Scheduling of Hypnotics and Implications for Treatment of Patients with Insomnia

Margaret Moline, PhD

Executive Director, Head of Orexin Platform Clinical Development

Lemborexant and E2086 International Project Lead

Alzheimer's Disease and Brain Health, Eisai, Inc

Disclosure and Disclaimer

- Margaret Moline, PhD, is an employee at Eisai
- The views and opinions expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of Eisai

Introduction

- Insomnia is a very common sleep disorder that increases in incidence with age
- Untreated or poorly treated insomnia is associated with clinically important comorbidities, including hypertension, metabolic disorders, cognitive difficulties, and mood disorders
- As first line therapy, clinical guidelines recommend a specific behavioral approach, cognitive behavioral therapy for insomnia (CBT-I)[1]
- However, major limitations to CBT-I include access due to a limited number of trained therapists, adherence rates, and cost, among others[2]
  - Numerous online programs are available
  - Data suggest that CBT-I may not be as effective in patients with objective short sleep[3]
- Therefore, pharmacotherapy may be the most appropriate option for the patient

[1] Sateia, et al. 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.

[2] Pal, et al. Management of Chronic Insomnia Using Cognitive Behavior Therapy for Insomnia (CBT-I) During COVID-19 Pandemic: Does One Shoe Fit All? Sleep Vigil. 2022;6(1):51-60.

[3] Bathgate, et al. Insomnia Patients With Objective Short Sleep Duration Have a Blunted Response to Cognitive Behavioral Therapy for Insomnia. Sleep. 2017 Jan 1;40(1):zsw012.

Considerations When Selecting a Hypnotic

- The most commonly used prescription hypnotics in the US are BzRAs (z-drugs, eg, zolpidem, eszopiclone) and trazodone[1]
- Dual orexin receptor antagonists (DORAs) are newest class of approved hypnotics, but are prescribed much less often than BzRAs and trazodone
- Balance between efficacy and safety required
  - Not all approved BZRAs treat both sleep onset and sleep maintenance difficulties
  - Trazodone not approved to treat insomnia
- Safety concerns with BzRAs (Schedule IV) †
  - BzRAs associated with tolerance, dependence, rebound insomnia, daytime sedation, falls risk, potential respiratory depression, concern with coadministration with opioids, cognitive/memory difficulty, and aberrant nocturnal behaviors (black box)
  - Gradual down-titration needed with benzodiazepines and typically recommended with z-drugs, meaning that abrupt discontinuation due to emergencies may pose a safety risk[2]
  - Not recommended for elderly patients per Beers list[3]
- Safety concerns with trazodone (not scheduled)
  - Most common AEs reported include daytime sedation[4]
  - Orthostatic hypotension can occur when elderly or patients with preexisting heart disease[5]
  - Psychomotor impairment also reported[4]
- Safety concerns with DORAs (Schedule IV) †
  - Most common adverse reactions reported include somnolence, headache and nightmares/abnormal dreams

† Reference: full prescribing information

[1] IQVIA National Prescription Audit (October 2022

[2] Croke L. Deprescribing Benzodiazepine Receptor Agonists for Insomnia in Adults. Am Fam Physician. 2019 Jan 1;99(1):57-58

[3] By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2019 Apr;67(4):674-694.

[4] Mendelson WB. A review of the evidence for the efficacy and safety of trazodone in insomnia. J Clin Psychiatry. 2005 Apr;66(4):469-76.

[5] Calvi A, et al. Antidepressant Drugs Effects on Blood Pressure. Front Cardiovasc Med. 2021 Aug 3;8:704281.

Hypnotic Scheduling

- Abuse potential of BzRAs well established[1]; CSA Schedule IV drug †
  - Zolpidem served as active comparator in HAP studies with DORAs
- Abuse potential of trazodone not established, and trazodone is not scheduled
  - Section 9 drug label: "Although trazodone hydrochloride has not been systematically studied in preclinical or clinical studies for its potential for abuse, no indication of drug-seeking behavior was seen in the clinical studies with trazodone hydrochloride."
  - There are some reports of abuse[2]
- Abuse potential of DORAs established; CSA Schedule IV drug †
  - In HAP studies that enrolled recreational sedative abusers, ratings of drug liking were not different from zolpidem, and all are Schedule IV
  - 4 DORAs with unique chemical structure all have negative findings for abuse potential in animal behavioral studies
    - 3 are approved for the treatment of insomnia with no evidence for dependence or rebound insomnia (one failed in Phase 3)†
- FDA presentations[3;4]
  - "Although, a recommendation for scheduling takes under consideration all data related to the abuse potential of the drug collected though the development of the drug, in the majority of cases a positive signal of potential for abuse in human abuse liability (HAP) studies will result in a scheduling recommendation"
  - Real-world evidence suggests low recreational use[4]

† Reference: full prescribing information

[1] Zaami S, et al. Designer BDZs and Z-drugs: Pharmacology and Misuse Insights. Curr Pharm Des. 2022;28(15):1221-1229

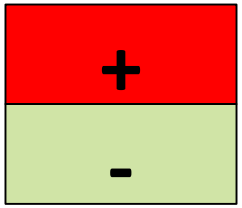
[2] https://americanaddictioncenters.org/trazodone-abuse

[3] Calderon S, et al. Evaluation of human abuse potential (HAP) studies for drugs with novel mechanisms of action. Presented at the 2020 Annual Meeting of the College on Problems of Drug Dependence

[4] Caro Y, et al. Human abuse potential results in the context of abuse detected postmarketing. Presented at the 2022 Annual Meeting of the College on Problems of Drug Dependence

Comparisons of Abuse Potential

Data	BzRAs (IV)	DORAs (IV)	Trazodone for Insomnia (not scheduled)
Nonclinical evidence	+	-	Not known
Physical dependence/withdrawal	+	-	Not known
Rebound insomnia	+	-	Not known
Real-world evidence of abuse	+	Limited data	Very limited data
Human abuse potential study in recreational hypnotic abusers	+	+	Not known



= Evidence of abuse potential

= No evidence of abuse potential

Summary and Consequences for Treatment Decisions

- Current efforts underway globally to decrease the use of BzRAs and BZs
  - Alternative treatment options should be available to replace these drugs for patients whose insomnia remains chronic
  - Desire to avoid BzRAs and BZs has led to increased off-label use of trazodone, a drug not approved to treat insomnia
  - Despite the lack of evidence for efficacy, clinicians may prescribe trazodone in part due to the belief that is it safer because it is not scheduled (primary market research with health care professionals [HCPs])
- Listing DORAs in the same schedule as BzRAs may lead to incorrect assumptions around safety profiles
  - Important due to differences in overall safety profile between DORAs and BzRAs with respect to dependence, tolerance, rebound, ability to abruptly discontinue, and aberrant nocturnal behavior
  - Schedule IV may limit access to important treatment options, like DORAs, to underserved and underrepresented communities that may benefit from them since the pool of qualified prescribers is smaller for scheduled drugs
- Focusing the scheduling assessment on HAP studies for DORAs as discussed by FDA (Calderon, et al., 2020; Caro, et al., 2022) may merit reconsideration