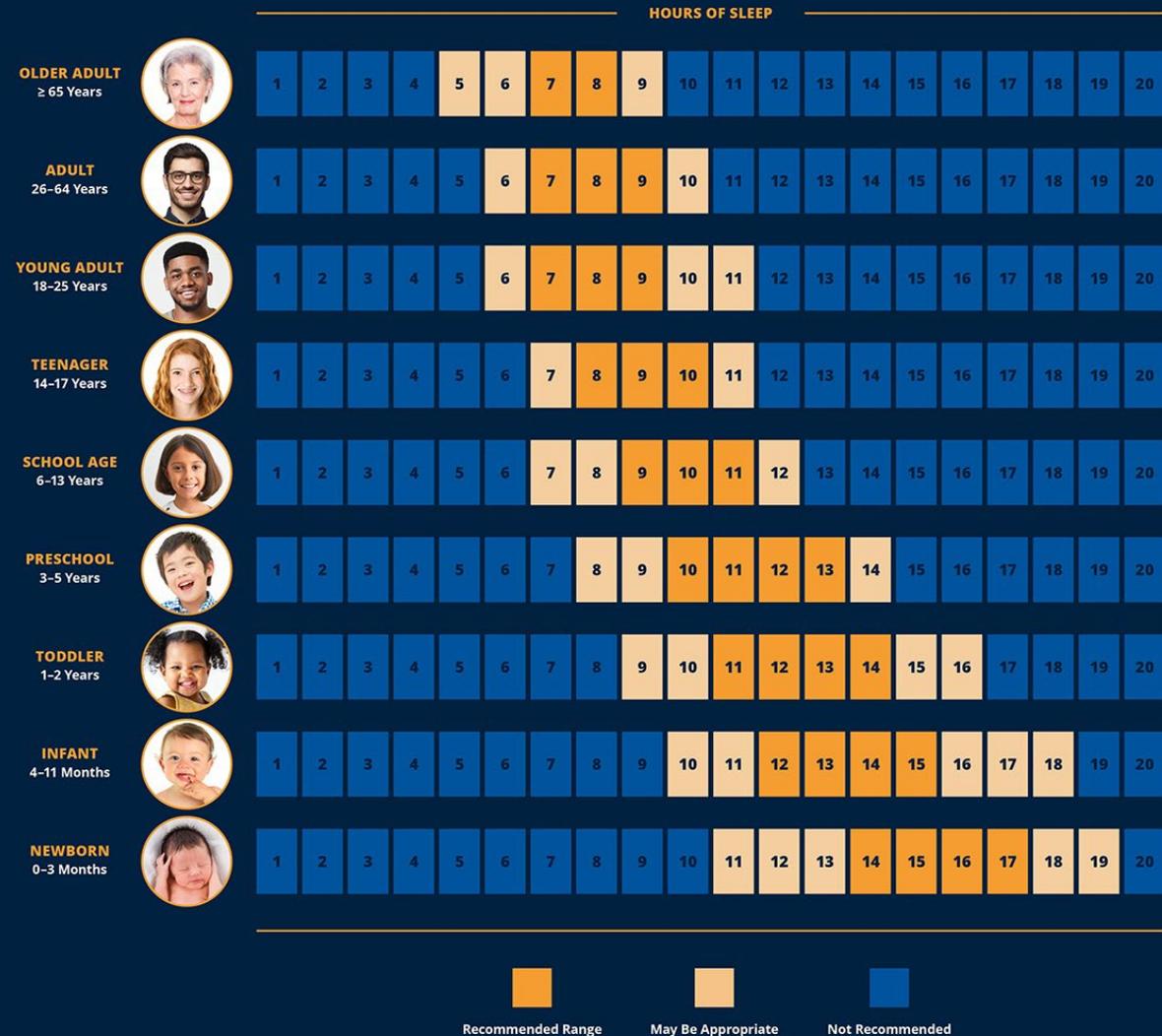
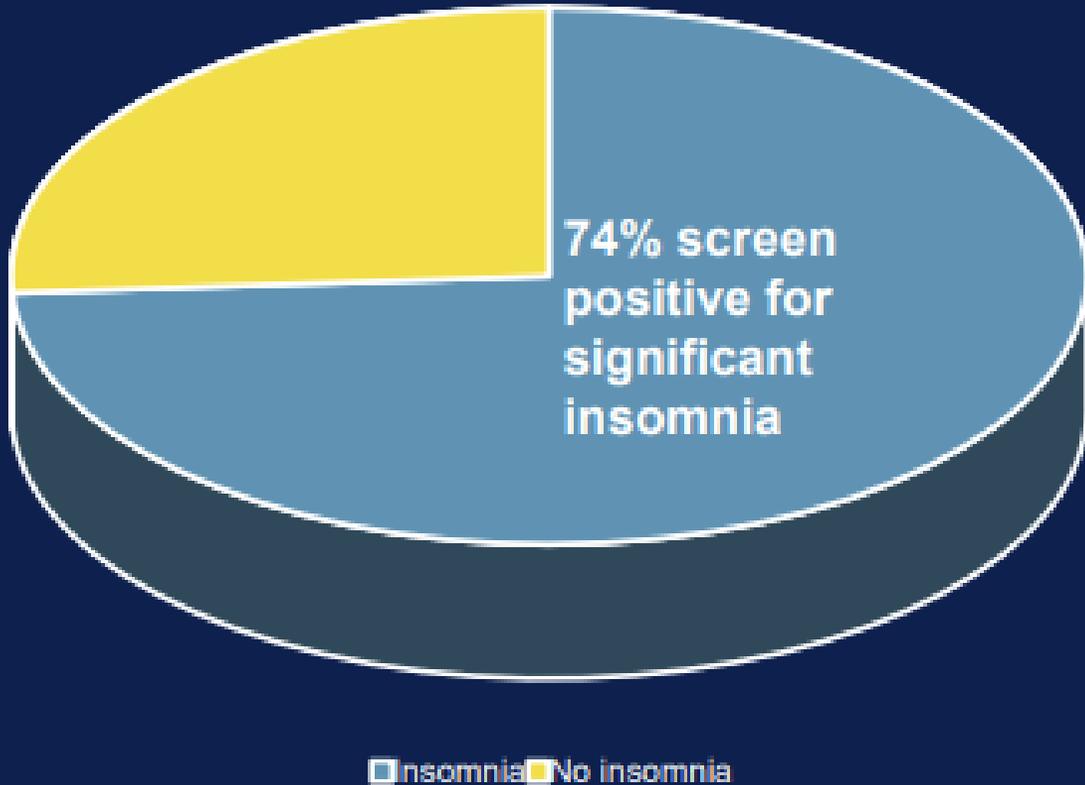# Why is insomnia important?

- Affects 30% of the general population
- 5-15% have chronic insomnia

- Public health importance
  - Associated with decreased quality of life, higher risk of falls, accidents, psychological illnesses, suicide rate, chronic pain
  - Increased cardiovascular disease, blood pressure
  - Economic/Societal Burden: Increased healthcare costs, work absences, lower productivity

Matheson EM, Brown BD, DeCastro AO. Treatment of Chronic Insomnia in Adults. Am Fam Physician. 2024 Feb;109(2):154-160. PMID: 38393799.

Insomnia Disparities

- Age: Increases with older age

- Sex: Higher persistence in females starting in puberty.

  - Hormonal fluctuations

- Gender: Primary caregiver, work strain, social support

- Social Determinants of Health

- Neighborhood level factors

  - Rates of poverty, unemployment, air quality, STRESS

  - Trauma, discrimination

Zhang et al. SLEEP 2006; Suh et al. Curr Psych Rep 2018; Rottapel et al. Sleep Health 2019; Nielsen et al. Biol Sex Diff 2021

Insomnia among OUD patients

Prevalence of insomnia among a buprenorphine treatment sample

74% screen positive for significant insomnia

Insomnia | No insomnia

- ▶ Insomnia exists across the OUD recovery
  - ▶ Opioid use
  - ▶ Withdrawal
  - ▶ Recovery Stress
- ▶ Insomnia highly prevalent for years after cessation of substance use

Eglovitch M, Parlier-Ahmad AB, Legge C, Chithranjan S, Kolli S, Violante S, Dzierzewski JM, Huhn AS, Wilkerson A and Martin CE (2023) Patient reported preferences for sleep interventions among women receiving buprenorphine for opioid use disorder. *Front. Psychiatry* 14:1244156. doi: 10.3389/fpsyt.2023.1244156

Insomnia in OUD patients

▶ Patient reported priority.

  ▶ 'If I do get proper sleep, I don't have cravings. So sleep is very important.'

  ▶ 'If you're not getting sleep, then you're not gonna be able to handle those triggers as well…'

  ▶ 'If you don't get enough sleep, then you are up thinking about all kind of negative things that can cause you to want to relapse…'

Roehrs et al. Pharm, Biochem, Beh. 2021

Addressing insomnia in clinic

- Step 1: Screen and Diagnosis
- Step 2: Define patient's goals
- Step 3: Individualized treatment plan
  - CBT
  - Medications

Case JL

- **JL is a 26-year-old single woman who is on your walk-in schedule for insomnia.**
  - You note from her chart, she sees a colleague of yours for MOUD for several months and goes to an LAC.

  - What else do you want to know?

Step 1: Insomnia Workup and Diagnosis

DSM-5 Definition of Insomnia Disorder

Dissatisfaction with sleep quality or quantity and ≥1 of the following:

- ❏ Difficulty initiating sleep
- ❏ Difficulty maintaining sleep
- ❏ Early morning wakening

Sleep disturbance occurs despite adequate opportunity for sleep

Sleep difficulty occurs ≥ 3 nights/wk for ≥ 3 months

APA. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.* 2013.

Validated Insomnia Tools

- Score 0-28
  - 8-14: Sub-threshold insomnia
  - 15-21 Moderate
  - 22-28 Severe

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

Morin CM; Belleville G; Bélanger L; Ivers H. The insomnia severity index: psychometric indicators to detect insomnia cases and evaluate treatment response. *SLEEP* 2011;34(5):601-608.

Step 2: Evaluate Patient's Goals

- ▶ Prior Experiences
  - ▶ Sleep hygiene
  - ▶ Behavioral therapies
  - ▶ Medications

- ▶ Barriers
  - ▶ Access to treatment/CBT
  - ▶ Willingness to take medication

Patient Goal Examples
Get to sleep without a medication
Be awake during day
Have techniques to get to sleep easier

Case JL

- **JL is a 26-year-old single woman who is on your walk-in schedule for insomnia.**
  - You note from her chart, she sees a colleague of yours for MOUD for several months and goes to an LAC.
  - No other medications, history.
  - 5+years, happens almost every night. Tries to go to bed around 9 and get up around 6 every night. Lies awake for an hour or 2 before going to sleep, often has night time wakeups.
  - Feels tired during day.
  - Goals: avoid medications if able, get enough sleep to be functional at work.

  - Where do you start with treatment?

Step 3: Individualized care plan

- Non-pharmacologic treatments
  - Address comorbid conditions: psychiatric diagnoses, pain
  - Identify and modify sleep-interfering medications
  - Mindfulness meditation
    - Reduce stress, promote relaxation

Sleep Hygiene
Sleep Behaviors

Trouble sleeping?

10 TIPS *for* BETTER SLEEP

1 Go to bed at the right time

Set a bedtime, and don't get into bed before it. This may be later than you currently go to bed if you are already spending a lot of time in bed. You should stay up past your set bedtime if you are not feeling sleepy. ☑

2 The 20 minute rule

Often people with insomnia notice that their mind begins to race when they turn off the light. You can stop this by leaving your bed when you don't fall asleep (or fall back to sleep) after 20 minutes of lying in bed. Plan ahead to do a relaxing activity when you leave the bed. Return to bed when sleepy. Repeat after 20 minutes, as needed. ☑

3 Get out of bed each morning at the same time (or earlier)

If you can, sleep until it is your planned time to rise and start your day. Don't sleep or stay in bed past your rise time, regardless of how late you were up the night before. ☑

4 Nap wisely

Don't nap if you don't need to. Avoid napping by getting active (ex. 20-minute walk). When a nap can't be avoided, limit yourself to a 10–20 minute power nap. Finish your nap before 3 pm. ☑

5 Spend less time in bed

This may sound odd at first, but most people with insomnia spend a lot of time

6 Distract your mind

It is hard to fall asleep when your mind is active – worrying about finances, health, relationships, or tomorrow's to-do list. Give your mind a chance to slow down and let sleep take over. Try these distraction techniques to help you fall asleep: ☑

- *Grocery cart exercise*: using your imagination, slowly walk through a grocery store and fill your cart, paying attention to each item you select.
- *Word list challenge*: think of a 5-letter word and come up with 5-10 words that start with each letter of the word. Add variety by choosing a theme – animals, names, cities, etc.

7 Take time to relax

Before getting into bed, there are many ways to prepare your body and mind for sleep. Add a relaxation technique to your bedtime routine that lets you do this. Examples include: low light reading before getting into bed, the 4-7-8 breathing exercise, and toe-to-head progressive muscle tightening and relaxing. ☑

8 Make being in bed about being asleep

Use your bed only for sleep, sex, & sickness if you are not sleeping well. Stop reading, writing, socializing, working, or snuggling with pets in bed. Any type of screen is to be avoided. ☑

9 Bust your sleep myths

Many people worry that they aren't getting enough sleep, and this keeps them up at night. What are your sleep myths? Busting them might be a part of what helps you get your sleep back. ☑

CBT-insomnia

- First line Treatment:
  - As effective for chronic insomnia as medications
    - More durable, life long skills
  - Low risk/adverse events

Mitchell MD, Gehrman P, Perlis M, Umscheid CA. Comparative effectiveness of cognitive behavioral therapy for insomnia: a systematic review. BMC Fam Pract. 2012 May 25;13:40. doi: 10.1186/1471-2296-13-40. PMID: 22631616; PMCID: PMC3481424.

Cognitive-Behavioral Therapy for Insomnia: An Effective and Underutilized Treatment for Insomnia

Jeffrey Rossman, PhD

- **As effective as medication, but…..**
- Underutilized
  - 1. Shortage of trained cbt-I practitioners
  - 2. Patient beliefs

CBTi vs. Sleeping Pills
for treating Insomnia

Sleepwell
mysleepwell.ca

CBTi
FIRST-LINE EVIDENCE-BASED TREATMENT FOR INSOMNIA

VS

Sleeping Pills
ANY MEDICATION OR SUBSTANCE USED TO MAKE YOU SLEEPY

CBTi		Sleeping Pills
First-line treatment for insomnia.	**EXPERT RECOMMENDATIONS**	Second-line treatment for insomnia.
Designed to fix the causes of insomnia, including what keeps it going.	**HOW IT WORKS**	Effect chemicals in the brain. Doesn't address the underlying causes of insomnia.
More effective than sleeping pills overall. Notice improved sleep within 1-2 weeks of getting started.	**EFFECTIVENESS**	More effective than CBTi in the first week only. Get to sleep 10-15 minutes faster and sleep for 20-25 minutes longer.
A 6-week program can lead to months and years of better sleep.	**DURATION**	Lose effect over time with nightly use and can lead to taking higher doses.
Prevents insomnia from returning.	**PREVENTION**	Don't prevent insomnia. Often cause sleep problems when stopped abruptly.
Safe, with very few restrictions on who can use it. Can experience daytime sleepiness, reduced alertness, and slowed reactions when starting time-in-bed restriction therapy.	**RISKS**	Next-day sedation, memory problems, confusion, impaired driving, loss of balance, falls, broken bones & other injuries, pneumonia, drug dependence & withdrawal, drug interactions, overdose.
For teens and adults of all ages with or without other health issues. It can be modified to suit your needs.	**WHO COULD USE IT**	Sleeping pills are only to be used short-term by adults and are not recommended for children or people 65 and older.

Cognitive Behavioral Therapy for Insomnia: How It Works & What to Expect

Common CBT Techniques and Tools for Insomnia

1. Keeping a sleep diary
2. Stimulus control
3. Promoting sleep hygiene
4. Sleep restriction therapy
5. Cognitive therapy
6. Relaxation training
7. Paradoxical intention

CHOOSING *therapy*

Educate: explore beliefs, set goals

Work with natural sleep drive to improve sleep

Use strategies to reduce barriers to sleep

SLEEP LOG

|								
DAY OF THE WEEK	Monday							
CALENDAR DATE	3/25/96							
1. Yesterday I napped from___to___(note time of all naps).	1:30-2:45 PM							
2. Last night I took____mg. of ____ or____of alcohol as a sleep aid.	Ambien 5 mg.							
3. Last night I turned off the lights and attempted to fall asleep at_____ (AM or PM?)	11:30 PM							
4. After turning off the lights it took me about ___ minutes to fall sleep.	40 Min.							
5. I woke from sleep_____times. (Do not count your final awakening here)	2 Times							
6. My awakenings lasted _____ minutes. (List each awakening separately.	25 Min. 40 Min.							
7. Today I woke up at_____(AM or PM?) NOTE this is your final awakening.	6:30 AM							
8. Today I got out of bed for the day at ___ (AM or PM?).	7:15 AM							
9. I would rate the quality of last night's sleep as: 1 = very poor 4 = good; 2 = poor 5 = excellent; 3 = fair.	3							
10. When I awoke today I felt: 1 = not all rested 4 = rested; 2 = slightly rested 5 = well rested; 3 = somewhat rested	2							

Sleep Restriction

- Rationale
  - Most patients with insomnia spend too much time in bed
    - Decreases drive to sleep

- General strategy
    - Measure sleep efficiency (time asleep/time in bed).
      - Attempt to match them, **goal 85-90%**
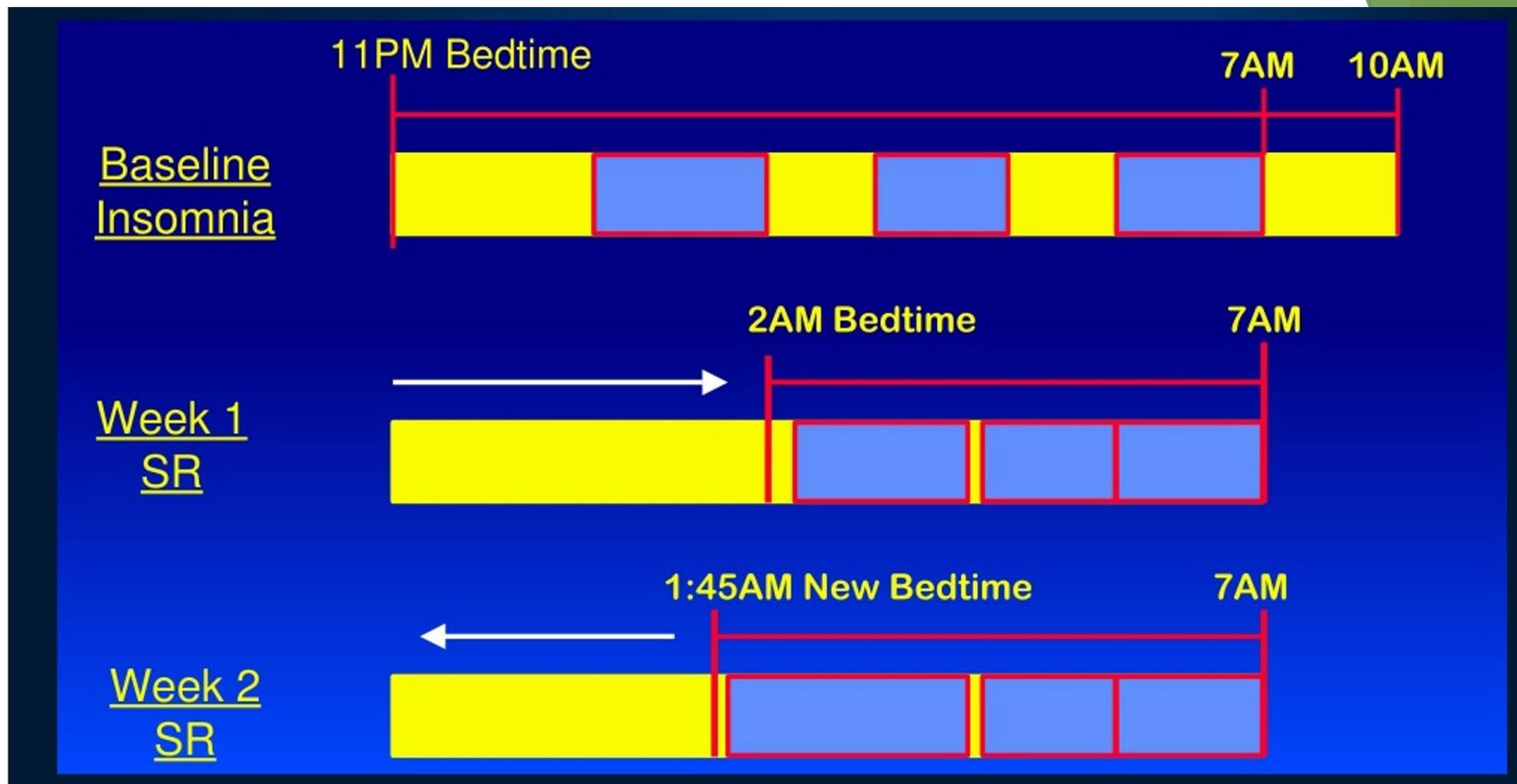
- If <85%, match time in bed with time asleep. Use wake up time as end point.
- Once >85%, increase sleep time by 15minutes every 5 days as long as stays >85%

Effect of smartphone-based cognitive behavioral therapy app on insomnia: a randomized, double-blind study

Yosuke Watanabe [1], Taiyo Kuroki [1], Daisuke Ichikawa [1], Motohiro Ozone [2], Naohisa Uchimura [2], Taro Ueno [1]
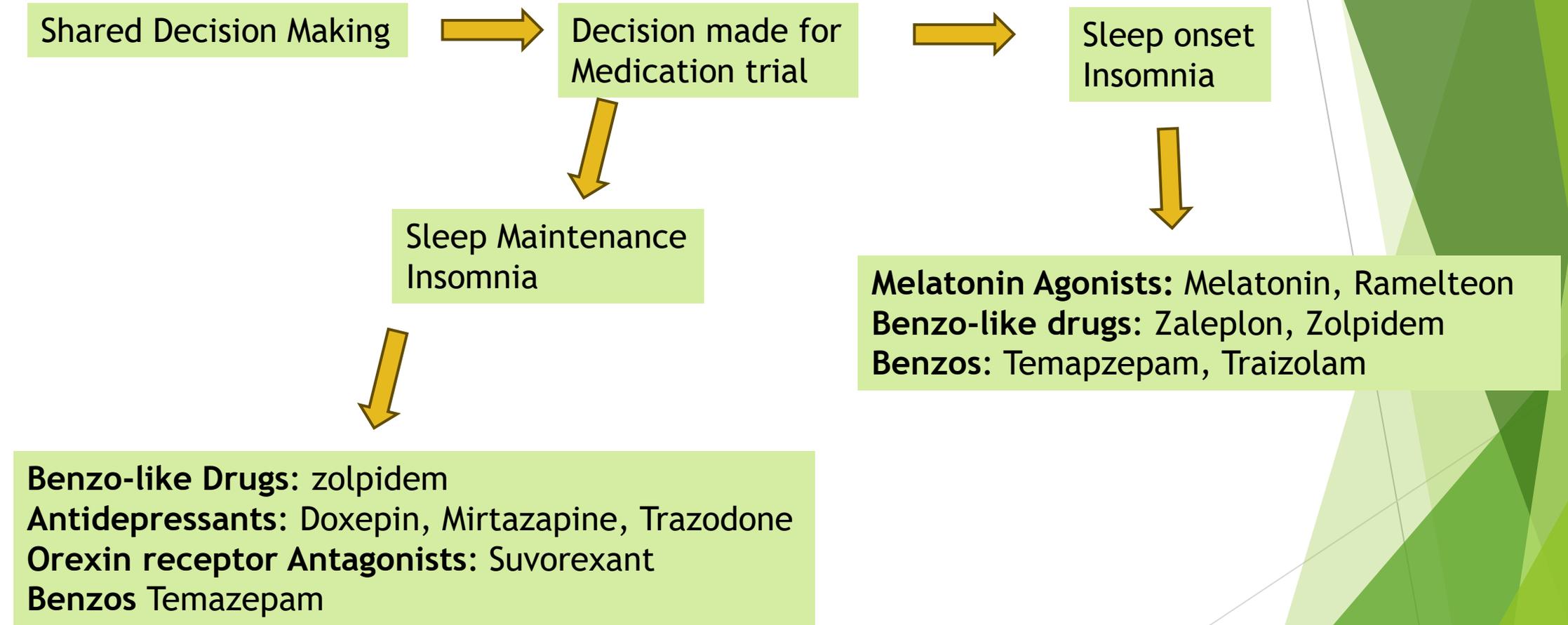
Affiliations + expand

Abstract

- Sleepio: 6week program, $$$$
- CBTi Coach Free

CBT-I in OUD

- One small study showed significant improvement in patients with insomnia with CBT-I.

- Small study (n=22): Outpatient MOUD program

  - CBT-I vs Standard of care. CBT-I very effective but barriers including sustainability/scalability

Pharmacotherapy

Shared Decision Making → Decision made for Medication trial → Sleep onset Insomnia

Decision made for Medication trial → Sleep Maintenance Insomnia

Sleep onset Insomnia →

Melatonin Agonists: Melatonin, Ramelteon
Benzo-like drugs: Zaleplon, Zolpidem
Benzos: Temapzepam, Traizolam

Sleep Maintenance Insomnia →

Benzo-like Drugs: zolpidem
Antidepressants: Doxepin, Mirtazapine, Trazodone
Orexin receptor Antagonists: Suvorexant
Benzos Temazepam

AASM Recs

Table 5—Summary of "critical" outcomes by indication.

Recommended for Treating Sleep Onset Insomnia	
Eszopiclone	**Sleep latency:** Mean reduction was 14 min greater, compared to placebo (95% CI: 3 to 24 min reduction); **Quality of sleep*:** Moderate-to-Large[a] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 2, "Harms" *This recommendation is based on trials of 2 mg and 3 mg doses of eszopiclone.*
Ramelteon	**Sleep latency:** Mean reduction was 9 min greater, compared to placebo (95% CI: 6 to 12 min reduction); **Quality of sleep*:** No improvement[b] in quality of sleep, compared to placebo; **Side effects:** See Recommendation 7, "Harms" *This recommendation is based on trials of 8 mg doses of ramelteon.*
Temazepam	**Sleep latency:** Mean reduction was 37 min greater, compared to placebo (95% CI: 21 to 53 min reduction); **Quality of sleep*:** Small[a] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 6, "Harms" *This recommendation is based on trials of 15 mg doses of temazepam.*
Triazolam	**Sleep latency*:** Mean reduction was 9 min greater, compared to placebo (95% CI: 4 to 22 min reduction); **Quality of sleep*:** Moderate[c] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 5, "Harms" *This recommendation is based on trials of 0.25 mg doses of triazolam.*
Zaleplon	**Sleep latency:** Mean reduction was 10 min greater, compared to placebo (95% CI: 0 to 19 min reduction); **Quality of sleep*:** No improvement[b] in quality of sleep, compared to placebo; **Side effects:** See Recommendation 3, "Harms" *This recommendation is based on trials of 5 mg and 10 mg doses of zaleplon.*
Zolpidem	**Sleep latency:** Mean reduction was 5–12 min greater, compared to placebo (95% CI: 0 to 19 min reduction); **Quality of sleep*:** Moderate[a] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 4, "Harms" *This recommendation is based on trials of 10 mg doses of zolpidem.*

AASM Recs

	Recommended for Treating Sleep Maintenance Insomnia
Doxepin	**Total sleep time:** Mean improvement was 26–32 min longer, compared to placebo (95% CI: 18 to 40 min improvement); **Wake after sleep onset:** Mean reduction was 22–23 min greater, compared to placebo (95% CI: 14 to 30 min reduction); **Quality of sleep*:** Small-to-moderate[a] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 8, "Harms" *This recommendation is based on trials of 3 mg and 6 mg doses of doxepin.*
Eszopiclone	**Total sleep time:** Mean improvement was 28–57 min longer, compared to placebo (95% CI: 18 to 76 min improvement); **Wake after sleep onset:** Mean reduction was 10–14 min greater, compared to placebo (95% CI: 2 to 18 min reduction); **Quality of sleep*:** Moderate-to-Large[a] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 2, "Harms" *This recommendation is based on trials of 2 mg and 3 mg doses of eszopiclone.*
Temazepam	**Total sleep time:** Mean improvement was 99 min longer, compared to placebo (95% CI: 63 to 135 min improvement); **Wake after sleep onset:** Not reported; **Quality of sleep*:** Small[a] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 6, "Harms" *This recommendation is based on trials of 15 mg doses of temazepam.*
Suvorexant	**Total sleep time:** Mean improvement was 10 min longer, compared to placebo (95% CI: 2 to 19 min improvement); **Wake after sleep onset:** Mean reduction was 16–28 min greater, compared to placebo (95% CI: 7 to 43 min reduction); **Quality of sleep*:** Not reported; **Side effects:** See Recommendation 1, "Harms" *This recommendation is based on trials of 10, 15/20, and 20 mg doses of suvorexant.*
Zolpidem	**Total sleep time:** Mean improvement was 29 min. longer, compared to placebo (95% CI: 11 to 47 min. improvement); **Wake after sleep onset:** Mean reduction was 25 min greater, compared to placebo (95% CI: 18 to 33 min reduction); **Quality of sleep*:** Moderate[a] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 4, "Harms" *This recommendation is based on trials of 10 mg doses of zolpidem.*

AASM Not Recommended

	Not Recommended for Treating either Sleep Onset or Sleep Maintenance Insomnia
Diphenhydramine	**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" *This recommendation is based on trials of 50 mg doses of diphenhydramine.*
Melatonin	**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" *This recommendation is based on trials of 2 mg doses of melatonin.*
Tiagabine	**Total sleep time:** Mean improvement was 1–7 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" *This recommendation is based on trials of 4 mg doses of tiagabine.*
Trazodone	**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" *This recommendation is based on trials of 50 mg doses of trazodone.*
L-tryptophan	**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" *This recommendation is based on trials of 250 mg doses of tryptophan.*
Valerian	**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" *This recommendation is based on trials of variable dosages of valerian and valerian-hops combination.*

Medications

-
  - Benadryl
    - CONS: next day grogginess, rapid tolerance, anticholinergic effects
  - Hydroxyzine (Vistaril, Atarax)
    - Initial insomnia
    - CONS: next day sedation
  - Doxylamine (NyQuil):
    - Similar to benadryl in efficacy and side effects

- Sedating Antidepressants
  - Trazodone
    - PROS: relatively safe in all age groups
    - CONS: priapism, orthostasis, dry mouth
  - Mirtazapine (Remeron)
    - PROS: good for patients who feel like their minds are active at night; useful in treating anxiety and depression; less risk of sexual dysfunction
    - CONS: weight gain, orthostasis, dry mouth
  - Doxepin (Silenor)
    - PROS:, it is an effective hypnotic with relatively few anticholinergic side effects
    - CONS: expensive if you use 3 or 6mg dose
  - Amitriptyline (Elavil)
    - PRO's: can be helpful for pain and migraine disorders
    - CONS: anticholinergic and cardiovascular effects

Samhsa.gov

Medications

- Melatonin Receptor Agonists
- Melatonin & Remelteon (Rozerem)
  - Mimics physiological melatonin produced by pineal gland: blood levels rise at sunset & peak in the middle of the night
  - Reproduces the homeostatic drive toward sleep
  - Greater benefit than placebo at improving insomnia in individuals with sleep onset difficulties
  - CONS: not sedating (in and of itself) – doesn't work immediately
- Ramelteon (Rozerem):
  - Outperformed placebo in clinical trials
  - No next day sedation

- Other
- Gabapentin (Neurontin)
  - CONS: risk of misuse; possibility of respiratory ataxia, weight gain
  - PROS: good for sleep maintenance and RLS; shorter half life than antihistamines →less risk of next day sedation
- Clonidine
- Seroquel
  - PROS: helpful for comorbid anxiety disorder (especially treatment refractory anxiety) and mood disorder (esp bipolar)
 - CONS: metabolic syndrome (possibly less likely at lower doses), increased appetite and weight gain (at any dose)

Medications

-
- Bind selectively to specific subunits on the GABA receptor that induces sleep but does not provide the same anxiolytic effects as benzos
  - Alpha 1 subunit – responsible for sedating effect
- Eszopiclone (Lunesta) -chronic
- Zaleplon (Sonata)-initial insomnia
  - Good for patients with initial insomnia
- Zolpidem (Ambien)-acute insomnia
- **Recommend prescribing half max dose in women**
  - The FDA has noted that zolpidem blood levels above 50 ng/mL appear capable of impairing driving to a degree that increases accident risk. The FDA found that 15% of women and 3% of men had zolpidem concentrations exceeding 50 ng/mL 8 hours after taking 10 mg of zolpidem

- Benzos
- FDA approved: Triazolam (1.5-5.5h), Temazepam (9-18h), Estazolam (15-30h), Quazepam (24-150h), Flurazepam (40-100h)
- Not FDA-approved but still used: Clonazepam (20-80h), Lorazepam (10-20h)
- PROS:
  - Effective in helping with insomnia?
  - Provides some anxiolytic benefit and antidepressant benefits
- CONS:
  - Falls, hang-over effects, cognitive effects; and possible dementia especially in the elderly (although causal relationship has not been proven)
  - Concerns that it may worsen depression over the long term
  - Dependence, addiction
  - Respiratory depression-problems with osa/oxygen
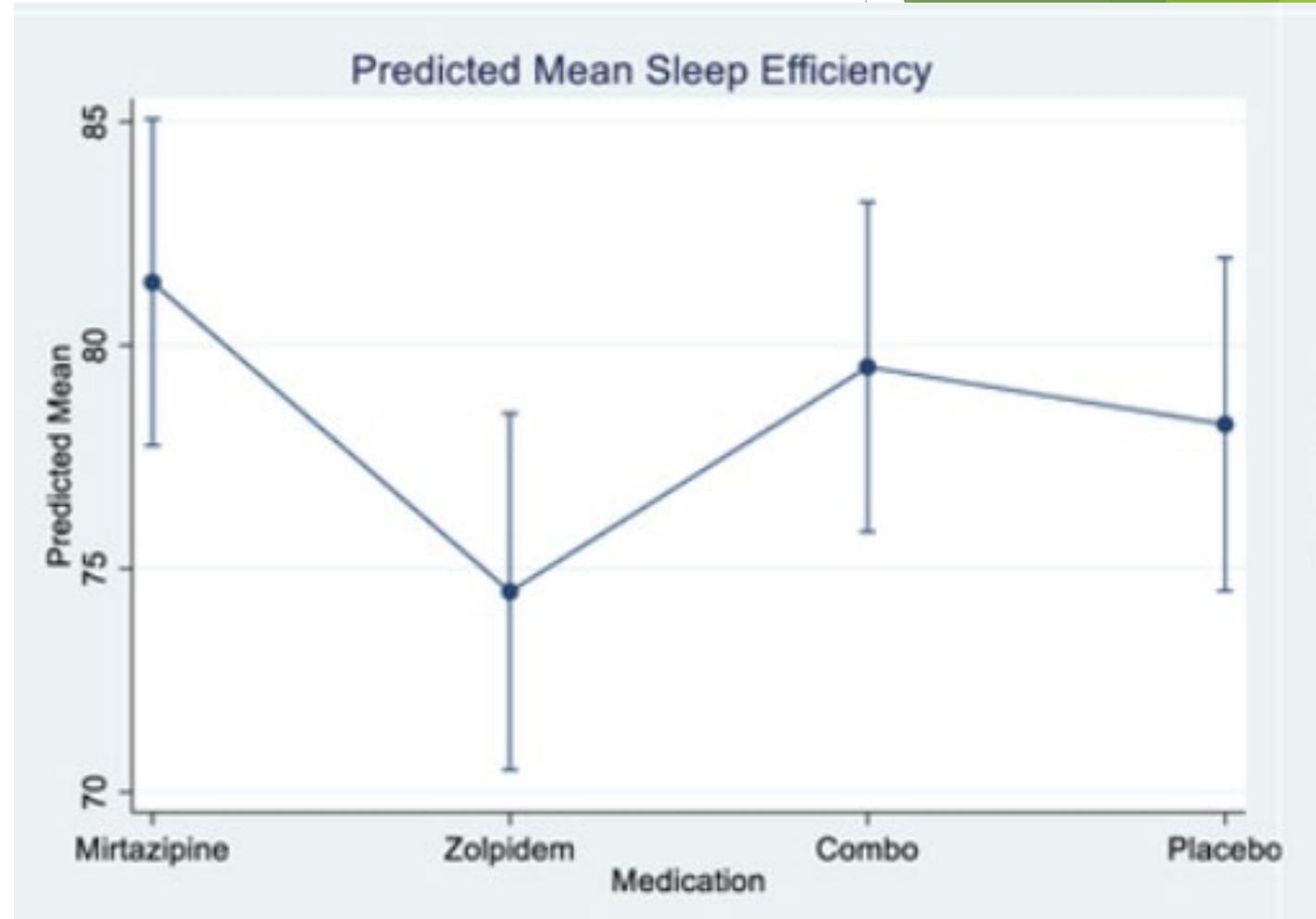 - Risk of overdose and death (especially when used with opioids)

Orexin Antagonists

- Suvorexant (Bellsomra)

- Lemborexant (Dayvigo) – released 2020

- PROS: no daytime sedation, good for initiation and maintenance of sleep

- CONS: unclear if any issues due to long-term use; EXPENSIVE/insurance?

Orexin Neurons

BELSOMRA targets and inhibits orexin
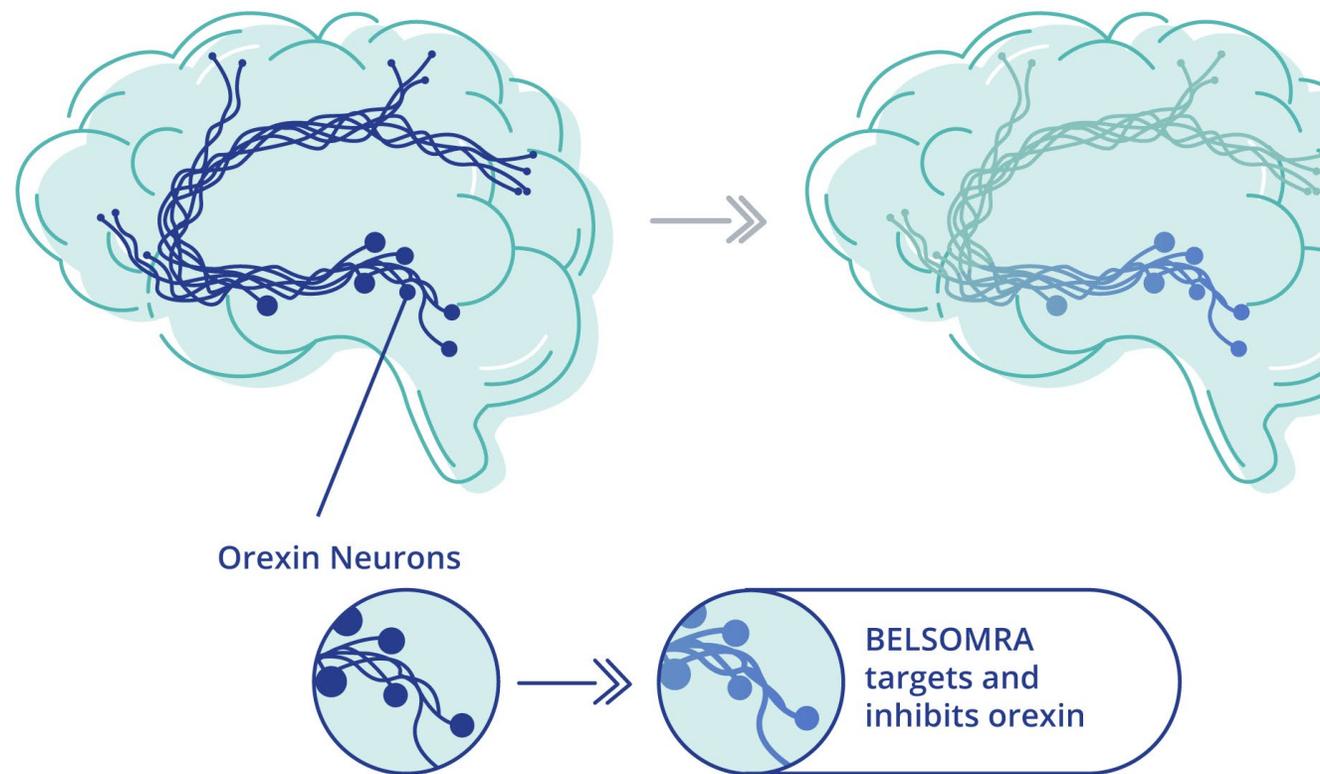
Which medications have been studied in patients with OUD?

- Small randomized, double blind
  - N=10
  - Medication vs placebo over 1week periods
    - Zolpidem
    - Mirtazapine
    - Zolpidem +mirtaz
    - Placebo

Predicted Mean Sleep Efficiency

Stein et al. A pilot trial of sleep medications for sleep-disturbed methadone maintenance patients. JAM. 2020

Trazodone

- Stein 2012

- Methadone patients randomized to Trazodone 50mg or placebo. Allowed to self titrate to 150mg

- N=137, 3 months

- No significant difference

	Mean (SD)			
	Total (n = 137)	Placebo (n = 68)	Trazodone (n = 69)	t (p =)
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)

Melatonin

- Ghaderi 2018
  - N=28 randomized to melatonin or placebo x12 weeks
  - No significant sleep improvements

Ghaderi A, Banafshe HR, Mirhosseini N, Motmaen M, Mehrzad F, Bahmani F, Aghadavod E, Mansournia MA, Reiter RJ, Karimi MA, Asemi Z. The effects of melatonin supplementation on mental health, metabolic and genetic profiles in patients under methadone maintenance treatment. Addict Biol. 2019 Jul;24(4):754-764. doi: 10.1111/adb.12650. Epub 2018 Jun 27. PMID: 29949232.

Orexin Antagonist

- Suvorexant
  - Med vs placebo double-blind, randomized
  - N=38 patients with OUD
  - 60minutes improvement in sleep time/night!
  - $$

Suvorexant=sleep maintenance

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

TREATING SLEEP PROBLEMS OF PEOPLE IN RECOVERY FROM SUBSTANCE USE DISORDERS

▶ Non pharm #1

▶ Meds

   ▶ Doxepine, Mirtazapine, Trazodone,

   ▶ Avoid benzos

   ▶ Z drugs-short term, monitor for abuse potential

American Academy of Sleep Medicine recommended pharmacologic agents for the treat of insomnia in adults

Drug name (generic/brand)	Drug class (primary mechanism of action)	Evidence for improving sleep onset parameters	Evidence for improving sleep maintenance parameters	Risks of harm & common side effects	Pregnancy category/ Evidence of use in lactation	Clinical trial findings among patients receiving MOUD to treat insomnia
Zolpidem 10mg	BZD receptor agonist (non-BZD sedative hypnotic)	Significant	Significant	benefit > harm (amnesia confusion, somnambulance)	Cat. B/ preferred; low levels; rapid elimination from milk; breastfeed before dose	poor sleep outcomes (worse than placebo & other medication protocols)
Suvorexant 10, 15, 20mg	Dual Orexin Receptor Antagonist	Minimal	Significant	benefit > harm (diarrhea, dizziness, headache, abnormal dreams)	Cat. C/ unknown; consider alternate or monitor infant if mother needs med	↑ total sleep time
Doxepin 3, 6mg	Tricyclic Antidepressant	Minimal	Significant	benefit > harm (blurry vision, HTN, constipation, urinary retention	Cat C/ avoid in breastfeeding	may be useful; ↓ sleep disturbance observed
Ramelteon 8mg	Melatonin Receptor Agonist	Significant	Minimal	benefit > harm dizziness, dysgeusia, fatigue, insomnia	Cat C/ low levels in milk; consider alternate or monitor older infant	NA
Eszopiclone 2, 3mg	BZD receptor agonist/ (non-BZD sedative hypnotic)	Significant	Significant	benefit > harm (headache, dysgeusia, drowsiness)	Cat C/ unknown; consider alternate or monitor older infant	NA
Zaleplon 10mg	BZD receptor agonist/ (non-BZD sedative hypnotic)	Significant	Minimal	benefit > harm (headache, n/v, abd pain, weakness)	Cat C/ unknown; not recommended during lactation	NA
Temazepam 15mg	Benzodiazepine	Significant	Significant	benefit > harm (anxiety, confusion, lethargy)	Cat X/ low levels in milk; breastfeed before mother's dose	NA
Triazolam 0.25mg	Benzodiazepine	Significant	Significant	benefit = harm (headache, dizziness, n/v)	Cat X/ unknown; consider alternate or monitor older infant	NA

Medications **not recommended** by the American Academy of Sleep Medicine for the treat of insomnia in adults

Drug name (generic/brand)	Drug class (primary mechanism of action)	Evidence for improving sleep onset parameters	Evidence for improving sleep maintenance parameters	Risks of harm & common side effects	Pregnancy category/ Evidence of use in lactation	Clinical trial findings among patients receiving MOUD to treat insomnia
Diphenhydramine 50mg	1st Gen Antihistamine	Minimal	Minimal	benefit = harm (blurry vision, urinary retention)	Cat. B/ minimize dose/ frequency; larger dose may ↓milk supply	NA
Melatonin 2mg	OTC Supplement– Agonizes melatonin receptors	Minimal	Minimal	benefit = harm (headache, nausea)	n/a; naturally in breastmilk; no data on safety of OTC use	improved subjective sleep quality
Tiagabine 4mg	Antiepileptic	N/A (min-mod worsening)	N/A (min-mod worsening)	harm > benefit (dizziness, lack of concentration, weakness, tremor)	Cat. C/ unknown; consider alternate	NA
Trazodone 50mg	Serotonin Modulator (receptor antagonist + reuptake inhibitor)	Minimal	Minimal	harm > benefit (headache, fatigue)	Cat. C/ use cautiously; low levels in milk	no improvement vs placebo
L-tryotophan 250mg	OTC Supplement (amino acid)	Minimal	Minimal	harm > benefit (abd pain, N/V/D)	n/a; naturally in breastmilk- no data on safety of OTC use	NA
Valerian variable dosages	OTC Supplement	Minimal	Minimal	benefit = harm (headache, GI upset, dizziness)	n/a; not recommended during lactation	NA

Other medications used to treat insomnia, not included in AASM recommendations

Drug name (generic/brand)	Drug class (primary mechanism of action)	Evidence for improving sleep onset parameters	Evidence for improving sleep maintenance parameters	Risks of harm & common side effects	Pregnancy category/Evidence of use in lactation	Clinical trial findings among patients receiving MOUD to treat insomnia
Mirtazapine	Tetracyclic Antidepressant	Significant	Significant	harm > benefit (↑weight/ ↑lipids, dry mouth)	Cat. C; use cautiously; low levels in milk	superior to zolpidem in all measures of sleep quality
Gabapentin	Antiepileptic	Significant	Significant	harm> benefit (dizziness, fatigue, peripheral edema)	Cat. C; use cautiously	improved sleep in patients on naltrexone
Hydroxyzine	1st Gen Antihistamine	Minimal	Minimal	benefit = harm (drowsiness, dry mouth)	Cat. C; low dose or use other med	NA
Quetiapine	2nd Gen Antipsychotic	Minimal	Minimal	harm> benefit (↑weight, lipids, BP; orthostasis)	Cat. C/ use possible if mother needs 2nd Gen antipsychotic	NA

*MOUD: methadone, buprenorphine, naltrexone

Take Aways

- Treat as own diagnosis
- Important for all patients including patients with SUD history
- CBT-I #1 and has some easy starter items
- Medications
  - Doxepin, Mirtazapine, Ramelteon, Orexin antagonists
  - Gabapentin, Lyrica, Trazodone
  - 2nd line: Meds with abuse potential
    - Short term treatment best
    - Risks/benefits

Patient Resources

- Mysleepwell.ca
  - Patient handouts
    - 10tips to better sleep
    - CBTi vs medication
- Deprescribing.org
  - Patient handouts and provider education

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The enemy of sleep