TREATMENTS FOR CHRONIC INSOMNIA

Alex Hu, MD

Image Credit: https://www.theguardian.com/society/2020/aug/02/coronavirus-lockdown-increase-insomnia-uk-sleep-mothers

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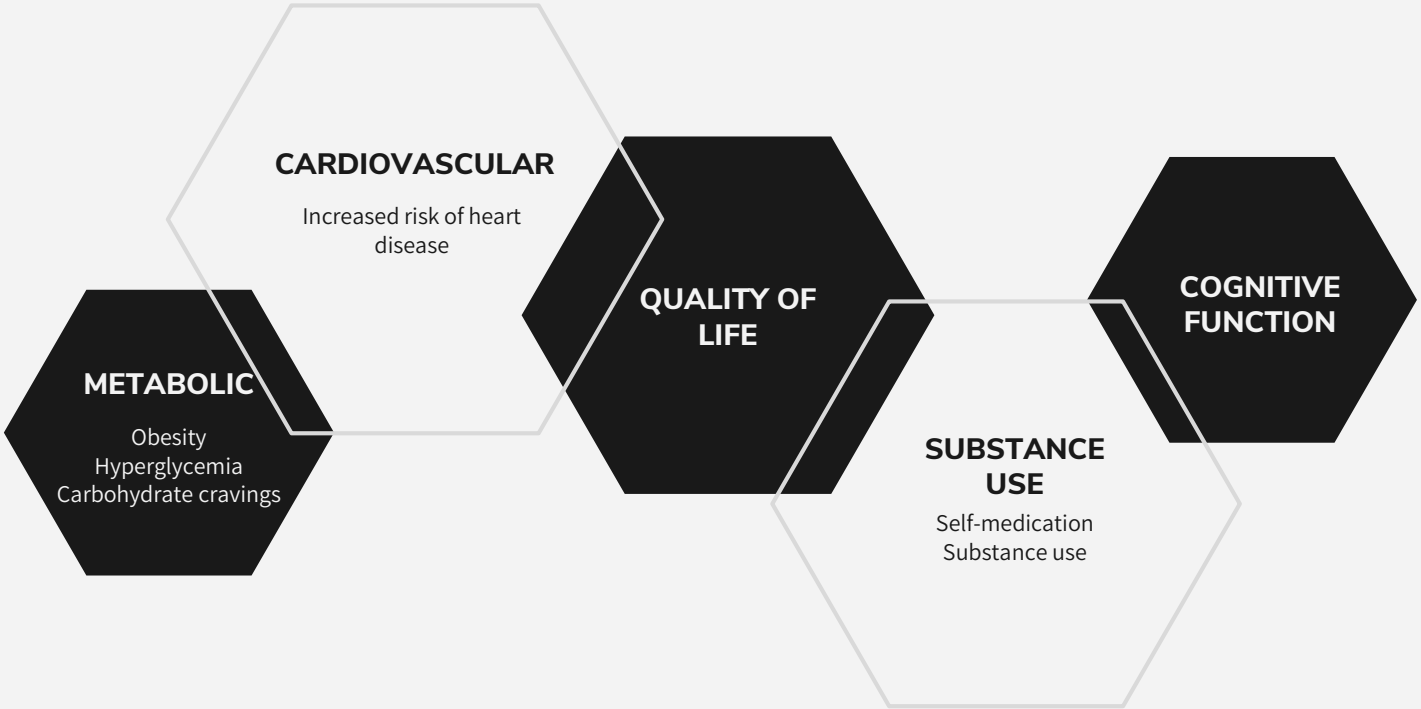
DIAGNOSTIC CRITERIA

International Classification of Sleep Disorders (ICSD-3)

- Difficult initiating or maintaining sleep, or waking up too early
- Despite adequate opportunity and circumstances for sleep
- Causes daytime impairment
- Not better explained by another sleep disorder

Source: American Academy of Sleep Medicine. International Classification of Sleep Disorders, 3rd ed, American Academy of Sleep Medicine, Darien, IL 2014.

ADVERSE OUTCOMES



Please refer to **Dr. Maurer's presentation** on Medhub 4/22/2020

SLEEP HYGIENE

Last hour before bed is “wind-down” time. Can have a light snack during this time.

Eat regular meals every day

Limit liquid consumption to 8-10 oz in the evening

Avoid caffeinated products and alcohol several hours before bedtime

Quiet, dark, and cool room environment (typically 65°F)

Exercise regularly, but avoid activities that increase body temperature within 1.5 hours of bed

Avoid negative stimuli at bedtime (noises, lights, temperature variations)

SLEEP HYGIENE

Recommendation: Clinicians not use sleep hygiene as single-component therapy, but may be included in multicomponent interventions

Sleep latency

Table S74. Diary-determined sleep latency (minutes), post treatment differences, sleep hygiene vs. control

Study	Delivery method	Sleep hygiene			Control			Mean Difference, [95% CI]
		Mean	SD	Total	Mean	SD	Total	
Edinger 2005	In-person delivery	15.1	11.13	17	15.9	16.8	9	-0.80 [-12.98, 11.38]

Wake after sleep onset

Table S75. Diary-determined WASO (minutes), post treatment differences, sleep hygiene vs. control

Study	Delivery method	Sleep hygiene			Control			Mean Difference, [95% CI]
		Mean	SD	Total	Mean	SD	Total	
Edinger 2005	In-person delivery	50.5	28.4	17	65.7	31.2	9	-15.20 [-39.65, 9.25]

Total sleep time

Table S82. Diary-determined total sleep time (minutes), post treatment differences, sleep hygiene vs. control.

Study	Delivery method	Sleep hygiene			Control			Mean Difference, [95% CI]
		Mean	SD	Total	Mean	SD	Total	
Edinger 2005	In-person delivery	424.8	61.85	17	432.5	54.3	9	-7.70 [-53.78, 38.38]

Table S83. Actigraphy-determined total sleep time (minutes), post treatment differences, sleep hygiene vs. control

Study	Delivery method	Sleep hygiene			Control			Mean Difference, [95% CI]
		Mean	SD	Total	Mean	SD	Total	
Edinger 2005	In-person delivery	421.6	51.13	17	428.7	78.3	9	-7.10 [-63.74, 49.54]

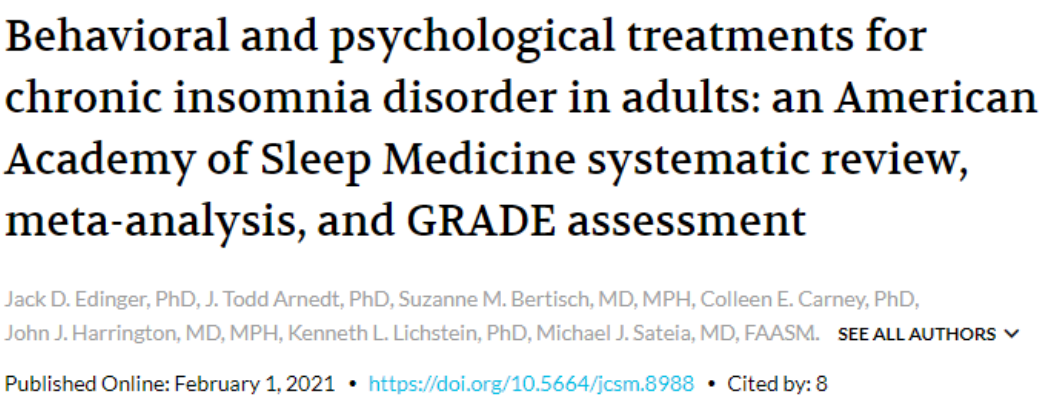
Source: Edinger JD, Wohlgemuth WK, Krystal AD, Rice JR. Behavioral Insomnia Therapy for Fibromyalgia Patients: A Randomized Clinical Trial. *Arch Intern Med.* 2005;165(21):2527–2535. doi:10.1001/archinte.165.21.2527

CBT-I

- **American College of Physicians**
  - All adult patients receive CBT-I as the initial treatment for chronic insomnia disorder **(strong)**
  - Clinicians use a shared decision-making approach to decide whether to add pharmacologic therapy in adults in whom CBT-I was unsuccessful **(weak)**
- **American Academy of Sleep Medicine**
  - Clinicians use multicomponent CBT-I for treatment of chronic insomnia disorders in adults **(strong)**

CBT-I

- Meta-analysis of 49 randomized control trials showed clinically significant improvements in remission and responder rates with CBT-I compared to controls
- Improvements in **sleep latency** (12.68 minutes lower versus control) and **wake after sleep onset** (18.96 minutes lower), **insomnia severity**, **total wake time** (39.6 minutes lower)
- Treatment gains are potentially durable over the long term without need for additional interventions and with minimal side effects



Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment

Jack D. Edinger, PhD, J. Todd Arnedt, PhD, Suzanne M. Bertisch, MD, MPH, Colleen E. Carney, PhD, John J. Harrington, MD, MPH, Kenneth L. Lichstein, PhD, Michael J. Sateia, MD, FAASM. SEE ALL AUTHORS

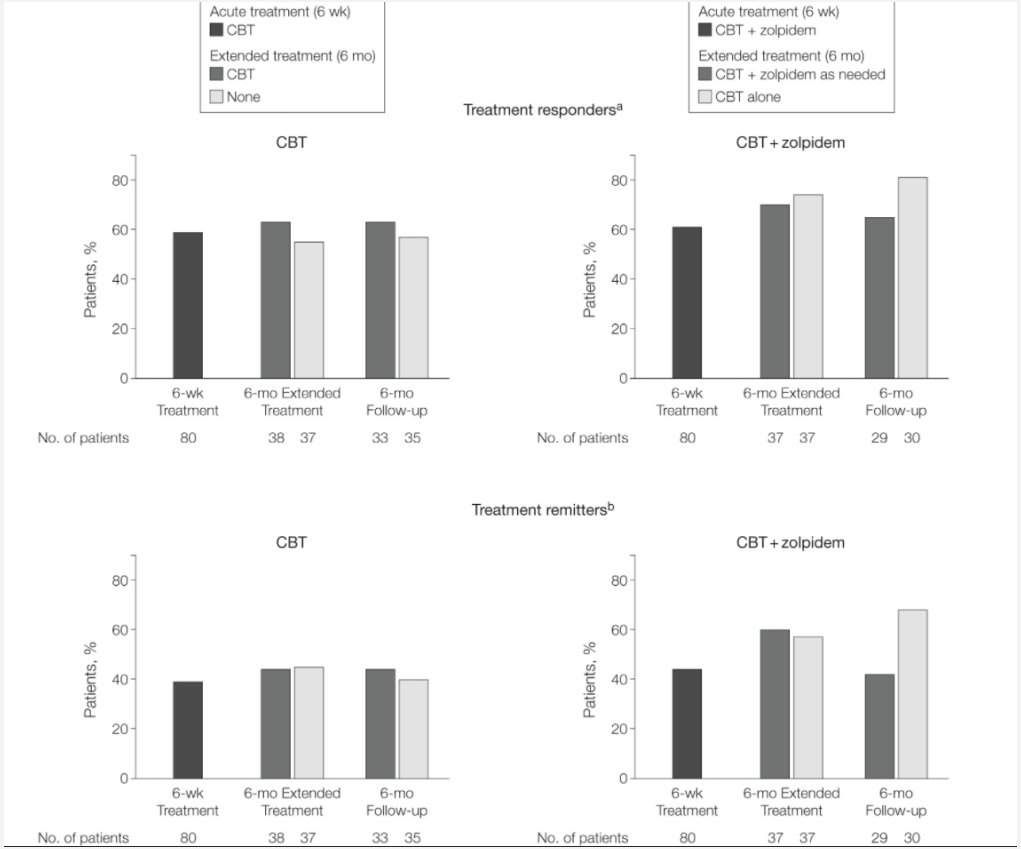
Published Online: February 1, 2021 • https://doi.org/10.5664/jcsm.8988 • Cited by: 8

Source: Edinger JD, Arnedt JT, Bertisch SM, Carney CE, Harrington JJ, Lichstein KL, Sateia MJ, Troxel WM, Zhou ES, Kazmi U, Heald JL, Martin JL. Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. J Clin Sleep Med. 2021 Feb 1;17(2):263-298. doi: 10.5664/jcsm.8988. PMID: 33164741; PMCID: PMC7853211.

CBT, Singly and Combined with Medication for Persistent Insomnia

JAMA, 2009

- CBT (with or without zolpidem 10mg) increased sleep latency, WASO, and efficiency
- Combined with larger increase in TST
- Best long-term outcome obtained with combined therapy, followed by CBT alone

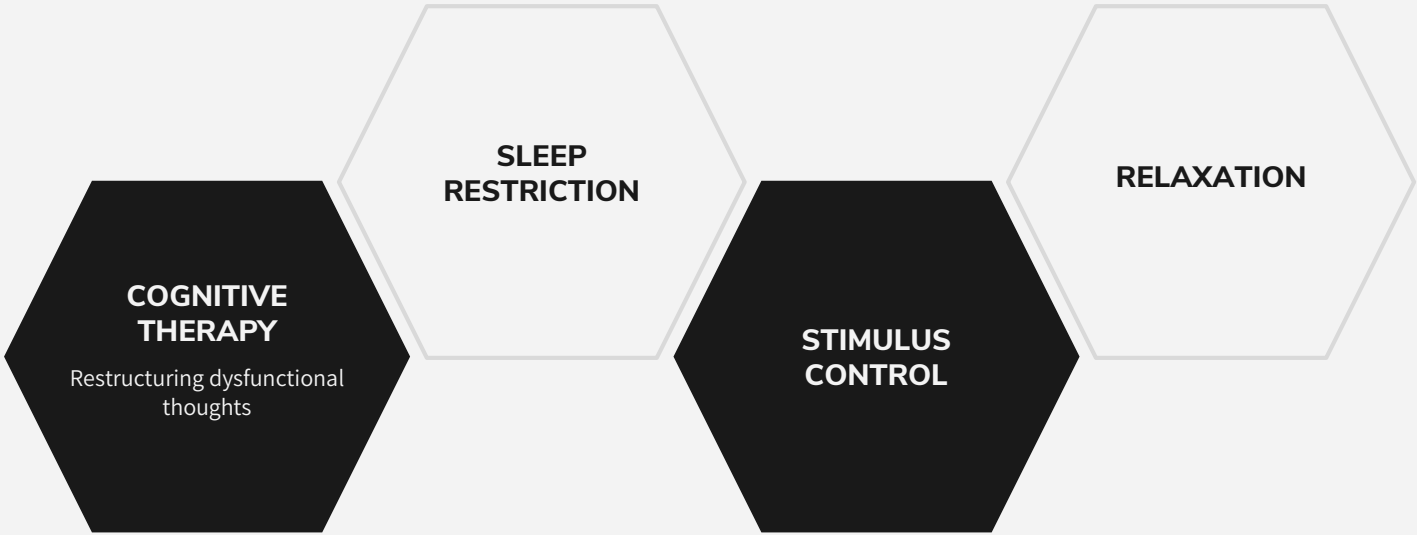


Source: Morin CM, Vallières A, Guay B, et al. Cognitive Behavioral Therapy, Singly and Combined With Medication, for Persistent Insomnia: A Randomized Controlled Trial. *JAMA*. 2009;301(19):2005–2015. doi:10.1001/jama.2009.682

WHAT IS CBT-I?

- CBT-I is a **multicomponent** approach that addresses common thoughts and behaviors that interfere with optimal sleep
- Delivered face-to-face through individual or group sessions, or remotely (online, telephone)
- Typical program lasts about 6 weeks, through 4 to 10 one-hour sessions

MULTICOMPONENT

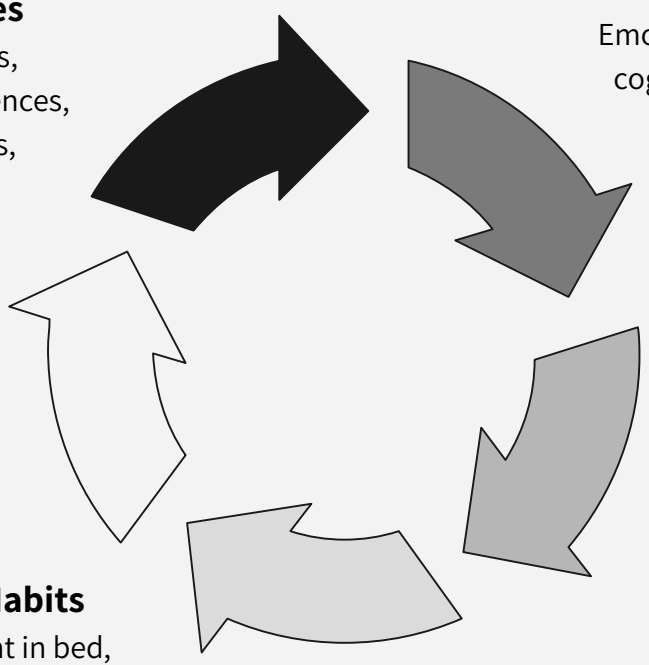


Source: Edinger JD, Arnedt JT, Bertisch SM, Carney CE, Harrington JJ, Lichstein KL, Sateia MJ, Troxel WM, Zhou ES, Kazmi U, Heald JL, Martin JL. Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2021 Feb 1;17(2):255-262. doi: 10.5664/jcsm.8986. PMID: 33164742; PMCID: PMC7853203.

BREAKING THE CYCLE

Beliefs and Attitudes
Worrying over sleep loss, wondering about consequences, unrealistic expectations, misattributions

Arousal
Emotions such as fear or sadness, cognitive thoughts, physiologic reactions



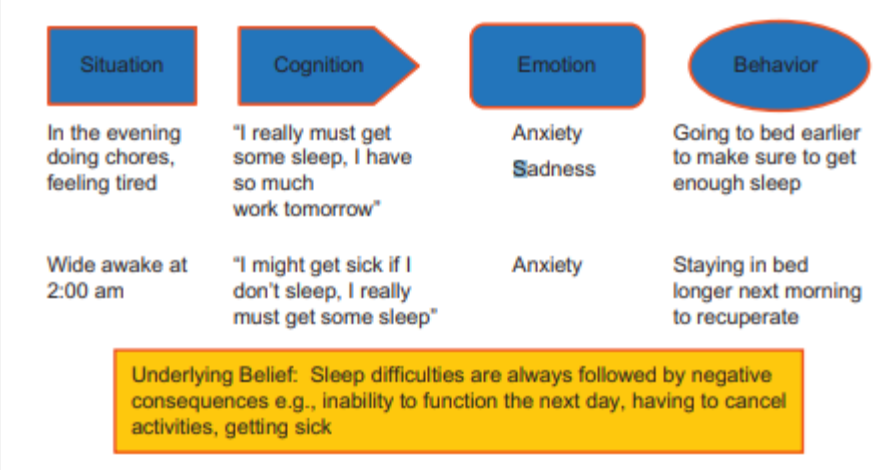
Consequences
Fatigue, performance impairments, mood disturbance, anxiety

Maladaptive Habits
Excessive time spent in bed, irregular sleep schedule, daytime napping, self-medication

Source: https://www.med.upenn.edu/cbti/assets/user-content/documents/Morin_CognitiveTherapyforDysfunctionalBeliefsaboutSleepandInsomnia_BTSD.pdf

COGNITIVE THERAPY

- Identify dysfunctional thoughts, recognize connection between cognitions, emotions, and behaviors, examine the evidence for or against these thoughts, substitute more realistic interpretations, and modify core beliefs



Source: https://www.med.upenn.edu/cbti/assets/user-content/documents/Morin_CognitiveTherapyforDysfunctionalBeliefsaboutSleepandInsomnia_BTSD.pdf

COGNITIVE THERAPY

- Educate patients on role of cognitive processes in regulating emotions, physiologic arousal, and behavior
- Identify dysfunctional thoughts to eventually question their validity. **Home practice is highly important**

TABLE 11.1 Example of a Standard Three-column Automatic Thoughts Record Form

Situation (Specify Date and Time)	Automatic Thoughts (What was Going Through Your Mind?)	Emotions (Rate Each Emotion's Intensity on a Scale of 1–100%)
09/28 Watching TV in the evening	"I must sleep well tonight, I have so much work tomorrow"	Anxious (50%)
09/29 Lying in bed awake at 2 am	"This has to stop! I can't go on living like this. This is going to make me ill" "I have to get some sleep!"	Anxious (75%) Discouraged/sad (60%)

Source: https://www.med.upenn.edu/cbti/assets/user-content/documents/Morin_CognitiveTherapyforDysfunctionalBeliefsaboutSleepandInsomnia_BTSD.pdf

COGNITIVE THERAPY

- Encourage patients to view thoughts as only one of many possible interpretations
- Find alternatives by weakening the association between sleeplessness and negative thoughts that maintain an aroused state
- **Home practice continues to be important**

What is the evidence for and against this idea?

What makes you think this will happen?

What are the chances that this will happen?

What's the worst that could happen?

What are alternative ways of seeing the situation?

What is the most realistic outcome?

TABLE 11.2 Example of a Standard Five-column Automatic Thoughts Record Form

Situation (Specify Date and Time)	Automatic Thoughts (What was Going Through Your Mind?)	Emotions (Rate each Emotion's Intensity on a Scale of 1–100%)	Alternative Thoughts (How Can I See This Situation Differently?)*	Emotions (Rate Each Emotion's Intensity on a Scale of 1–100%)

Source: https://www.med.upenn.edu/cbti/assets/user-content/documents/Morin_CognitiveTherapyforDysfunctionalBeliefsaboutSleepandInsomnia_BTSD.pdf

SLEEP RESTRICTION THERAPY

- Sleep restriction therapy aims to make sleep opportunity equal to average total sleep time (determined by a sleep diary)
- Example: If you sleep an average of 6 hours nightly, and you have to wake up at 5am, you would start by going to sleep at 11pm for 1 week every day (including days off)
- Each week, time spent in bed is extended by 15 to 30 minutes as long as sleep efficiency is 85% or more. If sleep efficiency is less than 80% then time is further restricted

Clinical psychologist at UCSD: https://www.youtube.com/watch?v=DRiBGBB3kz0

Source: https://stanfordhealthcare.org/medical-treatments/c/cognitive-behavioral-therapy-insomnia/procedures/sleep-restriction.html

STIMULUS CONTROL AND RELAXATION THERAPY

STIMULUS CONTROL

Extinguish association between bedroom and wakefulness and restore its association with sleep

Establish a consistent wake-time

Go to bed only when sleepy, get out of bed when unable to sleep, use the bedroom for sleep and sex only, wake up the same time every morning, and refrain from daytime napping

RELAXATION THERAPY

Abdominal breathing, progressive muscle relaxation, autogenic training

Guided imagery training, meditation

Source: Edinger JD, Arnedt JT, Bertisch SM, Carney CE, Harrington JJ, Lichstein KL, Sateia MJ, Troxel WM, Zhou ES, Kazmi U, Heald JL, Martin JL. Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2021 Feb 1;17(2):255-262. doi: 10.5664/jcsm.8986. PMID: 33164742; PMCID: PMC7853203.

POTENTIAL HARMS

- Principal harms of CBT-I are daytime fatigue and sleepiness, mood impairment (i.e. irritability), cognitive difficulties (i.e. attention problems)
- Studies have shown that daytime sleepiness is increased and psychomotor performance impaired during the initial phases of sleep restriction therapy
- These typically occur in the early stages of treatment when behavioral therapies are introduced and are temporary

Source: Edinger JD, Arnedt JT, Bertisch SM, Carney CE, Harrington JJ, Lichstein KL, Sateia MJ, Troxel WM, Zhou ES, Kazmi U, Heald JL, Martin JL. Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2021 Feb 1;17(2):255-262. doi: 10.5664/jcsm.8986. PMID: 33164742; PMCID: PMC7853203.
Source: Kyle SD, Miller CB, Rogers Z, Siriwardena AN, Macmahon KM, Espie CA. Sleep restriction therapy for insomnia is associated with reduced objective total sleep time, increased daytime somnolence, and objectively impaired vigilance: implications for the clinical management of insomnia disorder. *Sleep*. 2014;37(2):229–237.

CBT-I RESOURCES

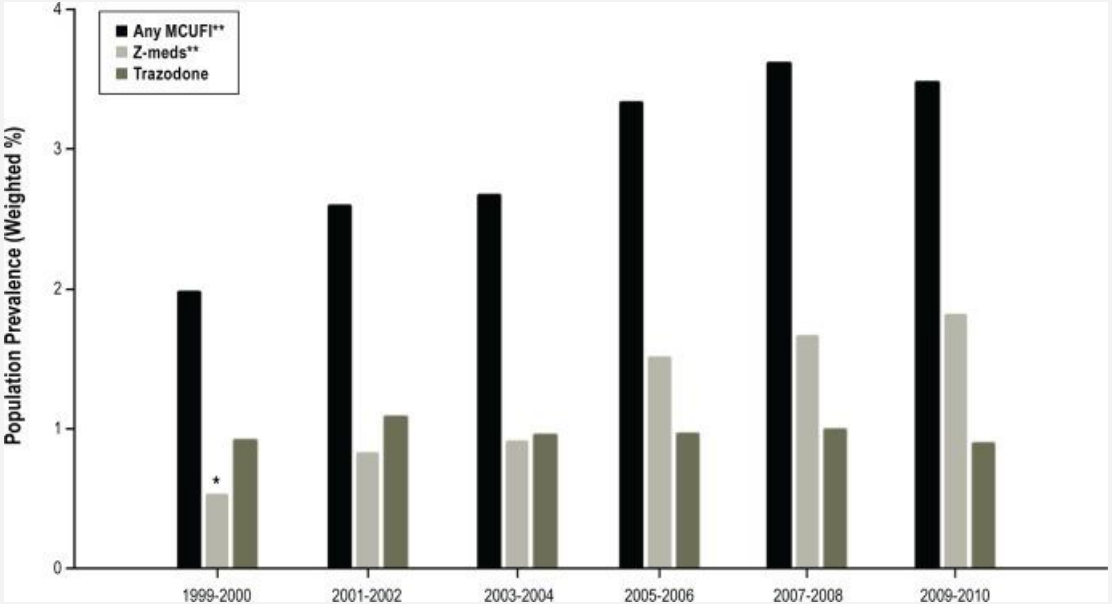
Resource	Description	Cost
CBT for Insomnia	5 session online CBT-I	$25 - 50
CBT I-Coach	Structured program from the VA that teaches strategies to improve sleep and help alleviate symptoms of insomnia	Free
Sleepio	Evidence based CBT-I online and mobile application	$300 for 12 months
SlumberPro	Self-help program requiring about 30-60 minutes daily, lasting 4-8 weeks	$40
Go To Sleep	6 week CBT-I program through Cleveland Clinic of Wellness	$3.99 for mobile application, $40 for website
SHUTi	6 week CBT-I program evaluated in 2 randomized control trials involving adults with insomnia and cancer survivors	$135 for 16 weeks
Mediation Oasis	Relax and rest guided meditation application	$2.79

OTHER THERAPIES

- AASM has **conditional recommendation** for use for brief therapies for insomnia (1-4 session CBT-I), or single component stimulus control, sleep restriction therapy, or relaxation therapy
- No recommendations for CBT alone, biofeedback, paradoxical intention, intensive sleep training, or mindfulness therapies

Source: Edinger JD, Arnedt JT, Bertisch SM, Carney CE, Harrington JJ, Lichstein KL, Sateia MJ, Troxel WM, Zhou ES, Kazmi U, Heald JL, Martin JL. Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2021 Feb 1;17(2):255-262. doi: 10.5664/jcsm.8986. PMID: 33164742; PMCID: PMC7853203.

PHARMACOLOGIC TREATMENTS



Evaluation of 32,328 participants using NHANES data from 1999-2010

Source: Bertisch SM, Herzig SJ, Winkelman JW, Buettner C. National use of prescription medications for insomnia: NHANES 1999-2010. *Sleep.* 2014;37(2):343-349. Published 2014 Feb 1. doi:10.5665/sleep.3410

SAFE PRESCRIBING PRACTICES

- Prescribe the lowest possible effective dosage
- Avoid combining with alcohol and other sedatives, including opiates
- Use with caution in older adults
- Use with caution in patients with renal and liver dysfunction
- Instruct patients on proper timing of medication in relation to desired sleep onset, and against use if insufficient time between planned bedtime and rise time
- Discuss side effects such as somnolence, daytime impairment, complex sleep-related behaviors
- Assess for suicidal ideation before prescribing, and monitor closely while treating insomnia
- Schedule regular follow-up to assess ongoing need for medication

PHARMACOLOGIC TREATMENTS

OREXIN RECEPTOR ANTAGONIST

Suvorexant
Lembrorexant

BZD RECEPTOR AGONISTS

Eszopiclone
Zaleplon
Zolpidem

BENZODIAZEPINES

Temazepam
Triazolam
Flurazepam
Estazolam
Quazepam

HETEROCYCLICS

Trazodone
Doxepin

OVER THE COUNTER

Diphenhydramine
Melatonin
L-tryptophan
Valerian

OTHER

Tiagabine
Ramelteon

Source: Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017 Feb 15;13(2):307-349. doi: 10.5664/jcsm.6470. PMID: 27998379; PMCID: PMC5263087.

PHARMACOLOGIC TREATMENTS

REGULATORY APPROVAL FOR INSOMNIA

Orexin Receptor Antagonists
Benzodiazepines
BZRAs
Histamine receptor antagonist
Melatonin receptor agonist

OFF-LABEL

Antidepressants
Antiepileptics
Antipsychotics
Antihypertensives
Anxiolytics

SLEEP ONSET

Eszopiclone
Zaleplon
Zolpidem
Triazolam
Temazepam
Ramelteon

SLEEP MAINTENANCE

Doxepin
Eszopiclone
Zolpidem
Temazepam
Suvorexant

Source: Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017 Feb 15;13(2):307-349. doi: 10.5664/jcsm.6470. PMID: 27998379; PMCID: PMC5263087.

OREXIN RECEPTOR ANTAGONISTS

Recommendation: We suggest clinicians use suvorexant as a treatment for sleep maintenance insomnia in adults

- **Examples:** Lembrorexant (5mg), Suvorexant (10mg)
- **Mechanism:** OX1R and OX2R antagonists. Orexin system promotes and stabilizes wakefulness.
- Improvements in all categories, but clinical significance only for WASO at the 10mg and 20mg dosages
- Harms: Studied in 2 primary RCTs, neither of which had a difference in adverse rates compared to placebo. Primary side effects are **somnolence** (dose-dependent)
- Contraindicated in narcolepsy but no evidence to point to emergence of symptoms

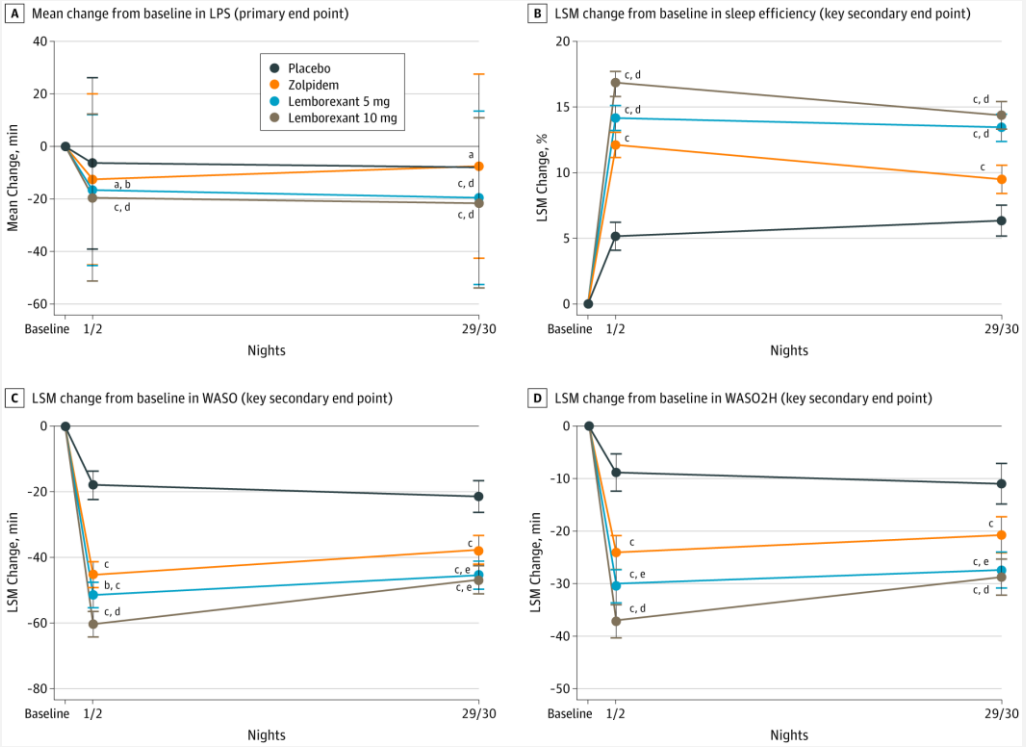
	TST	SL	WASO	QOS
Diphenhydramine	✓	✓	✓	✓
Doxepin	✓	✓	✓	✓
Eszopiclone	✓	✓	✓	✓
Melatonin		✓		✓
Ramelteon		✓		✓
Suvorexant	✓	✓	✓	✓
Temazepam	✓	✓	✓	✓
Tiagabine	✓		✓	✓
Trazodone	✓	✓	✓	✓
Triazolam		✓		✓
Tryptophan		✓	✓	✓
Valerian-hops		✓		✓
Zaleplon	✓	✓		✓
Zolpidem	✓	✓	✓	✓

TST = total sleep time, SL = sleep latency, WASO = wake after sleep onset, QOS = quality of sleep.

Source: Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017 Feb 15;13(2):307-349. doi: 10.5664/jcsm.6470. PMID: 27998379; PMCID: PMC5263087.

OREXIN RECEPTOR ANTAGONISTS

- Comparison of lemborexant (5 and 10mg) with placebo and zolpidem XL (6.25mg) for 1 month
- 1006 participants aged 55 years and older with insomnia
- Showed greater improvements in both LPS (latency to persistent sleep), SE, and WASO compared to placebo and zolpidem
- Overall incidence of adverse events were similar among all groups. Falls reported by 4 participants (all in lemborexant group)



Source: Rosenberg R, Murphy P, Zammit G, et al. Comparison of Lemborexant With Placebo and Zolpidem Tartrate Extended Release for the Treatment of Older Adults With Insomnia Disorder: A Phase 3 Randomized Clinical Trial. *JAMA Netw Open.* 2019;2(12):e1918254. doi:10.1001/jamanetworkopen.2019.18254

OREXIN RECEPTOR ANTAGONISTS

- Systematic review performed by American College of Physicians also found Suvorexant (15 or 20mg) improved ISI score, SL, TST, WASO versus placebo (Moderate quality evidence)
- Suvorexant has been studied in adults with cognitive impairment, and has regulatory approval in patients with mild to moderate Alzheimer disease
- Schedule IV controlled substance (relatively low abuse potential, limited dependence risk).

Source: Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD; Clinical Guidelines Committee of the American College of Physicians. Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2016 Jul 19;165(2):125-33. doi: 10.7326/M15-2175. Epub 2016 May 3. PMID: 27136449.

BZD RECEPTOR AGONISTS

Recommendation: We suggest clinicians use eszopiclone as a treatment for sleep onset and sleep maintenance insomnia in adults

Recommendation: We suggest clinicians use zaleplon as a treatment for sleep onset insomnia in adults

Recommendation: We suggest clinicians use zolpidem as a treatment for sleep onset and sleep maintenance insomnia in adults

	TST	SL	WASO	QOS
Diphenhydramine	✓	✓	✓	✓
Doxepin	✓	✓	✓	✓
Eszopiclone	✓	✓	✓	✓
Melatonin		✓		✓
Ramelteon		✓		✓
Suvorexant	✓	✓	✓	✓
Temazepam	✓	✓	✓	✓
Tiagabine	✓		✓	✓
Trazodone	✓	✓	✓	✓
Triazolam		✓		✓
Tryptophan		✓	✓	✓
Valerian-hops		✓		✓
Zaleplon	✓	✓		✓
Zolpidem	✓	✓	✓	✓

TST = total sleep time, SL = sleep latency, WASO = wake after sleep onset, QOS = quality of sleep.

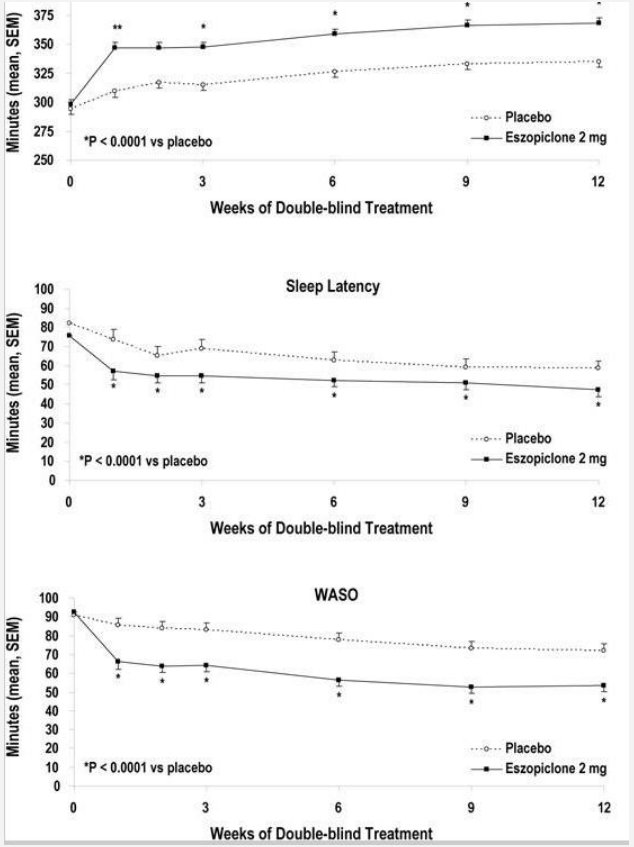
BZD RECEPTOR AGONISTS

- **Examples**: Eszopiclone (1mg), Zaleplon (5mg), Zolpidem (5mg IR, 1.75mg SL, 6.25mg ER)
- **Mechanism:** Enhance inhibitor action of GABA at the GABA-A receptor complex. Greater selectivity for GABA-A which may limit range of side effects and anxiolytic effects
- Eszopiclone: Improvement in SL by 14 minutes (SD), TST by 27.53 minutes, WASO by 10.02 minutes, SE by 4.83%. None met clinical significance except SE at the 3mg dosage
- Zaleplon: 2 studies included in AASM study. Reduction in SL by 10 minutes. Not clinically significant.
- Zolpidem: Improvement in SL by 11.65 minutes (PSG) TST by 28.91 minutes (PSG), WASO by 25.46 minutes (PSG), SE by 6.12%. All met clinical significance except for SE. The majority of studies evaluated dosage of 10mg for < 12 weeks. Longest study was over a period of 8 months.

Source: Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017 Feb 15;13(2):307-349. doi: 10.5664/jcsm.6470. PMID: 27998379; PMCID: PMC5263087.

BZD RECEPTOR AGONISTS

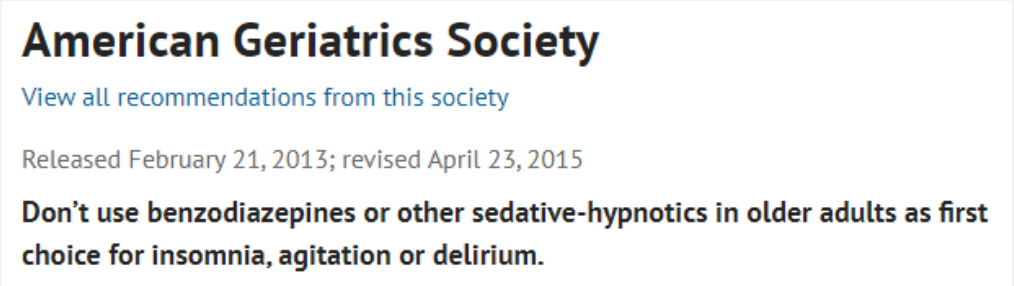
- 2010 study published in Sleep evaluating eszopiclone 2mg in 388 older adults (aged 65-85 years) over a 12 week period
- Subjects treated with eszopiclone had increased TST, WASO, and SL
- Most common AE (59.3% for eszopiclone, 50.5% for placebo) were headache, unpleasant taste, and nasopharyngitis.
- AE of interest in older adults were dizziness (4.1% versus 1.5%), falls (1.0% versus 0.5%), attention disturbance (0.5% versus 0.5%)



Source: Ancoli-Israel S, Krystal AD, McCall WV, et al. A 12-week, randomized, double-blind, placebo-controlled study evaluating the effect of eszopiclone 2 mg on sleep/wake function in older adults with primary and comorbid insomnia. *Sleep.* 2010;33(2):225-234. doi:10.1093/sleep/33.2.225

BZD RECEPTOR AGONISTS

- Most common side effects are somnolence, drowsiness, and dizziness. AASM meta-analysis found increases in risk for dizziness, headache, and somnolence
- Studies are mixed on evidence of rebound insomnia after discontinuation
- Noted that evaluation of daytime impairment was limited. 4 out of 5 evaluated studies showed no evidence of daytime impairment
- FDA boxed warning for complex sleep behaviors. Using data from the FDA Adverse Event Reporting System, they found 62 cases of complex sleep behaviors resulting in serious injuries or death between 1992 and 2018, with 4 additional cases reported in medical literature



Source: Choosing Wisely: https://www.choosingwisely.org/clinician-lists/american-geriatrics-society-benzodiazepines-sedative-hypnotics-for-insomnia-in-older-adults/
Source: Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017 Feb 15;13(2):307-349. doi: 10.5664/jcsm.6470. PMID: 27998379; PMCID: PMC5263087.
Source: https://www.fda.gov/media/123819/download

BENZODIAZEPINES

AASM recommendation: Use triazolam for sleep onset, and temazepam for sleep onset and maintenance
ACP recommendation: Evidence insufficient to determine benefits of BZD

- **Examples:** Estazolam, Flurazepam, Quazepam, Temazepam, Triazolam
- **Mechanism:** Enhancing inhibitory action of GABA-A receptor complex
- Temazepam has been best studied with improvements in SL, TST, SE. Insufficient data for WASO.

	TST	SL	WASO	QOS
Diphenhydramine	✓	✓	✓	✓
Doxepin	✓	✓	✓	✓
Eszopiclone	✓	✓	✓	✓
Melatonin		✓		✓
Ramelteon		✓		✓
Suvorexant	✓	✓	✓	✓
Temazepam	✓	✓	✓	✓
Tiagabine	✓		✓	✓
Trazodone	✓	✓	✓	✓
Triazolam		✓		✓
Tryptophan		✓	✓	✓
Valerian-hops		✓		✓
Zaleplon	✓	✓		✓
Zolpidem	✓	✓	✓	✓

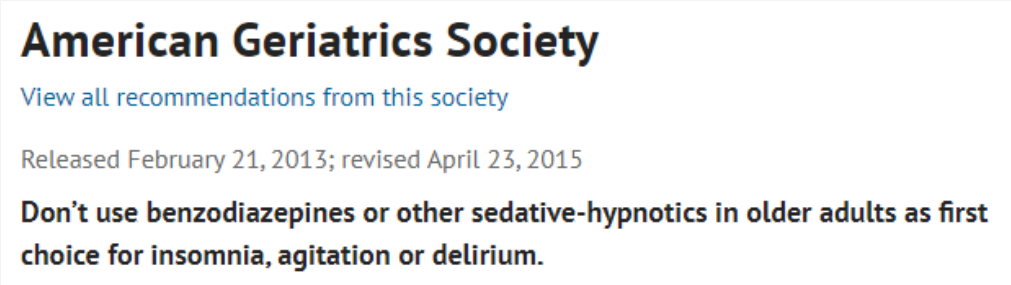
TST = total sleep time, SL = sleep latency, WASO = wake after sleep onset, QOS = quality of sleep.

Source: Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD; Clinical Guidelines Committee of the American College of Physicians. Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2016 Jul 19;165(2):125-33. doi: 10.7326/M15-2175. Epub 2016 May 3. PMID: 27136449.

Source: Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017 Feb 15;13(2):307-349. doi: 10.5664/jcsm.6470. PMID: 27998379; PMCID: PMC5263087.

BENZODIAZEPINES

- Most common side effects are somnolence, drowsiness, dizziness, and ataxia
- FDA boxed warning regarding increased risk of profound sedation, respiratory depression, coma, and death when used with opioid medications
- Generally avoided due to longer half-lives, higher risk of dependence and habituation, and availability of safer options



Source: Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017 Feb 15;13(2):307-349. doi: 10.5664/jcsm.6470. PMID: 27998379; PMCID: PMC5263087.

Source: Choosing Wisely: https://www.choosingwisely.org/clinician-lists/american-geriatrics-society-benzodiazepines-sedative-hypnotics-for-insomnia-in-older-adults/

DOXEPIN

Recommendation: We suggest clinicians use doxepin as treatment for sleep maintenance insomnia

- **Mechanism:** Tricyclic antidepressant with antihistaminic activity
- Approved at very low doses (3 and 6mg) allowing for limited activity at additional receptors thus minimizing side effects
- Improvements in TST by 26.14 minutes (PSG) at 3mg and 6mg, WASO by 22.17 minutes, quality of sleep, SE by 6.78%. All met clinical significance.
- ACP systematic review: Doxepin improved mean ISI scores, SL, TST, WASO.

	TST	SL	WASO	QOS
Diphenhydramine	✓	✓	✓	✓
Doxepin	✓	✓	✓	✓
Eszopiclone	✓	✓	✓	✓
Melatonin		✓		✓
Ramelteon		✓		✓
Suvorexant	✓	✓	✓	✓
Temazepam	✓	✓	✓	✓
Tiagabine	✓		✓	✓
Trazodone	✓	✓	✓	✓
Triazolam		✓		✓
Tryptophan		✓	✓	✓
Valerian-hops		✓		✓
Zaleplon	✓	✓		✓
Zolpidem	✓	✓	✓	✓

TST = total sleep time, SL = sleep latency, WASO = wake after sleep onset, QOS = quality of sleep.

Source: Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD; Clinical Guidelines Committee of the American College of Physicians. Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2016 Jul 19;165(2):125-33. doi: 10.7326/M15-2175. Epub 2016 May 3. PMID: 27136449.

Source: Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017 Feb 15;13(2):307-349. doi: 10.5664/jcsm.6470. PMID: 27998379; PMCID: PMC5263087.

DOXEPIN

- **Harms:** 3mg dosage without increase in somnolence or headache. 6mg dosage with slight increase in somnolence. No differences in diarrhea or URI when compared to placebo. No difference in next-day residual effects
- 2012 study published in Sleep Medicine evaluated Doxepin 6mg in 254 elderly adults, and found significant improvements in TST and WASO, no anticholinergic effects or memory impairment, and safety profile comparable to placebo
- Recommended by AAFP for use in older adults and those with concomitant depression

Source: Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017 Feb 15;13(2):307-349. doi: 10.5664/jcsm.6470. PMID: 27998379; PMCID: PMC5263087.

Source: Lankford A, Rogowski R, Essink B, Ludington E, Heith Durrence H, Roth T. Efficacy and safety of doxepin 6 mg in a four-week outpatient trial of elderly adults with chronic primary insomnia. Sleep Med. 2012 Feb;13(2):133-8. doi: 10.1016/j.sleep.2011.09.006. Epub 2011 Dec 24. PMID: 22197474.

Source: Am Fam Physician, 2017. Insomnia: Pharmacologic therapy

TRAZODONE

AASM recommendation: We suggest clinicians **not use** trazodone
ACP recommendation: Insufficient evidence on sleep outcomes

- **Mechanism:** Antidepressant with multiple actions (SRI, antagonism of 5-HT2A, 5-HT2B, alpha-1A, alpha-2C
- Typical dosage 50 to 100mg, with minimal improvement above 150mg
- **Harms:** In one study, Trazodone had significantly higher incidence of headache and somnolence. Other side effects include blurred vision, diarrhea, congestion, and weight loss.
- Boxed warning about suicidal ideation in children and young adults

	TST	SL	WASO	QOS
Diphenhydramine	✓	✓	✓	✓
Doxepin	✓	✓	✓	✓
Eszopiclone	✓	✓	✓	✓
Melatonin		✓		✓
Ramelteon		✓		✓
Suvorexant	✓	✓	✓	✓
Temazepam	✓	✓	✓	✓
Tiagabine	✓		✓	✓
Trazodone	✓	✓	✓	✓
Triazolam		✓		✓
Tryptophan		✓	✓	✓
Valerian-hops		✓		✓
Zaleplon	✓	✓		✓
Zolpidem	✓	✓	✓	✓

TST = total sleep time, SL = sleep latency, WASO = wake after sleep onset, QOS = quality of sleep.

Source: Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD; Clinical Guidelines Committee of the American College of Physicians. Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2016 Jul 19;165(2):125-33. doi: 10.7326/M15-2175. Epub 2016 May 3. PMID: 27136449.

Source: Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017 Feb 15;13(2):307-349. doi: 10.5664/jcsm.6470. PMID: 27998379; PMCID: PMC5263087.

TRAZODONE

- **Efficacy:** AASM used a single study (Walsh, 1998) to investigate, and found no clinically significant improvement in TST, WASO, SL, or NOA. There was a modest improvement in SL, TST, and WASO
- A newer systematic review in 2018 evaluated 7 trials totaling 429 patients. They found no significant differences in SE, SL, TST, WASO versus placebo. Patients receiving trazodone perceived better SQ and reduction in NA
- A newer study in 2020 which did not study Trazodone specifically, did find a trend towards benefit as a second-line strategy for those who failed zolpidem

Source: Yi XY, Ni SF, Ghadami MR, Meng HQ, Chen MY, Kuang L, Zhang YQ, Zhang L, Zhou XY. Trazodone for the treatment of insomnia: a meta-analysis of randomized placebo-controlled trials. Sleep Med. 2018 May;45:25-32. doi: 10.1016/j.sleep.2018.01.010. Epub 2018 Feb 7. PMID: 29680424.

Source: Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017 Feb 15;13(2):307-349. doi: 10.5664/jcsm.6470. PMID: 27998379; PMCID: PMC5263087.

Source: Morin CM, Edinger JD, Beaulieu-Bonneau S, Ivers H, Krystal AD, Guay B, Bélanger L, Cartwright A, Simmons B, Lamy M, Busby M. Effectiveness of Sequential Psychological and Medication Therapies for Insomnia Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2020 Nov 1;77(11):1107-1115. doi: 10.1001/jamapsychiatry.2020.1767. PMID: 32639561; PMCID: PMC7344835.

MELATONIN

Recommendation: We suggest clinicians not use melatonin as treatment for sleep onset or sleep maintenance insomnia

- **Mechanism:** Agonist at the melatonin receptors, which decreases evening arousal and reinforces circadian periodicity
- Physiologic doses are typically 1 to 3mg for older adults, and doses below 1mg may be as effective as higher doses, taken a few hours before bedtime
- **Harms:** Not well established. Reported are vivid dreams, daytime somnolence, headache, dizziness, stomach cramps, irritability

	TST	SL	WASO	QOS
Diphenhydramine	✓	✓	✓	✓
Doxepin	✓	✓	✓	✓
Eszopiclone	✓	✓	✓	✓
Melatonin		✓		✓
Ramelteon		✓		✓
Suvorexant	✓	✓	✓	✓
Temazepam	✓	✓	✓	✓
Tiagabine	✓		✓	✓
Trazodone	✓	✓	✓	✓
Triazolam		✓		✓
Tryptophan		✓	✓	✓
Valerian-hops		✓		✓
Zaleplon	✓	✓		✓
Zolpidem	✓	✓	✓	✓

TST = total sleep time, SL = sleep latency, WASO = wake after sleep onset, QOS = quality of sleep.

Source: Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017 Feb 15;13(2):307-349. doi: 10.5664/jcsm.6470. PMID: 27998379; PMCID: PMC5263087.

MELATONIN

- **Efficacy:** AASM had 3 studies included with adequate data, and found no clinically significant increase in SL, TST, WASO, QOS.
- Systematic review in 2020 of 18 studies, of 17988 subjects, noted statistically significant but small increase in SL and TST with lack of consensus of clinical significance, however ultimately concluded that existing evidence is limited due to disparate methodological quality of reviewed papers

Source: Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017 Feb 15;13(2):307-349. doi: 10.5664/jcsm.6470. PMID: 27998379; PMCID: PMC5263087.

Source: Low TL, Choo FN, Tan SM. The efficacy of melatonin and melatonin agonists in insomnia - An umbrella review. J Psychiatr Res. 2020 Feb;121:10-23. doi: 10.1016/j.jpsychires.2019.10.022. Epub 2019 Nov 2. PMID: 31715492.

OTHER MEDICATIONS

Recommendation: We suggest clinicians use ramelteon as treatment for sleep onset insomnia

Not recommended: Diphenhydramine, tryptophan, tiagabine, valerian

Source: Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017 Feb 15;13(2):307-349. doi: 10.5664/jcsm.6470. PMID: 27998379; PMCID: PMC5263087.

CONCLUSION

- Treatment should begin with behavioral treatments such as sleep hygiene
- All patients with chronic insomnia should receive CBT-I
- Pharmacological treatments are varied, and usage depends in part on the patient population and individualized benefit and risk evaluation
- Medications recommended by the AASM for chronic insomnia include orexin receptor antagonists, BZRAs, BZD, ramelteon, and doxepin
- Per the AGS, use of BZRAs and BZD should be avoided in older adults (however, some studies have demonstrated efficacy of BZRAs in older adults)