

# Orexin antagonists for insomnia

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## Clinical question

Are orexin antagonists safe and effective for treatment of primary insomnia?

## Bottom line

Orexin antagonists help people fall asleep about 9 minutes faster and increase total sleep time by about 19 minutes versus placebo over the course of 1 to 3 months. About 8% of those taking orexin antagonists will experience next-day somnolence compared with 2% taking placebo.

## Evidence

Seven systematic reviews of RCTs were found<sup>1-7</sup>; we report mainly on the most recent and comprehensive review. Differences were statistically significant unless indicated.

- Versus placebo
  - In a systematic review<sup>1</sup> (13 RCTs, 7875 patients, mean age about 55 years) of sleep diary outcomes, orexin antagonists changed the following after 1 to 3 months:
    - Sleep onset (65 min at baseline) was about 9 minutes faster with orexin antagonists (47 min until sleep onset) than with placebo (56 min).
    - Total sleep time increased by about 19 minutes.
    - Time awake after falling asleep was about 9 minutes less.
    - Sleep quality improved about 5% (ie, improved 0.2 points on 4-point scale, which is not likely clinically meaningful).<sup>8</sup>
    - No clinical differences between number of awakenings or feeling refreshed on awakening.
  - Other reviews had similar findings.<sup>2-6</sup>
    - Insomnia score response<sup>6</sup>: 55% versus 42% (placebo), number needed to treat=8.
  - An RCT with 12 months' follow-up had similar results.<sup>9</sup>
  - Adverse events
    - There was no difference in the rate of patients stopping treatment owing to adverse effects.<sup>2,3,7,10</sup>
    - The most common adverse events<sup>1</sup> reported included somnolence (8.3% vs 2.2% [placebo], number needed to harm [NNH]=16) and fatigue, dry mouth, and abnormal dreams (each about 2% to 3% vs 1% with placebo).
    - Rates of excessive daytime sleepiness were 0.6% versus 0.3% (placebo), NNH=290; rates of sleep paralysis<sup>10</sup> were 0.6% versus 0% (placebo), NNH=155.
    - Effects on risk of falling are unclear (4 small observational studies in hospitals) and range from increased to decreased association.<sup>11-14</sup>

—One observational study suggests fracture risk is similar between suvorexant and z drugs.<sup>15</sup>

- Versus active comparator
  - An RCT comparing 5 mg or 10 mg lemborexant versus zolpidem extended release<sup>16</sup> found the following:
    - Sleep onset with lemborexant was 5 to 7 minutes better (dose dependent).
    - Time awake after falling asleep ranged from no difference to being about 15 minutes better with zolpidem.
    - No difference was noted in time asleep.
    - Dropout owing to adverse events: 0.9% versus 2.7% with zolpidem.
  - Limitations: Outcome reporting was incomplete, run-ins were used, and the RCTs were industry sponsored.

## Context

- There was similar efficacy in those older than age 65.<sup>17</sup>
- Studies suggest minimal withdrawal symptoms, but there is limited evidence.<sup>2,14,16,18</sup>
  - Abuse potential not formally assessed in insomnia RCTs.
- Nonpharmacologic sleep restriction therapy is effective.<sup>19</sup>
- Lemborexant (available in Canada) costs approximately \$50 for 30 tablets.<sup>20</sup>

## Implementation

Insomnia affects around 30% of patients in primary care populations.<sup>21</sup> Management requires addressing contributing factors. In a primary care cohort,<sup>21</sup> primary insomnia constituted 12% of insomnia cases but other overlapping factors included depression and anxiety (50%), general health problems (43%), restless leg syndrome (22%), sleep apnea (9%), and alcohol or other substance use problems (12%). Guidelines recommend treating insomnia with cognitive behavioural therapy, noting that sleep consolidation and dysfunctional beliefs about sleep should be incorporated into treatment.<sup>22</sup> Validated online tools for practitioners and patients are available.<sup>23</sup>

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### Competing interests

None declared

### References

1. Xue T, Wu X, Chen S, Yang Y, Yan Z, Song Z, et al. The efficacy and safety of dual orexin receptor antagonists in primary insomnia: a systematic review and network meta-analysis. *Sleep Med Rev* 2022;61:101573. Epub 2021 Nov 26.
2. McElroy H, O'Leary B, Adena M, Campbell R, Monfared AAT, Meier G. Comparative efficacy of lemborexant and other insomnia treatments: a network meta-analysis. *J Manag Care Spec Pharm* 2021;27(9):1296-308. Epub 2021 Jun 12.
3. Kuriyama A, Tabata H. Suvorexant for the treatment of primary insomnia: a systematic review and meta-analysis. *Sleep Med Rev* 2017;35:1-7. Epub 2016 Oct 28.

4. Chiu HY, Lee HC, Liu JW, Hua SJ, Chen PY, Tsai PS, et al. Comparative efficacy and safety of hypnotics for insomnia in older adults: a systematic review and network meta-analysis. *Sleep* 2021;44(5):zsa260.
5. Wang L, Pan Y, Ye C, Guo L, Luo S, Dai S, et al. A network meta-analysis of the long- and short-term efficacy of sleep medicines in adults and older adults. *Neurosci Biobehav Rev* 2021;131:489-96. Epub 2021 Sep 21.
6. Wilt TJ, MacDonald R, Brasure M, Olson CM, Carlyle M, Fuchs E, et al. Pharmacologic treatment of insomnia disorder: an evidence report for a clinical practice guideline by the American College of Physicians. *Ann Intern Med* 2016;165(2):103-12. Epub 2016 May 3.
7. Kishi T, Nomura I, Matsuda Y, Sakuma K, Okuya M, Ikuta T, et al. Lemborexant vs suvorexant for insomnia: a systematic review and network meta-analysis. *J Psychiatr Res* 2020;128:68-74. Epub 2020 May 28.
8. Herring WJ, Connor KM, Ivgy-May N, Snyder E, Liu K, Snively DB, et al. Suvorexant in patients with insomnia: results from two 3-month randomized controlled clinical trials. *Biol Psychiatry* 2016;79(2):136-48. Epub 2014 Oct 23.
9. Michelson D, Snyder E, Paradis E, Chengan-Liu M, Snively DB, Hutzelmann J, et al. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2014;13(5):461-71. Epub 2014 Mar 27.
10. Na HJ, Jeon N, Staatz CE, Han N, Baek IH. Clinical safety and narcolepsy-like symptoms of dual orexin receptor antagonists in patients with insomnia: a systematic review and meta-analysis. *Sleep* 2024;47(2):zsad293.
11. Ishibashi Y, Nishitani R, Shimura A, Takeuchi A, Touko M, Kato T, et al. Non-GABA sleep medications, suvorexant as risk factors for falls: case-control and case-crossover study. *PLoS One* 2020;15(9):e0238723. Erratum in: *PLoS One* 2021;16(10):e0259430.
12. Ishigo T, Takada R, Kondo F, Ibe Y, Nakano K, Tateishi R, et al. Association suvorexant and ramelteon use with the risk of falling: a retrospective case-control study [article in Japanese]. *Yakugaku Zasshi* 2020;140(8):1041-9.
13. Sogawa R, Emoto A, Monji A, Miyamoto Y, Yukawa M, Murakawa-Hirachi T, et al. Association of orexin receptor antagonists with falls during hospitalization. *J Clin Pharm Ther* 2022;47(6):809-13. Epub 2022 Mar 1.
14. Torii H, Ando M, Tomita H, Kobaru T, Tanaka M, Fujimoto K, et al. Association of hypnotic drug use with fall incidents in hospitalized elderly patients: a case-crossover study. *Biol Pharm Bull* 2020;43(6):925-31.
15. Adomi M, Maeda M, Murata F, Fukuda H. Comparative risk of fracture in community-dwelling older adults initiating suvorexant versus z-drugs: results from LIFE study. *J Am Geriatr Soc* 2023;71(1):109-120. Epub 2022 Oct 2.
16. Rosenberg R, Murphy P, Zammit G, Mayle D, Kumar D, Dhadda S, 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. Errata in: *JAMA Netw Open* 2020;3(4):e206497, *JAMA Netw Open* 2021;4(8):e2127643.
17. De Crescenzo F, D'Alò GL, Ostinelli EG, Ciabattini M, Di Franco V, Watanabe N, et al. Comparative effects of pharmacological interventions for the acute and long-term management of insomnia disorder in adults: a systematic review and network meta-analysis. *Lancet* 2022;400(10347):170-84.
18. Herring WJ, Connor KM, Snyder E, Snively DB, Zhang Y, Hutzelmann J, et al. Suvorexant in elderly patients with insomnia: pooled analyses of data from phase III randomized controlled clinical trials. *Am J Geriatr Psychiatry* 2017;25(7):791-802. Epub 2017 Mar 8.
19. Allan GM, Lindblad AJ, Varughese J. Trouble sleeping: spend less time in bed? *Can Fam Physician* 2017;63:613 (Eng), e363-4 (Fr).
20. *McKesson Pharmaclik* [website]. Available from: <https://clients.mckesson.ca/catalog>. Accessed 2023 Nov 27.
21. Arroll B, Fernando A 3rd, Falloon K, Goodyear-Smith F, Samaranyake C, Warman G. Prevalence of causes of insomnia in primary care: a cross-sectional study. *Br J Gen Pract* 2012;62(595):e99-103.
22. 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;13(2):307-49.
23. *Sleepwell* [website]. Halifax, NS: Dalhousie University; 2024. Available from: <https://mysleepwell.ca>. Accessed 2023 Nov 16.

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