PHARMACOLOGY

Insomnia

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DISCLOSURE

None

Use Statement

OBJECTIVES

1. Identify the appropriate drugs and drug classes for managing insomnia.
2. Explain the mechanism of action of benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonists ("z-hypnotics"), melatonin receptor agonists, and orexin receptor antagonists and correlate to the underlying pathophysiology of insomnia
3. Describe adverse effects and contraindications to benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonists ("z-hypnotics"), melatonin receptor agonists, and orexin receptor antagonists
4. Describe the clinically important drug interactions of benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonists ("z-hypnotics"), melatonin receptor agonists, and orexin receptor antagonists
5. State drugs and drug classes that may cause insomnia

SLEEP PHYSIOLOGY RELEVANT TO PHARMACOLOGY

Neuronal systems where neurotransmitters and neuropeptides act to control the sleep–wake cycle lie in the brainstem, hypothalamus, and basal forebrain, with connections in the thalamus and cortex

Wakefulness promoted by

- Noradrenergic, histaminergic, and acetylcholine-containing neurons (modulate cortical and subcortical neurons)
- Excitatory amino acids (ie, glutamate) and stimulating neuropeptides (e.g., substance P, thyrotropin-releasing factor, corticotropin-releasing factor)

SLEEP PHYSIOLOGY RELEVANT TO PHARMACOLOGY

Sleep takes over as the wakefulness-maintaining neuronal systems weaken and sleep-promoting neurons become active

- Opiate peptides (e.g., enkephalin, endorphin) and GABA promote sleep

DEFINITIONS

Sedative = drug that decreases activity, moderates excitement, and calms the recipient

Hypnotic = drug that produces drowsiness and facilitates the onset and maintenance of a state of sleep that resembles natural sleep in its electroencephalographic characteristics and from which the recipient can be aroused easily

ACTIVE LEARNING

What is the most important INHIBITORY neurotransmitter in the CNS?

With this is mind, how might you modulate this neurotransmitter in the management of insomnia?

PHARM STRATEGIES FOR INSOMNIA

1. Benzodiazepines
   - Enhance GABA-mediated inhibition
2. Nonbenzodiazepine benzodiazepine receptor agonists “Z-hypnotics”
   - Enhance GABA-mediated inhibition
3. Melatonin receptor agonists
4. Orexin receptor antagonists

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BENZODIAZEPINES

Insomnia

GABA

Most important INHIBITORY transmitter in the CNS

GABA Receptor	Receptor Mechanism	Relevant Drugs
GABA-A	Inhibitory; ↑ Cl^- conductance	Sedative hypnotics (barbiturates, benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonists) Selected anticonvulsants (gabapentin, tiagabine, vigabatrin)
GABA-B	Inhibitory (presynaptic); ↓ Ca2+ conductance Inhibitory (postsynaptic); ↑ K+ conductance	Agonists (baclofen)

BENZODIAZEPINE MECHANISM OF ACTION

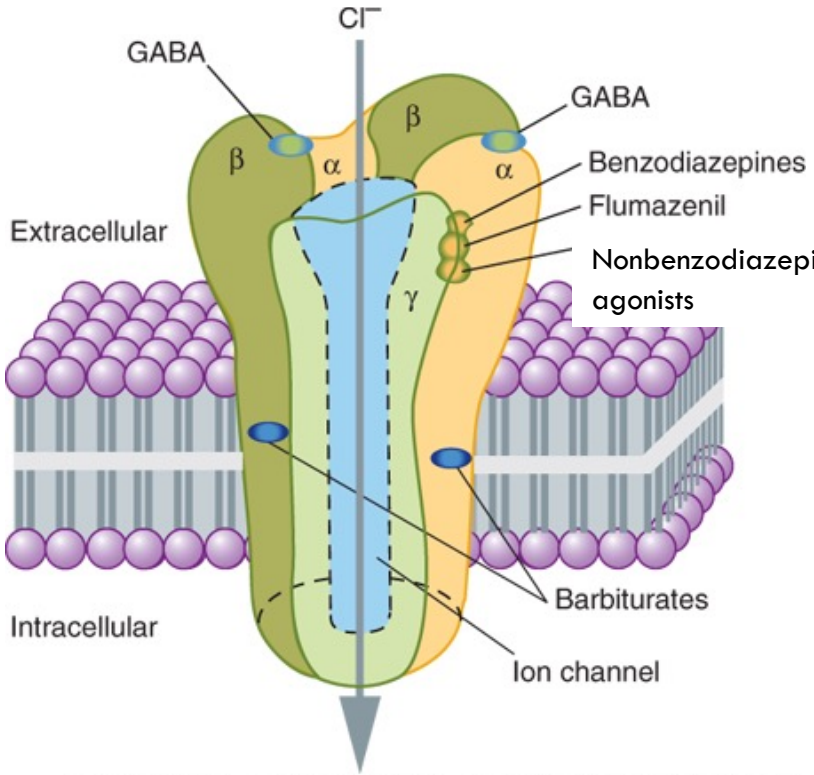
Bind to receptors located on a subunit of the GABA-A receptor-chloride ion channel macromolecular complex

- Pentameric ligand-gated, anion-conducting channel

Bind to site **DISTINCT** from GABA

Binding increases the affinity of the GABA-A receptor for GABA → **increased frequency of chloride channel opening**

Cl- flux hyperpolarizes or stabilizes the post-synaptic cell, reducing the chance that excitatory stimuli will initiate action potentials



B. G. Katzung, M. Kruidering-Hall, R. L. Tuan, T. W. Vanderah, A. J. Trevor
Katzung & Trevor's Pharmacology: Examination & Board Review, 13e

BENZODIAZEPINE MECHANISM OF ACTION

Sedation, hypnosis, decreased anxiety, muscle relaxation, anterograde amnesia, anticonvulsant activity

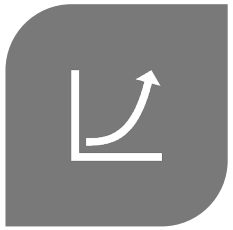
Sedation progresses to hypnosis to stupor with increasing dose

Relieve insomnia by reducing sleep latency and increasing total sleep time

Increase stage 2 sleep

Decrease REM, stage 3, and stage 4 sleep

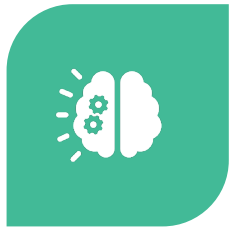
SALIENT CNS ADVERSE EFFECTS OF BENZODIAZEPINES



TOLERANCE

AFTER 2-4 WEEKS CONTINUOUS USE

DAYTIME SEDATION



ANTEROGRADE AMNESIA

USE LOWEST EFFECTIVE DOSAGE

REBOUND INSOMNIA

INCREASED WAKEFULNESS 1-2 NIGHTS AFTER ABRUPT DISCONTINUATION

DEPENDENCE AFTER PROLONGED USE

CAN LEAD TO WITHDRAWAL

BENZODIAZEPINES

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Alprazolam Diazepam Flurazepam Lorazepam Midazolam Oxazepam Temazepam Triazolam ***-am***	**Pregnancy (cleft lip or cleft palate)** Hepatic disease Respiratory disease or sleep apnea Older adults (CNS adverse effects ↑ d/t prolonged $t_{1/2}$)	Tolerance **Daytime sedation and performance impairment** **Anterograde amnesia** Rebound insomnia Paradoxical CNS stimulation Hangover Dependence after prolonged use (can lead to withdrawal)	CNS depressants enhance CNS depression of benzos

ACTIVE LEARNING

Consider the half-lives of the following benzodiazepines. How might this inform your benzodiazepine choice for patients? For an older adult patient?

Benzodiazepine	Half-life (hours)
Flurazepam	Long (40 to 114; 120 to 160 older adults)
Temazepam	Intermediate (8 to 15)
Triazolam	Short (2 to 5)

CLINICAL USE & ADME

Insomnia

Anxiety

Panic disorder

Spasticity

Status epilepticus

Eclampsia

Night terrors

Sleepwalking

Anesthetic

Administered PO, IV, PR

Extensive biotransformation in liver

Many active metabolites (increase duration of action of drug)

Benzos with long t1/2 (temazepam) should be avoided in older adults

REVERSAL AGENT - FLUMAZENIL

Specific benzodiazepine receptor ANTAGONIST

Binds with high affinity to benzodiazepine binding site on GABA-A receptor

Competitively antagonizes the binding and allosteric effects of benzodiazepines and other ligands

IV administration

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NONBENZODIAZEPINE BENZODIAZEPINE RECEPTOR AGONISTS (NBBRAs OR "Z-HYPNOTICS")

Insomnia

NONBENZODIAZEPINE BENZODIAZEPINE RECEPTOR AGONIST (NBBRA) MECHANISM OF ACTION

Structurally DIFFERENT from benzodiazepines

Interact with specific benzodiazepine receptors

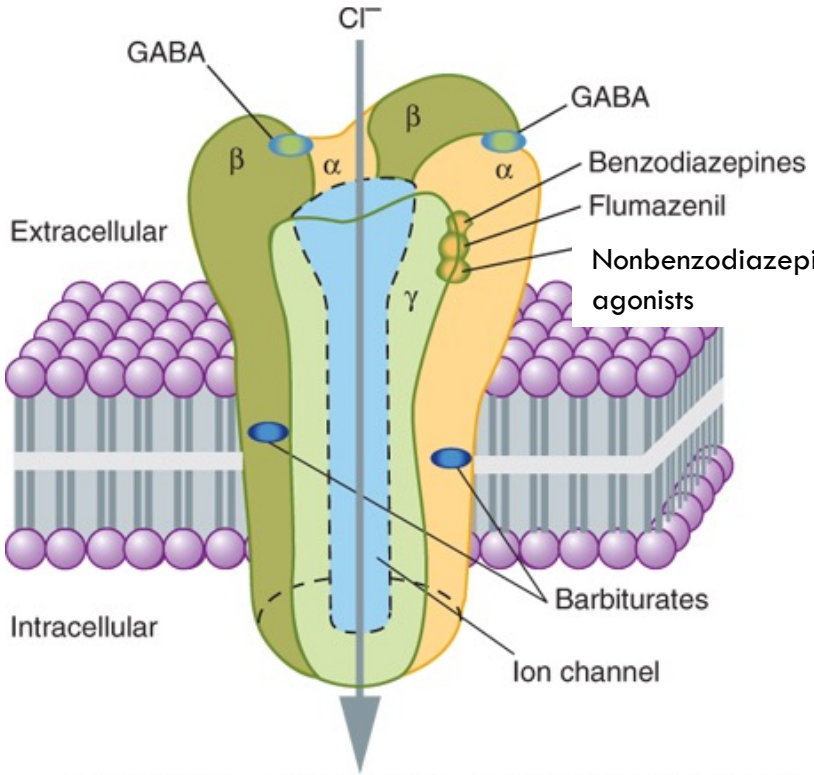
Bind more selectively

- Bind to receptors located on the BZ-1 subtype of GABA-A receptors that contain alpha-1 subunits

Bind to site DISTINCT from GABA

Binding increases the affinity of the GABA-A receptor for GABA → increased frequency of chloride channel opening

Cl- flux hyperpolarizes or stabilizes the post-synaptic cell, reducing the chance that excitatory stimuli will initiate action potentials



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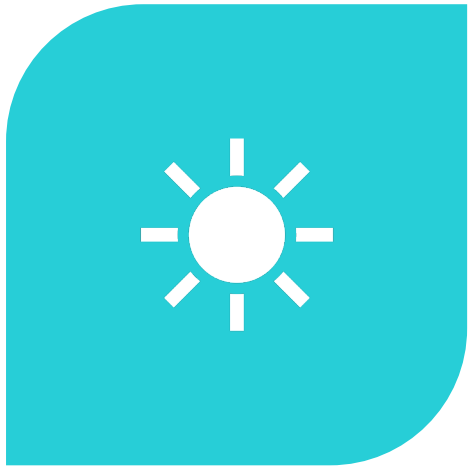
NONBENZODIAZEPINE BENZODIAZEPINE RECEPTOR AGONIST (NBBRA) MECHANISM OF ACTION

Hypnotic effects

No significant anxiolytic, muscle relaxant, or anticonvulsant effects

Little to no change in sleep architecture or sleep stages

SALIENT CNS ADVERSE EFFECTS OF NBBRAs



COMPLEX SLEEP BEHAVIORS

SLEEPWALKING, SLEEP DRIVING, ENGAGING IN ACTIVITIES WHILE NOT FULLY AWAKE

MODEST DAY-AFTER PSYCHOMOTOR IMPAIRMENT

DRIVING SIMULATION ON NBBRAs

https://www.youtube.com/watch?v=SMwmJGXhizc

NBBRAs (Z-)

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Zolpidem **Z**aleplon Es**z**opiclone **Z-**	**Alcohol use** Hepatic impairment Caution: depression, CNS depressant use, hx of alcohol or substance use disorder	Ataxia Headache Confusions **Modest day-after psychomotor depression** Amnesic effects	CNS depressants enhance CNS depression of benzos

CLINICAL USE & ADME

Insomnia

Rapid onset

Varying $t_{1/2}$ and durations of effect

Can be taken in the middle of the night (as long as individual has 4 or more hours left in bed)

Zaleplon and zolpidem have shortest $t_{1/2}$

REVERSAL AGENT - FLUMAZENIL

Specific benzodiazepine receptor ANTAGONIST

Binds with high affinity to specific sites on the GABA-A receptor

Competitively antagonizes the binding of NBBRAs

ACTIVE LEARNING

When might you prescribe a benzodiazepine over an NBBRA?

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MELATONIN RECEPTOR AGONISTS

Insomnia

MELATONIN

Endogenous hormone produced primarily in pineal gland

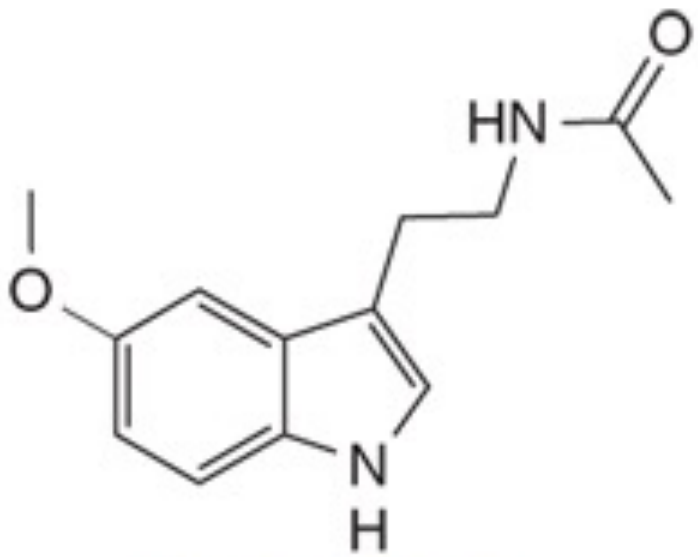
Circadian signaling molecule

- Levels increase in evening
- Levels decrease as night progresses

Synthesis influenced by environmental light

Lowers heart rate and body temperature

Helps sleep



MELATONIN

MELATONIN RECEPTORS

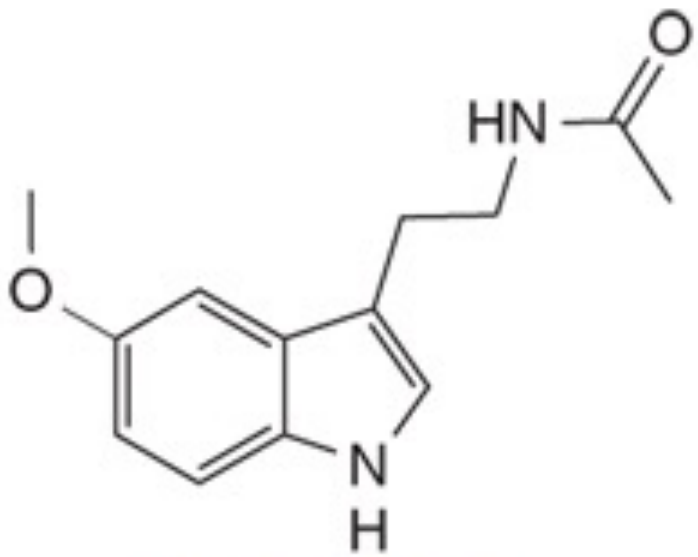
G-protein coupled receptors in suprachiasmatic nucleus

Melatonin-1 (MT-1)

- Binding promotes onset of sleep

Melatonin-2 (MT-2)

- Binding shifts timing of circadian system



MELATONIN

MELATONIN RECEPTOR AGONIST MECHANISM OF ACTION

Analog of melatonin

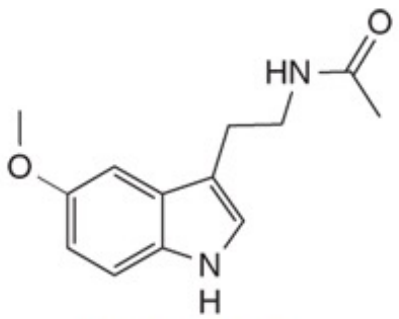
Agonist of MT-1and MT-2 receptors

Promotes onset of sleep

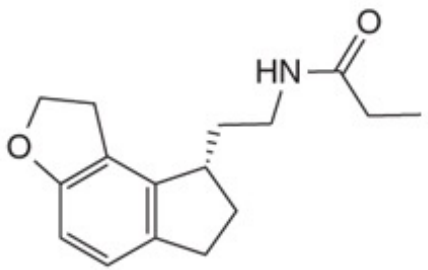
Reduces latency of persistent sleep

No effects on sleep architecture

No rebound insomnia or withdrawal symptoms



MELATONIN



RAMELTEON

MELATONIN RECEPTOR AGONISTS

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Ramelteon Tasimelteon ***-melteon***	Caution: Hepatic disease Respiratory disease or sleep apnea Avoid alcohol use	CNS depression Somnolence Headache Abnormal sleep-related activities	Inhibitors of P450 enzymes can increase serum concentrations Inducers of P450 enzymes can decrease serum concentrations

CLINICAL USES

Insomnia

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OREXIN RECEPTOR ANTAGONISTS

Insomnia

OREXIN (HYPOCRETIN)

Peptide found in hypothalamus that promotes and stabilizes wakefulness

Impacts histamine, acetylcholine, dopamine, serotonin, and norepinephrine

Orexin levels increase in the day and decrease at night

OREXIN RECEPTOR ANTAGONISTS MOA

Antagonize orexin 1 and 2 receptors

Decreases sleep onset latency

Enhances REM and non-REM sleep

OREXIN RECEPTOR ANTAGONIST (-OREXANT)

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Lemborexant Suvorexant Daridorexant ***-orexant***	Narcolepsy Cautions: Alcohol use Older adults Substance use disorders	Dizziness Nausea Fatigue Headache **Next day somnolence**	Hepatically metabolized to an active metabolite; avoid use with strong CYP3A4 inhibitors CNS depressants enhance CNS depression of benzos

CLINICAL USES

Insomnia

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SUMMARY

Insomnia

PRECAUTIONS

1. Therapy should be instituted with a low dose and maintained at the lowest effective dose
2. Continued nightly use should be avoided; patients should be encouraged to use them only when truly necessary and for no more than 2-4 weeks
3. Hypnotics with a rapid onset of action are preferable when the problem is falling asleep
4. If the problem is staying asleep, a hypnotic with a slower rate of elimination may be more appropriate

ACTIVE LEARNING

Many older adult patients have insomnia diagnoses. Which medications discussed today would be potentially appropriate for an older adult? Defend your answer.

OLDER ADULTS

Increased risk of adverse drug reactions

- Vulnerable to excessive sedation, cognitive impairment, delirium, balance problems

May have elevated mediation serum levels and prolonged effects due to decreased metabolism

Increased fall risk with severe consequences (i.e., traumatic brain injury, hip fracture) associated with benzodiazepines and nonbenzodiazepine benzodiazepine receptor agonists

- Benzodiazepines and nonbenzodiazepine benzodiazepine receptor agonists on Beer's Criteria List
  - **Nonbenzodiazepine benzodiazepine receptor agonists still used; ideally lowest effective dose**
  - If a benzodiazepine must be used, choose shorter acting

SELECTION GUIDANCE

	Sleep-onset insomnia	Sleep-maintenance insomnia	Treatment-resistant insomnia	Vulnerability to SUD	Comorbid depression or anxiety	Need for normal next-day fxn
DORAs	X	X		X		X
Benzos	X				X	
NBBRAs	X					
Doxepin		X		X		X
Ramelteon	X			X		
Anti-depressants*			X		X	
Antipsychotics*			X		X	

*Off-label use

Shaha 2023

SUMMARY TABLE

Drug	Onset	Duration	Recommendation
Zaleplon	<30 min	Ultra-short	Sleep onset Can be taken in the middle of the night
Zolpidem	<30 min	Ultra-short/short	Sleep onset/maintenance Can be taken in the middle of the night
Triazolam	<30 min	Short	Sleep onset
Ramelteon	<30 min	Short	Sleep onset
Suvorexant	30 min	Intermediate	Sleep maintenance
Temazepam	30 - 60 min	Intermediate	Sleep onset/maintenance
Flurazepam	<30 min	Long	Sleep onset/maintenance Useful if management of daytime insomnia is required

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MEDICATIONS THAT MAY CAUSE INSOMNIA

Insomnia

MEDICATIONS THAT MAY CAUSE INSOMNIA

Neuro	Over-the-counter allergy	Pulmonary	Antihypertensives
• Can cause sedation or stimulation, with individual variability • Selective serotonin reuptake inhibitors (SSRIs) • Serotonin norepinephrine reuptake inhibitors (SNRIs) • Monoamine oxidase inhibitors (MAOIs)	• Often contain stimulants such as **pseudoephedrine** or **phenylephrine** • Patients may not realize that this can contribute to insomnia	• Albuterol • Theophylline	• Beta-blockers may reduce melatonin levels

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ANY QUESTIONS?