



# RXs for Orexins? The efficacy and safety of orexin antagonists for insomnia

## CLINICAL QUESTION

**Are orexin antagonists safe and effective for primary insomnia?**

## BOTTOM LINE

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

## EVIDENCE

- 7 systematic reviews of randomized, controlled trials (RCTs).<sup>1-7</sup> Focusing on the most recent and comprehensive. Results statistically significant unless indicated.
- Systematic review<sup>1</sup> (13 RCTs, 7875 patients, mean age ~55 years) over ~1-3 months:
  - Sleep diary outcomes; compared to placebo, orexin antagonists changed:
    - Sleep onset: ~9 minutes faster [example: Baseline 65 minutes, 47 minutes with orexins versus 56 minutes (placebo)].
    - Total sleep time: Increased ~19 minutes.
    - Time awake after falling asleep: ~9 minutes less.
    - Sleep quality: Improved ~5% (example improved 0.2 points on a 4-point scale, not likely clinically meaningful).<sup>8</sup>
    - No clinical difference: Awakenings or feeling refreshed on awakening.
    - Other reviews<sup>2-6</sup> found similar.

- Response on insomnia score:<sup>6</sup> 55% versus 42% (placebo), NNT=8.
- One RCT with 12 months follow-up found similar.<sup>9</sup>
- Adverse events:
  - Stopping due to adverse effects: No difference.<sup>2,3,7</sup>
  - Most common adverse events:<sup>1</sup>
    - Somnolence 8.3% versus 2.2% (placebo), number needed to harm (NNH)=16.
    - Fatigue, dry mouth, abnormal dreams each ~2-3% versus 1% placebo.
  - Effects on falls unclear (4 small observational studies in hospitals): Range from associated with increased fall risk to decreased.<sup>10-13</sup>
    - One observational study suggests fracture risk similar between suvorexant and z-drugs.<sup>14</sup>
- RCT comparing 5 and 10mg Lemborexant to Zolpidem ER:<sup>15</sup>
  - Sleep onset: Lemborexant ~6 minutes better.
  - Time awake after falling asleep: Range from no difference to zolpidem ~15 minutes better.
  - Proportion of time asleep: No difference
  - Dropout due to adverse events: 0.9% versus 2.7% zolpidem.
- Limitations
  - RCTs industry sponsored, use of run-ins, incomplete outcome reporting.

## CONTEXT

- Similar efficacy<sup>16</sup> in those >65.
- Limited evidence suggests minimal withdrawal symptoms.<sup>2,13,15,17</sup>
  - Abuse potential not formally assessed in insomnia RCTs.
- Orexin inhibitors have been associated with sleep paralysis/complex sleep behaviors (example “sleep-driving”).<sup>18</sup>
- Non-pharmacologic sleep restriction therapy is effective.<sup>19</sup>
- Lemborexant (available in Canada) price: \$48/30 tablets.<sup>20</sup>

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