Insomnia Treatment Update

A Carlat Webinar

Garrett Rossi, MD

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Adult Psychiatrist, Atlanticare Regional Medical Center Pomona NJ

Conflicts and Disclosures

None

Learning Objectives

After the webinar, clinicians should:

1. Understand why the first-line treatment for insomnia is behavioral
2. Describe current pharmacotherapy approaches for the treatment of insomnia
3. Describe the indications for the use of benzodiazepines, nonbenzodiazepines, and sedating antidepressants
4. Understand the mechanism of action and how to use orexin antagonists in clinical practice

Why Is Insomnia Important to Treat?

- Chronic insomnia is highly prevalent, it effects 30% of the general population
- Insomnia is known to increase the risk of developing anxiety and depression
- Finding safe pharmacological options has been a challenge

Statistics provided by American Academy of Sleep Medicine

Nonpharmacological Treatments for Insomnia

- The American Academy of Sleep Medicine recommends cognitive behavioral therapy for insomnia (CBT-I) as a first-line treatment with strong evidence base
- Behavioral and psychological intervention that addresses the psychological and social mechanisms of chronic insomnia
- 4-8 sessions required on average, effects are maintained long term, better tolerated than medications
- Extensively studied over 130 clinical trials

Mitchell MD et al. BMC Fam Pract. 2012;25;13:40.

Pharmacological Treatment for Insomnia

- Not considered first line
- FDA approved medications for insomnia are intended for short-term use only
- Easily accessible and rapid onset of action
- Risks include daytime sleepiness, cognitive dysfunction, physiological dependence, falls in older adults
- Medications do not address the behavioral, psychological, or environmental factors

Benzodiazepine Hypnotics

- Bind to alpha-1, alpha-2, alpha-3, and alpha-5 subunits of the GABA-A receptor
- Alpha subunit expression differs throughout the brain
- Hypnotic activity at different subunits will induce effects in addition to sedation (anxiolytic, anti-pain, tolerance)
- Higher risk of tolerance and withdrawal compared to nonbenzodiazepine hypnotics
- FDA-Approved Benzodiazepine Hypnotics: Estazolam, Flurazepam, Quazepam, Temazepam, Triazolam

Nonbenzodiazepine Hypnotics

- Bind selectively to alpha subunits of the GABA-A receptor
- selectivity for the alpha-2 and alpha-3 subunits, may have anxiolytic, antidepressant, and anti-pain effects
- Due to next-morning impairment, FDA recommends lower bedtime doses
- Eszopiclone
- Zaleplon
- Zolpidem

Sedating Antidepressants

- Primarily act as antihistamines
- Trazodone
- Doxepin
- Mirtazapine

Melatonin Agonist Ramelteon

- First melatonin agonist approved for insomnia
- Full agonist at the melatonin 1 and melatonin 2 receptors
- Dosage 8 mg at bedtime, no titration required
- Common side effects sedation, dizziness, fatigue, headaches
- Should not be used with fluvoxamine and in those with severe liver disease

New Kid on the Block

- Over the past several years orexin, antagonists have become popular treatment options for insomnia
- They are considered safer than hypnotics and sedating antidepressants

How do Orexin Antagonists Work?

- Orexin neurons are in the hypothalamus
- Orexin neurons produce orexin A and orexin B
- Orexin A and B will bind to orexin 1 and orexin 2 receptors
- They promote wakefulness by regulating monoamine neurotransmitters

Dual Orexin Antagonists (DORAs)

- Currently the DORAs are only FDA approved for insomnia
- Narcolepsy is the only absolute contraindication to using orexin antagonists for insomnia
- Severe hepatic impairment is a relative contraindication and should be tested for prior to prescribing the medication
- In randomized controlled trials, all DORAs reduce time to sleep onset, reduce awake time after sleep onset, and increase total sleep time
- Potential side effects: Somnolence, fatigue, complex sleep behaviors, sleep paralysis, hypnogogic/hypnopompic hallucinations, worsening depression, and suicidal ideation

Herring WJ et al, Biol Psychiatry 2016;79(2):136-148

Suvorexant

- FDA approved for insomnia in 2014
- Starting dose is 10 mg 30 minutes prior to sleep and can be titrated to a 20 mg maximum dose once per night
- The onset of action is 30 minutes
- Half-life is 10-22 hours
- Metabolized by CYP3A4 and 2C19

Lemborexant

- FDA approved in 2019
- Starting dose is 5 mg at 30 minutes prior to sleep and can be titrated to a maximum dose of 10 mg at bedtime
- Onset is < 30 minutes
- Half-life 17-19 hours
- Metabolized by CYP3A4/5

Daridorexant

- FDA approved for insomnia in 2022
- Starting dose is 25 mg 30 minutes prior to sleep, can be titrated to a maximum dose of 50 mg at bedtime
- Onset < 30 minutes
- Half-life 5.6-8.5 hours
- Metabolized by CYP3A4

Transitioning to DORAs From Z-Hypnotics or Benzodiazepines

- There is limited data at this time
- It’s not recommended to combine or cross-taper DORA medications with benzodiazepines or z-hypnotics
- One study found increased sedation when suvorexant was added to existing benzodiazepine treatment

Hatano M et al, Psychopharmacol Neurosci 2018;31;16(2):184-189

Summary

- Insomnia is prevalent and characterized by hyperarousal and insufficient homeostatic sleep drive
- First-line treatment for insomnia is nonpharmacological (CBT-I)
- There are several pharmacological approaches including benzodiazepines, nonbenzodiazepines, sedating antidepressants, melatonin agonists, and the new orexin antagonists