

Eszopiclone vs Zopiclone in the Management of Insomnia: A Comparative Review for Psychiatrists

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Abstract

Insomnia remains one of the most common sleep-related disorders managed in psychiatric practice, often coexisting with anxiety, depression, or substance use. Among the z-drugs, eszopiclone and zopiclone are frequently prescribed for their efficacy in sleep induction and maintenance.

However, differences in pharmacodynamics, regulatory approval, tolerability, and long-term data present critical considerations for psychiatrists.

This review synthesizes recent US and UK literature to compare eszopiclone and zopiclone, supporting evidence-based prescribing in diverse clinical contexts.

Introduction

Eszopiclone and zopiclone are nonbenzodiazepine hypnotics that modulate the GABA-A receptor complex to facilitate sleep onset and continuity. Zopiclone, a racemic compound consisting of two stereoisomers: the active S-enantiomer and the less active R-enantiomer, is approved in the UK and Europe while Eszopiclone, its S-enantiomer, is approved in the United States and recently in the UK. Though pharmacologically related, these drugs have differing clinical profiles, including regulatory constraints, adverse event spectra, and long-term efficacy, which are highly relevant for psychiatric practice.

Pharmacology

Eszopiclone acts as a stereoselective modulator of GABA-A receptors, particularly targeting $\alpha 1$, $\alpha 2$, and $\alpha 3$ subunits. Compared to zopiclone, it demonstrates a more consistent pharmacokinetic profile and fewer interindividual variations in metabolism.

Eszopiclone: half-life about 6 hours, metabolized primarily via CYP3A4.

Zopiclone: half-life 5–9 hours, metabolized via CYP3A4 and CYP2C8.

These pharmacokinetic differences contribute to eszopiclone's shorter residual activity and potentially improved safety profile regarding next-day performance.

Efficacy

Short-Term Treatment

Both drugs are effective for sleep initiation and maintenance. Randomized controlled trials demonstrate that eszopiclone improves total sleep time (TST) and wake-after-sleep onset (WASO) more consistently than zopiclone.

A 2023 meta-analysis found eszopiclone to offer higher sleep efficiency compared to zopiclone across multiple polysomnographic trials.

Long-Term Treatment

Eszopiclone is unique among hypnotics in having FDA approval for long-term use (up to 12 months), with multiple studies demonstrating sustained efficacy without evidence of tolerance or rebound.

Zopiclone lacks comparable long-term RCT data. UK prescribing guidelines recommend limiting its use to a maximum of 10 days to minimize risks of dependence and adverse cognitive outcomes.

Safety and Tolerability

Adverse Events

Dysgeusia (bitter or metallic taste) is the most common side effect for both agents, affecting around 50% of users. Other reported side effects include dizziness, headache, nausea, and dry mouth.

Residual Sedation and Impairment

The FDA issued a 2014 warning after evidence showed 3 mg of eszopiclone caused significant next-morning psychomotor impairment. The recommended starting dose was revised to 1 mg.

Zopiclone has similarly been shown to impair driving performance up to 11 hours post-dose.

Neuropsychiatric Adverse Effects

Recent pharmacovigilance analyses indicate eszopiclone is more associated with parasomnias such as sleepwalking, whereas zopiclone is linked to a wider spectrum of neuropsychiatric events, including aggression and confusion.

Dependence and Misuse Potential

Though both are Schedule IV substances, long-term studies of eszopiclone show no significant dose escalation, suggesting a lower misuse potential.

In contrast, zopiclone has been more frequently implicated in withdrawal, tolerance, and misuse, particularly in patients with co-occurring substance use disorders or prolonged use.

Special Populations: Geriatric Considerations

Both eszopiclone and zopiclone are included on the American Geriatrics Society's Beers Criteria due to risks of falls, delirium, and cognitive impairment.

Eszopiclone may be preferred in elderly patients due to its cleaner pharmacokinetic profile, although nonpharmacologic approaches remain first-line for this population group.

Zopiclone on the NICE is advised against long-term insomnia treatment in the elderly due to an increased risk of falls, confusion and delirium, slower metabolism and increased sensitivity to sedative effects and if it has to be used then a maximum of 3.75mg is recommended.

Cost and Availability

Eszopiclone:

- Generic available in the US; moderately priced.
- UK Licensing Status of Eszopiclone:
 1. Licensed name Lunivia available as 1mg, 2mg and 3mg oral tablets, approved on 1 February 25.
 2. UK marketing authorisation granted by MHRA.
 3. Some NHS local bodies such as Leicester, currently do not approved its prescribing due to concerns over cost-effectiveness or evidence.
 4. Prescribing is permitted under UK law but some NHS trusts have placed restrictions or have not recommended it.

Zopiclone: Is available generically and is inexpensive under the NHS formulary.

Clinical Recommendations

- Use eszopiclone for chronic insomnia when behavioural therapy is not effective or available, especially in patients needing maintenance treatment.
- Limit zopiclone to acute insomnia cases of no more than 10 days, particularly in patients with comorbid psychiatric or substance use risk.
- Avoid both drugs in elderly patients where possible due to increased fall risk.
- Monitor all patients on z-drugs for signs of tolerance, dependence, or neuropsychiatric symptoms.

Conclusion

While both eszopiclone and zopiclone provide effective short-term treatment for insomnia, eszopiclone offers more favourable long-term data and a slightly improved safety profile. Nonetheless, both agents should be prescribed with caution, emphasizing lowest effective dose and shortest duration necessary. Psychiatrists should consider these pharmacologic nuances alongside nonpharmacologic alternatives.

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