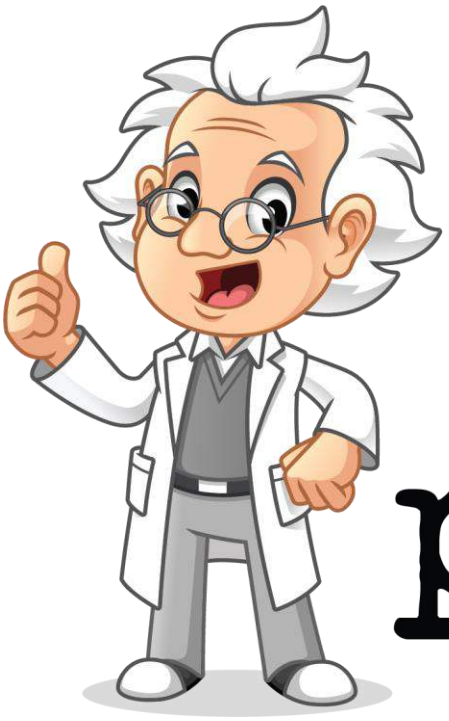

the PRUDENT prescriber

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In this edition:

What Should I Prescribe for Insomnia?

During my prescribing career I was ever hesitant of prescribing benzodiazepines and the "Z" sleep drugs. I would start discussions with patients seeking help with their insomnia with exhortations for sleep hygiene, diphenhydramine, and melatonin. When still sleepless in Happy Valley, they returned a few days or weeks later, I'd bring out the big guns: trazodone or doxepin. Simplistic? Uninformed? Yes, on both accounts.

I could have used the study that appeared in the July 16, 2022 Lancet by DeCrescenzo et al. from the University of Oxford. This systematic review (170 trials with 36 interventions in 47,950 participants) and network meta-analysis (154 double blind, randomized controlled trials with 30 interventions in 44,089 participants) aims to estimate the comparative effectiveness of pharmacological treatments for the acute and long-term treatment of adults with insomnia.

On the next few pages, I have summarized this study's findings and have supplemented these recommendations with data on drug doses, adverse effects, black boxes, half-lives, and costs with the footnoted references.

Drug & Cost for 30-day supply (6) (8)	Efficacy	Adverse Effects	Short term/ Long term Half Life (2)	Notes
eszopiclone (Lunesta) $8-$16	The study ranked eszopiclone and lemborexant as having the best profiles in terms of efficacy, acceptability and tolerability.	Serious: depression exacerbation, suicidality, hallucinations, complex sleep disorders, rare, can occur with first dose. {BLACK BOX} Common: unpleasant taste, headache, somnolence, Impairment of next day performance.	Improves sleep onset and maintenance. Short and long-term studies support efficacy and safety for up to six months. Half-life is 6 hours.	Start with 1 mg at bedtime. Max dose 3mg in <65 y, 1-2mg in >65 y Give at least seven hours before planned awakening. Taper doses gradually to discontinue if there is prolonged use. Do not take with or immediately after a meal due to delayed onset.
lemborexant (Dayvigo) 5mg (#30) $310-$314 10 mg (#30) $310-$314	The study ranked eszopiclone and lemborexant as having the best profile in terms of efficacy, acceptability and tolerability.	Serious: Driving impairment, sleep paralysis, cataplexy like symptoms. Common: Somnolence (7%-10%), headache (5%-6%), Abnormal dreams (1%-2%).	Improves sleep onset and maintenance. Half-life is 17-19 hours	Lemborexant was the most efficacious orexin antagonist for improving sleep in both the short term and long term, whereas seltorexant and suvorexant had better tolerability profiles. Daridorexant approved by the FDA in January 2022 did not show an overall material benefit in the treatment of insomnia disorder. Be aware of drug interactions with inducers and inhibitors of CYP3A4.
zolpidem Immediate release (SL, oral spray) $13-$15	More effective than placebo, melatonin, ramelteon and zaleplon.	Better tolerability profiles than lemborexant Complex sleep disorders, rare, can occur as soon as first dose. {BLACK BOX)	Approved for short-term treatment of insomnia. Improves sleep onset. There was insufficient evidence to support the prescription of zolpidem in long-term treatment. Half-life is 1.6-4 hours.	All zolpidem products taken with or immediately after a meal may delay onset. Be aware of drug interactions with inducers and inhibitors of CYP3A4. Initial dose: 6.25 mg-12.5 mg in males and 6.25 mg in females; Max dose in in males < 65 y 12.5 mg and 6.25 mg in all females and males >65y. For middle of the night awakening, use of sublingual Intermezzo. Take only if there are at least four hours remaining before planned wake time. $106-$175 for 30 doses.

Drug & Cost for 30-day supply (6) (8)	Efficacy	Adverse Effects	Short term/ Long term Half Life (2)	Notes
zolpidem Controlled release (Ambien, generics) $17-$27	More effective than placebo, melatonin, ramelteon and zaleplon	Better tolerability profiles than lemborexant Complex sleep disorders, rare, can occur as soon as first dose. {BLACK BOX)	Approved for short term treatment to improve sleep onset and maintenance. There was insufficient evidence to support the prescription of zolpidem in long-term treatment Half-life is 1.6–4 hours.	All zolpidem products taken with or immediately after a meal may delay onset. Be aware of drug interactions with inducers and inhibitors of CYP3A4. Dosing females: 6.25 mg at bedtime. Maximum dose 12.5 mg per day. Give immediately before bedtime and greater than seven hours before planned awakening. Take on an empty stomach. Dosing male patients: 6.25–12.5 mg at bedtime. Maximum dose 12.5 mg per day.
daridorexant (Quviviq) suvorexant (Belsomra) $417-$481	Suvorexant patients fall asleep 5–10 minutes sooner and stay asleep 15-25 minutes longer than those taking placebo. (5)	Suvorexant dose related adverse effects are greater in obese patients and women. Avoid doses greater than 10 mg.	Daridorexant half-life is 8 hours. Suvorexant half-life is 12 hours.	“Me-toos of the other orexin antagonist (lemborexant). Impairment of next day performance can occur.
Doxepin $90-$138	-In terms of time to fall asleep, doxepin is inferior to placebo.	Anticholinergic adverse events are dose dependent. Impairment of next day performance can occur.	Improves sleep maintenance, but not sleep onset.	Do not take within three hours of a meal due to the possibility of delayed onset and next day drowsiness.
Melatonin 25mg (#60) $2.40	Melatonergic interventions had poor efficacy, with no data in the long-term Less effective than zolpidem.	The purity and optimal doses are unclear. The common side effects are headache, pharyngitis, arthralgia, and back pain. Usually well tolerated.	Reduces time to fall asleep by 10 minutes. Half-life is 2-8 hours. -Take 3 to 5 hours before the desired time of sleep onset. (5)	It does not appear to be effective when taken at bedtime. (5)

Drug & Cost for 30-day supply (6) (8)	Efficacy	Adverse Effects	Short term/ Long term Half Life (2)	Notes
Ramelteon Rozerem $49-$51	Melatonergic interventions had poor efficacy, with no data in the long-term. Less effective than zolpidem. More effective than melatonin.	Common adverse effects include somnolence, dizziness, fatigue, and nausea. Hallucinations, agitation, mania, and complex sleep related behaviors have been reported.	Not limited to short term use. Half-life is 1-5 hours	Metabolized by CYP1A2.
Antihistamines diphenhydramine doxylamine diphenhydramine $1.20-$2.40 Doxylamine $2.70	Non-prescription antihistamines are not recommended for the treatment of insomnia due to poor evidence of efficacy. (4)	Anticholinergic effects	diphenhydramine: half-life 2-8 hours; maximum sedative effect in one to three hours after ingestion	Non-prescription antihistamines are not recommended for the treatment of insomnia due to poor evidence of efficacy. (4) If doxylamine is used, limit to two weeks duration.
Trazadone $4-$5	Limited efficacy data. (3)	Anticholinergic effects can be severe in the elderly (4)		Off label use. Short-term use in patients with insomnia and depression while awaiting the onset of other antidepressant medications is reasonable. The evidence for efficacy is sparse. (5)
Benzodiazepines temazepam $7-$12	For the short-term treatment of insomnia, the authors suggest that benzodiazepines with intermediate half-lives like temazepam have better acceptability than short acting or long-acting compounds.	Evaluate the benefit/risk ratio for each patient, start low and go slow, go short, look out for what else you prescribe, taper, and follow up frequently. Tolerance and dependence occur with prolonged use of benzodiazepines. (BLACK BOX) Increase risk of CNS toxicity when benzodiazepines are co-administered with opiates.	Temazepam is approved for the short-term treatment to improve sleep onset and total sleep time. There was insufficient evidence to support the prescription of benzodiazepines in long-term treatment.	Use caution when prescribing additional medications and prescribe the lowest effective dose for the shortest treatment duration possible and taper slowly, with regular follow-up. Don't consider for insomnia: flurazepam (100-hour half-life), quazepam (half-life 39–73 hours and cost), oxazepam (little data, off label use) and triazolam (cost $30-$38/mo) Temazepam does not interact with the CYP3A4 enzyme system.

(1) 2019 overview by Patricia Rios et al. (Systematic Reviews.2019;8:281)
(2) Applied Therapeutics: The Clinical Use of Drugs. 11th edition, 2018: 1762—79
(3) A Clinical Practice Guideline by the American College of Physicians: Pharmacological Treatment of Insomnia, Annals of Internal Medicine, July 19, 2016
(4) American Academies Sleep Medicine Clinical Practice Guideline. Journal Clinical Sleep Medicine. 2017 Feb 15
(5) The Medical Letter. December 17,2018
(6) GoodRx (accessed September 2022)
(7) epocrates (accessed September 2022)
(8) Cost range from the 3 least expensive pharmacies per GoodRx.com

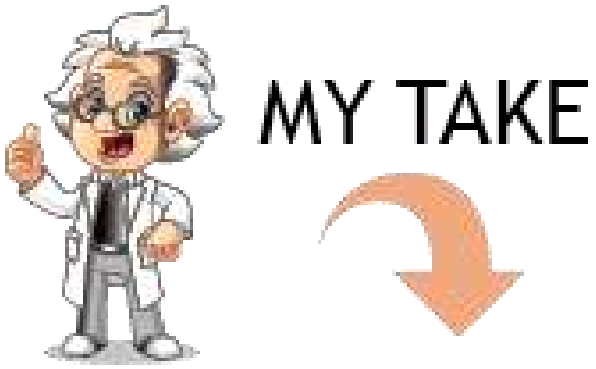
Thoughts from DeCrescenzo et al:

- Eszopiclone and lemborexant have the most favorable profiles, but eszopiclone might cause substantial adverse effects. Safety data on lemborexant are inconclusive.
- Many licensed drugs (including benzodiazepines daridorexant, suvorexantpo and trazodone) can be effective in the acute treatment of insomnia but are associated with poor tolerability, or lack of information about long-term effects.
- Melatonin, ramelteon and non-licensed drugs did not show overall material benefits.
- Benzodiazepines, doxylamine, eszopiclone, lemborexant, and zolpidem were judged more effective than placebo. (Moderate to high evidence of certainty)
- Benzodiazepines, eszopiclone, and zolpidem were more effective than melatonin, ramelteon and zaleplon. (Low to moderate evidence of certainty)
- In terms of head-to-head comparisons, after four weeks of treatment, short acting benzodiazepines were more effective than daridorexant, eszopiclone, and zolpidem. (High level of evidence)
- For the short-term treatment of insomnia, the authors suggest that benzodiazepines with intermediate half-lives like temazepam have better acceptability than short acting or long-acting compounds.
- The authors acknowledge the limitations of their study: mostly placebo-controlled studies and few head-to-head drug comparisons; many short-term studies, but few that looked at the efficacy and adverse effects with long-term use. There are large holes in the evidence for both efficacy and side effects of many of the OTC drugs that have been around for decades.

Cognitive-behavioral therapy for Insomnia (CBT-I):

- There is unanimous agreement among all the resources that I reviewed that CBT-I should be first line treatment. Its efficacy is well-established. Cognitive behavioral therapy is the multimodal combination of relaxation training, cognitive restructuring, stimulus control, sleep restriction, and sleep hygiene educational interventions.

- Limitations to more widespread utilization of CBT-I include limited availability of trained providers as well as time and cost considerations.
- Delivering CBT-I over the internet (eCBT-I) may be one method to overcome this challenge. A meta-analysis (Sleep Medicine Reviews. Dec.2016) evaluated the efficacy of eCBT-I. Eleven randomized controlled trials examining a total of 1460 participants were included. Results showed that eCBT-I improved insomnia severity, sleep efficiency, subjective sleep quality, wake after sleep onset, sleep onset latency and total sleep time. The effects were comparable to those found for face-to-face CBT-I and were generally maintained at 4–48 weeks of follow-up.



- In general, these drugs don't work very well. Their effect sizes are small. Some of these products are expensive. For the "orexin" antagonists, on average, it costs about a dollar a minute ($15) to go to sleep 15 minutes quicker each night.
- A week ago, I abandoned my 10-year nightly ingestion of 50 mg of diphenhydramine. I have slept well since.
- Based on this review, I would eliminate melatonin, ramelteon, doxylamine, diphenhydramine, and the ridiculously priced orexin antagonists from my insomnia pharmacopeia.
- It should pay dividends to teach sleep hygiene and discontinue drugs that interfere with sleep (alpha-blockers [doxazocin, tamsulosin], beta blockers, corticosteroids, SSRI antidepressants, ACE inhibitors, ARBs, cholinesterase inhibitors [donepezil, the drug I love to hate], second generation H1 antagonists [cetirizine], glucosamine and chondroitin and statins.)
- Whereas the DeCrescenzo study highlighted here recommends eszopiclone and lemborexant, the less robust 2019 Rios et al. comparative effectiveness/safety study (r**eference 1**) comes to other conclusions. They push for CBT-I and if it's ineffective or not available, recommend short courses of melatonin, zolpidem, suvorexant or doxepin.
- I found a couple of cognitive behavioral therapists in Grand Junction, but neither touts insomnia expertise. A Denver cognitive behavioral therapist for insomnia called me back within minutes of my secret shopper email and suggested I might well need at least three

months of therapy at $150 an hour. The price of CBT-I may be a bargain in the long run if it is as effective as some studies indicate. CBT-I's adverse event profile should be benign.

- Despite its black box, eszopiclone wins my vote as a reasonable insomnia drug to initiate therapy. It appears efficacious (although difficult to get a feel for effect size), has a reasonable adverse event profile and is cheap. I'd keep trazodone in my hip pocket as I've prescribed it frequently with good results. Temazepam would be my benzodiazepine of choice in the unusual situations where the benefits clearly outweigh the significant risks.
- Check out this resource on sleep hygiene produced by UC San Diego.

Looking for previous versions of the Prudent Prescriber newsletter? Good news, 10 YEARS of monthly editions are now available on rmhp.org.

Prudent Prescriber
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