

ECHO IDAHO



ECHO Idaho: Behavioral Health in Primary Care

Pharmacologic Treatment for Insomnia Disorder

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Abhilash K. Desai MD

Psychiatrist

Dr.abhilashdesai@icloud.com

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Learning Objectives

- Describe neurobiology of sleep-wake cycle
- Discuss potential risks and benefits of various psychopharmacological agents commonly used to treat insomnia
- Discuss importance of non-pharmacological interventions as primary interventions for treating chronic insomnia

Pre-Test

- Question 1: All of the following are key neurotransmitters thought to be involved in promoting sleep except:
 - (a) Galanin
 - (b) Histamine
 - (c) Melatonin
 - (d) Gama-aminobutyric acid

Pre-Test

- Question 2: All of the following are key neurotransmitters thought to be involved in promoting wakefulness except:
 - (a) Galanin
 - (b) Serotonin
 - (c) Norepinephrine
 - (d) Histamine

Pre-Test

- Question 3: Adverse effects outweigh beneficial effects for most patients with use of the following agent for chronic insomnia:
 - (a) zolpidem
 - (b) doxepin (3-6mg)
 - (c) temazepam
 - (d) ramelteon

Pre-Test

- Question 4: The following sleep promoting medication has an extended-release version and a transoral version?
 - (a) suvorexant
 - (b) zaleplon
 - (c) zolpidem
 - (d) eszopiclone

Pre-Test

- Question 5: The following sleep promoting agent has been found to have benefits in improving anxiety, depression, and pain besides sleep?
 - (a) suvorexant
 - (b) ramelteon
 - (c) eszopiclone
 - (d) triazolam

Pre-Test

- Question 6: These two are the best options for as-needed rescue medication to help speed the return to sleep in middle insomnia?
 - (a) zaleplon and eszopiclone
 - (b) zolpidem (transoral) and triazolam
 - (c) temazepam and zolpidem (transoral)
 - (d) zaleplon and zolpidem (transoral)

Pre-Test

- Question 7: Which of the following conditions should melatonin be considered as first line therapy for insomnia?
 - (a) insomnia in older adults
 - (b) insomnia in individuals with substance use disorder
 - (c) insomnia in individuals with autism or other neurodevelopmental disorders
 - (d) insomnia in long-term care populations

Pre-Test

- Question 8: This sleep promoting agent is especially well-suited for use in patients with obstructive sleep apnea and COPD who have sleep-onset problems?
 - (a) temazepam
 - (b) zolpidem
 - (c) doxepin (3-6mg)
 - (d) ramelteon

Pre-Test

- Question 9: Which of the following is highly selective H1 receptor antagonist?
 - (a) diphenhydramine
 - (b) doxylamine
 - (c) mirtazapine
 - (d) doxepin (3-6mg)

Pre-Test

- Question 10: Activity of histamine neurons is relatively high during this period of sleep.
 - (a) Early part.
 - (b) Middle part.
 - (c) Terminal part.
 - (d) It is the same throughout.

Pre-Test

- Question 11: Which of the following is treatment of choice for problems staying asleep at the end of the night?
 - (a) extended release zolpidem
 - (b) ramelteon
 - (c) trazodone
 - (d) doxepin (3-6mg)

Pre-Test

- Question 12: This is one of the first line agents for patients having sleep-onset plus sleep-maintenance insomnia
 - (a) doxepin (3-6mg)
 - (b) zaleplon
 - (c) ramelteon
 - (d) suvorexant

Pre-Test

- Question 13: Which of the following agent promotes sleep by antagonizing norepinephrine?
 - (a) doxepin (3-6mg)
 - (b) prazosin
 - (c) suvorexant
 - (d) mirtazapine

Pre-Test

- Question 14: This is the agent with best evidence for insomnia related to nightmares.
 - (a) doxepin (3-6mg)
 - (b) prazosin
 - (c) trazodone
 - (d) mirtazapine

Pre-Test

- Question 15: Weight gain has been linked to all of the following neurotransmitters except
 - (a) histamine
 - (b) 5-HT_{2c}
 - (c) acetylcholine
 - (d) dopamine

Pre-Test

- Question 16: All of the following medications are NOT recommended for treatment of chronic insomnia by the 2017 Clinical Practice Guidelines by the American Academy of Sleep Medicine except
 - (a) trazodone
 - (b) melatonin
 - (c) valerian
 - (d) zolpidem

Pre-Test

- Question 17: All of the following statements are true regarding use of trazodone in older adults except
 - (a) trazodone has same risk of falls as benzodiazepines in nursing home residents
 - (b) trazodone has same risk of falls as antipsychotics in older adults with dementia
 - (c) trazodone has same risk of mortality as antipsychotics in older adults with dementia
 - (d) trazodone increases the risk of orthostatic hypotension in older adults

Pre-Test

- Question 18: Which of the following non-pharmacological intervention has the best evidence for treatment of chronic insomnia?
 - (a) Cognitive Behavior Therapy for Insomnia (CBT-I)
 - (b) Bright light therapy
 - (c) Music therapy
 - (d) Exercise

Sleep

- Essential for emotional and cognitive fitness.
- Essential for brain to heal itself.
- Essential for healthy immune system.
- Essential for survival.

Insomnia

- Acute and Chronic
- Sleep onset and Sleep maintenance insomnia
- Insomnia (especially chronic insomnia) associated with high morbidity (including depression, Alzheimer's disease, risk of suicide) and increased mortality.
- Comprehensive assessment is recommended including assessment for drug-induced insomnia, insomnia due to other conditions (e.g., pain, depression, obstructive sleep apnea, restless leg syndrome, REM sleep behavior disorder, micronutrient deficiencies [e.g., hypomagnesemia, iron deficiency], endocrine dysfunction).
 - Qaseem A, Kansagara D, Forcica MA, Cooke M, Denberg TD. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2016;165(2):125–133
 - Desai and Grossberg 2017. *Psychiatric consultation in long-term care: A guide for healthcare professionals.* Cambridge University Press.

Neurobiology of Insomnia

- Increased inflammatory biomarkers (e.g., high sensitivity C reactive protein [CRP]).
 - Increased markers of oxidative stress.
 - Increased biomarkers for stress (e.g., increased serum cortisol levels)
 - Increased basal metabolic rate
 - Increased blood pressure
 - Increased consumption of glucose by the brain
- Winkelman JW. Insomnia disorder. New England Journal of Medicine 2015.

Key Neurotransmitters for Sleep-Wake Cycle

- Sleep-promoting networks: Gama-aminobutyric acid (GABA), galanin, melatonin.
- Wake-promoting networks: Hypocretin/orexin, norepinephrine, histamine, acetylcholine, serotonin, dopamine
 - Krystal AD. Treatment of Insomnia. American Psychiatric Association Publishing Textbook of Psychopharmacology. 5th Edition 2017.

Benzodiazepines

- Approved by FDA: triazolam, temazepam, flurazepam, estazolam, quazepam.
- Very broad effects and affect many brain systems, hence adverse effects outweigh benefits for most patients for treatment of chronic insomnia
 - Krystal AD. Treatment of Insomnia. American Psychiatric Association Publishing Textbook of Psychopharmacology. 5th Edition 2017.

Non-Benzodiazepine Benzodiazepine Receptor Agonists (BzRAs)

- Approved by FDA: zolpidem, zaleplon, eszopiclone
- Treatment of choice for short-term use of sleep onset insomnia
- Zolpidem is available as extended release and transoral (sublingual and oral spray) formulation
- Zaleplon and transoral zolpidem are options of choice for as-needed rescue medication to help speed return to sleep in middle insomnia
- Eszopiclone and extended release zolpidem are preferred for sleep-onset and sleep-maintenance insomnia (short-term use)
- Eszopiclone has been found to improve anxiety, depression and pain besides insomnia.

– Krystal AD. Treatment of Insomnia. American Psychiatric Association Publishing Textbook of Psychopharmacology. 5th Edition 2017.

BzRAs

- Zolpidem: 5mg, 10mg. Controlled release: 6.25mg, 12.5mg. Transoral (sublingual): 1.75mg, 3.5mg. In older adults: 5mg or 6.25mg.
 - Zaleplon: 5mg, 10mg. Max dose 20mg. In older adults: 5-10mg.
 - Eszopiclone: 1mg, 2mg, 3mg. In older adults: 1-2mg.
- Krystal AD. Treatment of Insomnia. American Psychiatric Association Publishing Textbook of Psychopharmacology. 5th Edition 2017.

BzRAs

- FDA recently (4/30/2019) issued new boxed warnings for zolpidem, eszopiclone and zaleplon regarding rare but serious risks of complex sleep behaviors (e.g., sleep walking, sleep driving) and related serious injuries associated with use of these hypnotics.
 - <https://www.fda.gov/drugs/drug-safety-and-availability/fda-adds-boxed-warning-risk-serious-injuries-caused-sleepwalking-certain-prescription-insomnia>

Melatonin-receptor agonist Melatonin

- First-line therapy for insomnia in patients with autism and other neurodevelopmental disorders (Krystal 2017).
 - May be considered for delayed sleep phase disorder and other circadian rhythm disorders.
 - May be considered for short-term use for sleep-onset insomnia.
 - Optimal dose of melatonin is yet to be established. In older adults: 0.2-1mg may suffice. In Autism: 1-10mg. (available as 200mcg to 20mg)
 - Prolonged-release formulation is available.
 - Melatonin is NOT recommended for chronic insomnia (AASM 2017)
 - Melatonin (high dose in some cases) may help REM Sleep Behavior Disorder
 - I recommend using eye-mask for creating total darkness.
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- Krystal AD. Treatment of Insomnia. American Psychiatric Association Publishing Textbook of Psychopharmacology. 5th Edition 2017.
 - AASM (American Academy of Sleep Medicine) Clinical Practice Guidelines. Journal of Clinical Sleep Medicine. 2017.

Melatonin-receptor agonist Ramelteon

- More potent than melatonin.
- 8mg nightly.
- One of the first line therapies for sleep onset insomnia.
- Well suited for patients with obstructive sleep apnea and COPD (Krystal 2017).
- May be used for chronic insomnia (Strength of recommendation: weak) (AASM 2017)
- Not well studied in older adults.
 - Krystal AD. Treatment of Insomnia. American Psychiatric Association Publishing Textbook of Psychopharmacology. 5th Edition 2017.
 - AASM (American Academy of Sleep Medicine) Clinical Practice Guidelines. Journal of Clinical Sleep Medicine. 2017.

Melatonin-receptor agonist Tasimelteon

- Approved for treatment of Non-24 hour Sleep-Wake Disorder (generally seen in individuals with congenital blindness).
- 20mg nightly.
- Not well studied in older adults.
 - Desai and Grossberg 2017. Psychiatric consultation in long-term care: A guide for healthcare professionals. Cambridge University Press.

Selective Histamine H1 Receptor Antagonist Doxepin (3-6mg)

- Doxepin in doses of 3-6mg is the only selective histamine H1 receptor antagonist available for treatment of insomnia (FDA approved).
- Largest effect size appears not at peak blood levels (3-4 hours after dosing) but in the last hour of an 8-hour night.
- Activity of histamine neurons is relatively high during the terminal period of sleep.
- For elderly, even these low doses may be associated with anti-cholinergic effects.
- Not well studied in older adults (3mg max in elderly).
- Available as liquid (10mg/ml); much cheaper than brand name 3-6mg pills.
 - Krystal AD. Treatment of Insomnia. American Psychiatric Association Publishing Textbook of Psychopharmacology. 5th Edition 2017.
 - AASM (American Academy of Sleep Medicine) Clinical Practice Guidelines. Journal of Clinical Sleep Medicine. 2017.

Hypocretin-Orexin Receptor Antagonist Suvorexant

- Elimination half-life: 9-13 hours.
 - 10-20mg nightly, 30 minutes before bedtime.
 - One of the first line therapies for sleep onset AND sleep maintenance insomnia.
 - Well suited for patients with obstructive sleep apnea and COPD (Krystal 2017).
 - May be used for chronic insomnia (Strength of recommendation: weak) (AASM 2017).
 - Day-time sedation, headache, dry mouth, sleep paralysis, parasomnias may be seen. Avoid in individuals with Narcolepsy.
 - Not well studied in older adults.
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- Krystal AD. Treatment of Insomnia. American Psychiatric Association Publishing Textbook of Psychopharmacology. 5th Edition 2017.
 - AASM (American Academy of Sleep Medicine) Clinical Practice Guidelines. Journal of Clinical Sleep Medicine. 2017.

Hypocretin-Orexin Receptor Antagonist Suvorexant

- A recent RCT found that suvorexant improved sleep in individuals with AD dementia by half an hour (AAN 2019).
- Some individuals with AD dementia have high levels of orexin in their CSF and this may contribute to disruption in their sleep-wake cycle (Gabelle et al 2017)
 - AAN:American Academy of Neurology 2019 Annual Meeting, Philadelphia.
 - Gabelle et al. *Neurobiology of Aging*. 2017;53:59-66.

Selective alpha-1 adrenergic receptor antagonists

- Prazosin, doxazosin, tamsulosin, terazosin
 - Prazosin is the medication most studied for Rx of nightmares
 - May cause orthostatic hypotension and dizziness
 - May be considered for treatment of insomnia related to nightmares and PTSD
 - Not approved by FDA for treatment of insomnia or nightmares.
 - Half-life: 2-3 hours.
 - Dose: 2-16mg nightly. Titration period – 5 weeks. Higher doses may be needed in select cases.
 - Not well studied in older adults.
- Krystal AD. Treatment of Insomnia. American Psychiatric Association Publishing Textbook of Psychopharmacology. 5th Edition 2017.

Non-selective anti-histaminics

- Diphenhydramine and doxylamine
 - Not recommended for treatment of chronic insomnia because risks outweigh benefits.
 - May be considered for short-term use to treat insomnia associated with allergies.
 - Tolerance often develops within three days.
- Krystal AD. Treatment of Insomnia. American Psychiatric Association Publishing Textbook of Psychopharmacology. 5th Edition 2017.

Antidepressant Trazodone

- Sedative effects through antagonization of histamine, norepinephrine, and 5-HT₂ receptors (Krystal 2017)
- Dose 12.5-150mg
- Elimination half life: 7-15 hours
- Often used for sleep maintenance insomnia along with an antidepressant (e.g., bupropion) in patients with depression and insomnia.
- May cause daytime sleepiness and orthostatic hypotension.
- NOT recommended for treatment of chronic insomnia (AASM 2017).
 - Krystal AD. Treatment of Insomnia. American Psychiatric Association Publishing Textbook of Psychopharmacology. 5th Edition 2017.
 - AASM (American Academy of Sleep Medicine) Clinical Practice Guidelines. Journal of Clinical Sleep Medicine. 2017.

Antidepressant Trazodone

- Low dose trazodone use was associated with falls at rates similar to benzodiazepines in nursing home populations (Bronskill 2018)
- Trazodone associated with falls at rates similar to antipsychotics in older adults with dementia but trazodone was associated with lower mortality risk compared to antipsychotics (Watt et al 2018).
 - Bronskill et al. Low-dose trazodone, benzodiazepines and falls-related injuries in nursing homes: A matched cohort study. Journal of American Geriatrics Society 2018.
 - Watt et al. Comparative risk of harm associated with trazodone or anti-psychotics in older adults with dementia: a retrospective cohort study. Canadian Medical Association Journal 2018.

Antidepressant Mirtazapine

- Sedative effects through antagonism of histamine and 5-HT₂ receptors (Krystal 2017)
- Dose 7.5-30mg
- Elimination half life: 20-40 hours
- Often used in low doses (7.5-15mg) for insomnia in older adults.
- May cause daytime sleepiness.
- As the dose increases, sedating effects may decrease because of increased norepinephrine neurotransmission at higher doses.
- Mirtazapine is not mentioned in Clinical Practice Guidelines for pharmacotherapy of chronic insomnia (AASM 2017).
 - Krystal AD. Treatment of Insomnia. American Psychiatric Association Publishing Textbook of Psychopharmacology. 5th Edition 2017.
 - AASM (American Academy of Sleep Medicine) Clinical Practice Guidelines. Journal of Clinical Sleep Medicine. 2017.

Tricyclic Antidepressants

- Amitriptyline, Doxepin and Trimipramine
- May be considered for insomnia in patients with treatment resistant depression.
 - Krystal AD. Treatment of Insomnia. American Psychiatric Association Publishing Textbook of Psychopharmacology. 5th Edition 2017.

Antidepressant induced insomnia

- SSRIs and Bupropion are associated with similar rates of insomnia.
 - Krystal AD. Treatment of Insomnia. American Psychiatric Association Publishing Textbook of Psychopharmacology. 5th Edition 2017.

Antipsychotic Olanzapine

- Elimination of half-life: 20-54 hours (Krystal 2017)
- May be considered to manage insomnia associated with mania, delirium, schizophrenia, and treatment-resistant depression.
- Day time sedation besides other risks.
- Clinical Practice Guidelines for pharmacotherapy of chronic insomnia does not mention olanzapine (AASM 2017)
 - Krystal AD. Treatment of Insomnia. American Psychiatric Association Publishing Textbook of Psychopharmacology. 5th Edition 2017.
 - AASM (American Academy of Sleep Medicine) Clinical Practice Guidelines. Journal of Clinical Sleep Medicine. 2017.

Antipsychotic Quetiapine

- Elimination of half-life: 7 hours (Krystal 2017)
- May be considered to manage insomnia associated with mania, delirium, schizophrenia, and treatment-resistant depression.
- Day time sedation besides other risks.
- Only one study mentioned in Clinical Practice Guidelines for pharmacotherapy of chronic insomnia (AASM 2017)
 - Krystal AD. Treatment of Insomnia. American Psychiatric Association Publishing Textbook of Psychopharmacology. 5th Edition 2017.
 - AASM (American Academy of Sleep Medicine) Clinical Practice Guidelines. Journal of Clinical Sleep Medicine. 2017.

Weight gain

- Associated with agents having antagonism at histamine, 5-HT_{2C} and acetylcholine receptors.
 - Krystal AD. Treatment of Insomnia. American Psychiatric Association Publishing Textbook of Psychopharmacology. 5th Edition 2017.
 - AASM (American Academy of Sleep Medicine) Clinical Practice Guidelines. Journal of Clinical Sleep Medicine. 2017.

Cannabidiol (CBD)

- Preliminary evidence has found beneficial effects of CBD for insomnia.
- There are potentially serious safety risks with all supplements including CBD due to possible contaminants because U.S. Food and Drug Administration does not regulate over-the-counter supplements with the same rigor as prescription medications.

– <https://www.health.harvard.edu/blog/cannabidiol-cbd-what-we-know-and-what-we-dont-2018082414476> .

Clinical Practice Guidelines for Pharmacologic Treatment of Chronic Insomnia

- Not recommended: Trazodone, melatonin, L-tryptophan, valerian.
- May be considered: zolpidem, zaleplon, eszopiclone, temazepam, ramelteon, suvorexant, doxepin (3-6mg); Strength of recommendation Weak.
 - AASM (American Academy of Sleep Medicine) Clinical Practice Guidelines. Journal of Clinical Sleep Medicine. 2017.

Nonpharmacological Treatments for Chronic Insomnia

- Cognitive Behavior Therapy – Insomnia (CBT-I) has the best evidence amongst all nonpharmacological interventions for treatment of chronic insomnia.
- Brief Behavior Therapy for Insomnia (BBTI) has next best evidence.
- Exercise, music therapy and bright light therapy / exposure to sunlight and outdoors may also be considered.
 - Wilson SJ, Nutt DJ, Alford C, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. *J Psychopharmacol.* 2010;24(11):1577–1601.
 - Qaseem A, Kansagara D, Forcica MA, Cooke M, Denberg TD. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2016;165(2):125–133.

CBT-I

- Cognitive Therapy
- Relaxation training
- Sleep hygiene training
- Sleep restriction
- Stimulus control
- CBT-i coach (best app; free; from Veterans Administration USA)
 - <https://aasm.org/resources/factsheets/insomnia.pdf>
 - Wilson SJ, Nutt DJ, Alford C, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. *J Psychopharmacol.* 2010;24(11):1577–1601.
 - Qaseem A, Kansagara D, Forcica MA, Cooke M, Denberg TD. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2016;165(2):125–133.

Other Interventions for Treatment of Insomnia

- Referral to consultant pharmacist for medication review to discontinue medications that may cause or contribute to insomnia. Consider checking anticholinergic burden score: www.acbcalc.com . Consider checking information on www.trchealthcare.com (Therapeutic Research Center).
- Referral to dietician for diet that promotes good sleep and eliminating food and drinks that may cause or contribute to insomnia (e.g., caffeine).
 - Wilson SJ, Nutt DJ, Alford C, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. *J Psychopharmacol.* 2010;24(11):1577–1601.
 - Qaseem A, Kansagara D, Forcica MA, Cooke M, Denberg TD. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2016;165(2):125–133.

Post-Test Answers Key

- 1: (b) histamine
- 2: (a) galanin
- 3: (c) temazepam
- 4: (c) zolpidem
- 5: (c) eszopiclone
- 6: (d) zaleplon and zolpidem (transoral)
- 7: (c) insomnia in individuals with autism and other neurodevelopmental disorders
- 8: (d) ramelteon
- 9: (d) doxepin (3-6mg)
- 10: (c) terminal part
- 11: (d) doxepin (3-6mg)
- 12: (d) suvorexant
- 13: (b) prazosin
- 14: (b) prazosin
- 15: (d) dopamine
- 16: (d) zolpidem
- 17: (c) trazodone has LOWER mortality than antipsychotics
- 18 (a) CBT

In summary

- Understanding the neurobiology of sleep-wake cycle is key to recognizing the importance of treating insomnia disorder and complexity of such an endeavor.
- Pharmacologic interventions for insomnia may carry more benefits than risks for acute insomnia but risk benefit ratio for chronic insomnia is unclear. Chose wisely 😊 (www.choosingwisely.org)
- CBT-I should be first line therapy for all patients with chronic insomnia.