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JUST KNOCK ME OUT: MEDICATIONS FOR INSOMNIA

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NO DISCLOSURES TO REPORT

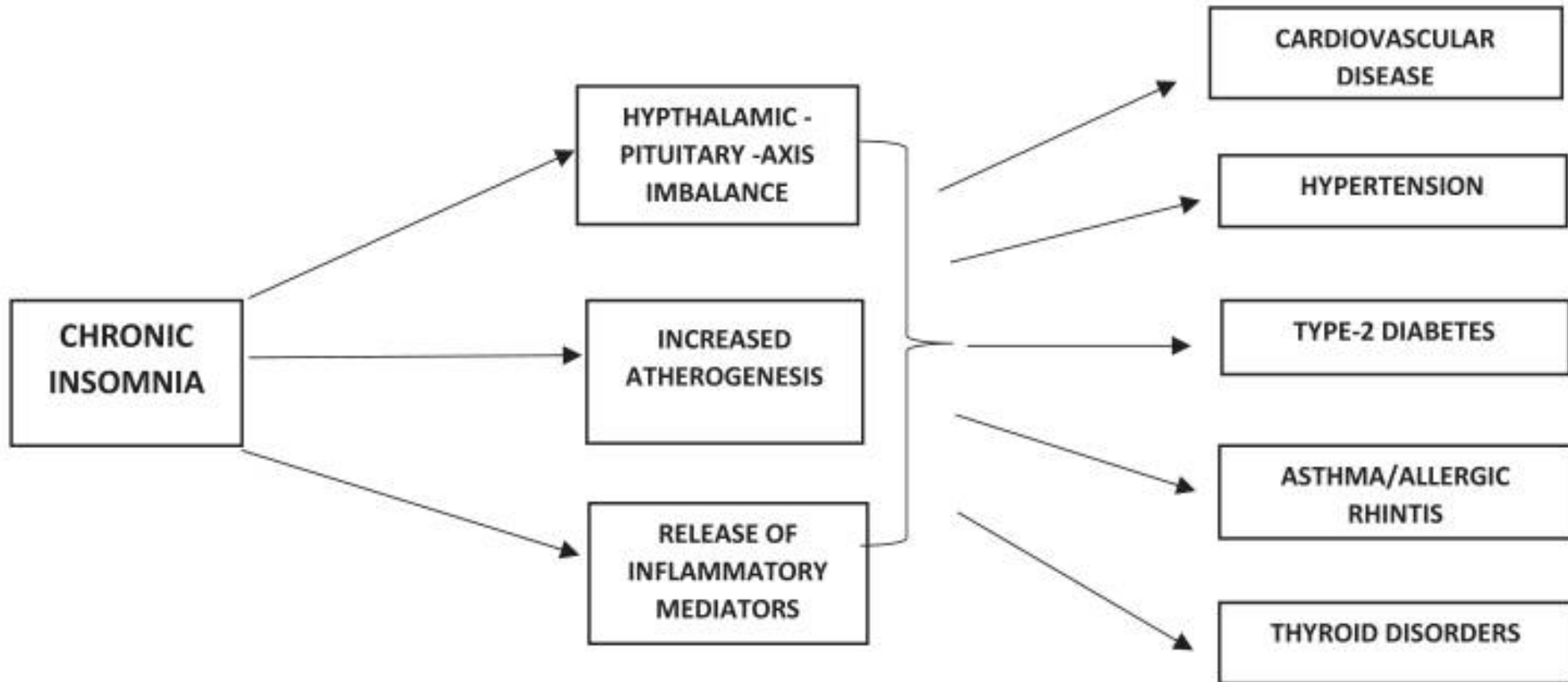
LEARNING OBJECTIVES

- Importance of insomnia diagnosis/treatment
- Define/diagnosis insomnia disorder
- Consider the broad differential in insomnia
- Explore FDA approved medication for insomnia
- Explore commonly used off label medications for insomnia
- Discuss current evidence of off label medications for insomnia

IMPORTANCE OF INSOMNIA DIAGNOSIS/MANAGEMENT

- **Quality of Life**
 - Commonly report fatigue, irritability, poor concentration, memory issues, and poor emotional regulation.
 - Treatment improves daytime functioning, mood, and overall life satisfaction.
- **Mental Health**
 - Untreated insomnia raises the risk for depression, anxiety, substance use, and suicidal ideation
 - Insomnia is an independent risk factor for depression; treating it (especially with CBT-I) can reduce depressive symptoms and relapse risk.
- **Physical Health**
 - Chronic insomnia is linked to higher risks of cardiovascular disease, hypertension, type 2 diabetes, and chronic pain.
 - Sleep disruption affects inflammation, metabolism, and stress hormones, all contributing to chronic disease.
- **Safety Risks**
 - Insomnia and sleep deprivation increase motor vehicle accidents, workplace errors, and occupational injuries.
 - Impaired reaction time and attention can be similar to alcohol intoxication.
- **Economic & Productivity Impact**
 - Insomnia causes absenteeism, presenteeism (reduced productivity at work), and higher healthcare costs.
 - Lost productivity due to insufficient sleep is estimated to cost billions annually in the U.S.

SEQUELAE OF UNTREATED INSOMNIA



IMPORTANCE OF INSOMNIA DIAGNOSIS/MANAGEMENT

- ~30–36% of adults report one or more insomnia symptom(s) in general population studies.¹
- U.S. survey data shows approximately 10-12% of adults report that they have been diagnosed with chronic insomnia by a healthcare provider.²
- Untreated insomnia disorder in the U.S. may cost as much as ~\$100 billion annually, with most of those costs coming from indirect impacts like reduced work performance and healthcare utilization.³
- There are important risk factors to consider with insomnia:⁴
 - Lower income, financial strain
 - Lower education
 - Women
 - Age

INSOMNIA DEFINITION

- Defined as predominant complaint of subjective dissatisfaction with sleep quantity or quality associated with one or more of the following:
 - Difficulty with sleep initiation
 - Difficulty maintaining sleep (nighttime awakenings)
 - Early morning awakenings

INSOMNIA DEFINITION

- DSM-V TR has suggested definitions for sleep initiation, maintenance, and awakening, though these are considered to be arbitrary
- Difficulty initiating sleep
 - Defined by subjective sleep latency of greater than 20-30 minutes
- Difficulty maintaining sleep
 - Defined as subjective time awake more than 20 - 30 minutes following sleep initiation
- Early morning awakening
 - Defined as waking at least 1 hour before the scheduled time and before total time asleep reaches 6.5 hours

INSOMNIA DISORDER DIAGNOSIS

Criteria:

- Must cause functional impairment
- Must occur at least 3x weekly
- Must occur despite adequate opportunity for sleep
- Must not be attributable to an alternative organic or psychiatric cause (i.e. substance use, narcolepsy, sleep apnea, insomnia from anxiety, etc.)*

Specifiers:

- Episodic: Symptoms last at least 1 month but last fewer than 3 months
- Persistent: Symptoms last 3 months or longer
- Recurrent: Two (or more) episodes within 1 year.

*Given sleep impairment is often multifactorial this is a challenging criteria to meet

DIFFERENTIAL DIAGNOSIS

- Sleep disorders:
 - Obstructive sleep apnea (very common)
 - Restless leg syndrome
 - Periodic leg movement disorder
 - Circadian rhythm disorders (ex. delayed sleep-wake phase disorder)
 - Narcolepsy
 - Psychiatric disorders:
 - Major depressive disorder
 - Bipolar disorder (hypomania, mania, depressive episodes)
 - Anxiety disorders
 - Schizophrenia
 - Posttraumatic stress disorder
 - Behaviorally insufficient sleep syndrome
 - Environmental issues/contributions
- Medical conditions
 - Thyroid disorders
 - Delirium
 - Acute or chronic pain syndromes
 - Dementia
 - Itching
 - Cardiac, lung, renal, or liver disease
 - Substances:
 - Marijuana
 - Cocaine
 - Methamphetamine
 - Alcohol
 - Nicotine
 - Caffeine
 - Etc.
 - Iatrogenic?

DIFFERENTIAL DIAGNOSIS: MEDICATIONS

- Nicotine patches/gum
 - Reducing total sleep time, decreasing REM sleep, and inducing vivid dreams or nightmares
- Beta blockers and alpha antagonists
 - Disruption of REM, difficulty with sleep initiation/maintenance
- Beta-agonists (e.g., albuterol) and theophylline
 - Activation, restlessness
 - May improve sleep if they reduce nighttime respiratory symptoms
- Diuretics
 - Nighttime awakenings to urinate
- Ketamine
 - Increasing slow-wave sleep, reducing nighttime wakefulness, and decreasing REM sleep in the short term; paradoxical effects
- Sleep medications
 - Often change sleep architecture, often reducing deep sleep, especially in long-term use

DIFFERENTIAL DIAGNOSIS: MEDICATIONS

- Antidepressant medications
 - Some may cause activation (prescribe in the morning), inhibition of REM sleep, and/or vivid dreams
 - Others may promote sleep
- Bupropion
 - Activation (prescribe in the morning and use XL); difficulty with sleep initiation/maintenance
- Steroids
 - Activation, restlessness, anxiety, reduce melatonin production (disrupt normal cortisol levels)
- Stimulant medications
 - Activation; difficulty with sleep initiation/maintenance
- Carbidopa/levodopa
 - Vivid dreams, difficulty with sleep initiation/maintenance
- Histaminergic medications
 - May decrease sleep quality, reduce deep sleep, cause next-day grogginess; paradoxical reactions
- Ropinirole, bromocriptine, and pramipexole
 - Daytime fatigue, “sleep attacks”

TREATMENTS FOR INSOMNIA

- Treat the underlying cause(s)
- CBT-insomnia
- Pharmacologic
 - Benzodiazepines
 - Nonbenzodiazepines hypnotics (Z-drugs)
 - Melatonin agonists
 - Dual orexin receptor antagonists
 - Antihistamines
 - Off-label treatments
 - Supplements

NON-PHARMACOLOGIC TREATMENTS

NON-PHARMACOLOGIC: CBT-INSOMNIA

- Considered gold-standard or 1st line intervention for the management of insomnia
 - If starting a medication, also utilize CBT-i concurrently
- Focuses on connection between thoughts, behaviors, and sleep that contribute to insomnia
- Treatment typically takes 6-8 sessions, though this may vary.
 - Some debate on whether maintenance therapy is helpful
- Sleep hygiene practices that are not incorporated into a course of CBT-i are not effective for management of chronic insomnia.⁵
- An RCT has found CBT-i to be more effective than non-benzodiazepines (z-drugs) in managing chronic insomnia.⁶

NON-PHARMACOLOGIC: CBT-INSOMNIA

- Components:
 - Cognitive restructuring which helps reframe inaccurate or unhelpful thoughts about sleep
 - Behavioral interventions such as relaxation training, stimulus control, and sleep restriction or compression
 - Psychoeducational interventions

NON-PHARMACOLOGIC: CBT-INSOMNIA

- Tools:
 - Consider sleep journals
 - Consider the having the patient use the CBT-i coach app
 - Created by the VA
 - Consider referral to 6-8 week therapy
 - Discuss sleep hygiene and physical activity
- May empower patients to contribute to improvements in sleep

PHARMACOLOGIC TREATMENTS

PHARMACOLOGIC: CONSIDERATIONS

- Psychotropic agents should be chosen based on:
 - Presenting sleep problem(s)
 - Comorbid diagnoses
 - Risks/adverse medication effects
- Patients who struggle with sleep initiation → short half-life agents
- Patients who struggle with late night awakenings or early morning awakenings → longer half-life agents
 - But not too long so they cause daytime fatigue
- No head-to-head trial comparing efficacy of various pharmacotherapies
- For acute insomnia, consider prescribing medication for only 1-4 weeks
 - Consider concurrent CBT-insomnia

PHARMACOLOGIC: CONSIDERATIONS

- If a patient has treatment resistant insomnia and cannot receive an adequate response to a monotherapy after multiple trials
 - Dual agent therapy may be needed OR
 - Sleep medicine specialist referral (if realistic/possible)
- When using more than one psychotropic agent for insomnia, it is important to avoid picking agents that have:
 - Metabolic or medication interactions
 - Overlapping side effect profiles
 - Similar mechanism of action for sleep initiation/maintenance

FDA APPROVED MEDICATIONS FOR INSOMNIA DISORDER

FDA-APPROVED MEDICATIONS

Generic	Brand Name	Drug Class	Receptor(s)	Onset (mins)	Dose (mg)	Sleep Indication
Quazepam	Doral	Benzodiazepine	GABA _A α-1, -2, -3, -5 subunits	30	7.5 - 15	Initiation/Maintenance
Estazolam	Prosom	Benzodiazepine		15 - 60	1 - 2	Initiation/Maintenance
Flurazepam	Dalmane	Benzodiazepine		30 - 60	15 - 30	Initiation/Maintenance
Temazepam	Restoril	Benzodiazepine		45 - 60	7.5 - 15	Initiation/Maintenance
Triazolam	Halcion	Benzodiazepine		15 - 30	0.125 - 0.25	Initiation

- Notice that commonly prescribed benzodiazepines are not listed as FDA approved medications for sleep
 - Lorazepam, clonazepam, diazepam, and alprazolam

FDA-APPROVED MEDICATIONS

Generic	Brand Name	Drug Class	Receptor(s)	Onset (mins)	Dose (mg)	Sleep Indication
Zolpidem	Ambien	Z-drug	GABA _A α-1 subunit	30	5* - 10	Initiation
Zolpidem CR	Ambien CR	Z-drug		30	6.25* - 12.5	Initiation/Maintenance
Zolpidem	Edluar	Z-drug		30	5* - 10	Initiation
Zolpidem	Intermezzo	Z-drug		30	1.75* - 3.5	Maintenance (Middle-of-the-night awakening)
Zolpidem	Zolpimist	Z-drug		30	5* - 10	Initiation
Zaleplon	Sonata	Z-drug		< 30	5 - 20	Initiation
Eszopiclone	Lunesta	Z-drug	GABA _A α-1, -2, -3, -5 subunits	15 - 30	1 - 3	Initiation/Maintenance

*Reduced dose for women

FDA-APPROVED MEDICATIONS

Generic	Brand Name	Drug Class	Receptor(s)	Onset (mins)	Dose (mg)	Sleep Indication
Suvorexant	Belsomra	Dual Orexin Receptor Antagonist	Orexin Antagonist	30 - 60	5 - 20	Initiation/Maintenance
Lemborexant	Dayvigo	Dual Orexin Receptor Antagonist	Orexin Antagonist	30 - 60	5 - 10	Initiation/Maintenance
Daridorexant	Quvivig	Dual Orexin Receptor Antagonist	Orexin Antagonist	30 - 60	25 - 50	Initiation/Maintenance
Ramelteon	Rozerem	Melatonin Agonist	Melatonin Agonist	15 - 30	8	Initiation
Tasimelteon	Hetlioz	Melatonin Agonist	Melatonin Agonist	15 - 30	20	*

*Non-24-Hour Sleep-Wake Disorder (Non-24) in adults and nighttime sleep disturbances in Smith-Magenis Syndrome (SMS)

FDA-APPROVED MEDICATIONS

Generic	Brand Name	Drug Class	Receptor(s)	Onset (mins)	Dose (mg)	Sleep Indication
Butabarbital	Butisol	Barbiturate	GABA _A α- and β- subunits	30 - 60	50 - 100	Initiation/Maintenance (2 weeks or less)
Secobarbital	Seconal	Barbiturate		~15	50 - 100	Initiation/Maintenance (2 weeks or less)
Doxepin	Silenor	Tricyclic Antidepressant H ₁ antagonism	H ₁ antagonism	30	3 - 6	Maintenance
Diphenhydramine	Benadryl (OTC)	First Generation Antihistamine	H ₁ antagonism	15 - 30	25 - 50	Initiation
Doxylamine	Unisom (OTC)	First Generation Antihistamine	H ₁ antagonism	30 - 60	25 - 50	Initiation/Maintenance

PHARMACOLOGIC: OFF-LABEL MEDICATIONS

Generic	Brand Name	Drug Class	Receptor(s)	Onset (mins)	Dose (mg)	Sleep Indication
Amitriptyline	Elavil	Tricyclic Antidepressant	H ₁ , α-1 antagonism	60 - 180	10 - 100	Initiation/Maintenance?
Nortriptyline	Pamelor	Tricyclic Antidepressant	H ₁ , α-1 antagonism	60 - 180	10 - 50	Initiation/Maintenance?
Hydroxyzine	Atarax	First Generation Antihistamine	H ₁ antagonism	15 - 30	25 - 100	Initiation/Maintenance?
Prazosin	Minipress	α ₁ antagonism	α-1 antagonism	30 - 90	1 - 15	Maintenance/Nightmares

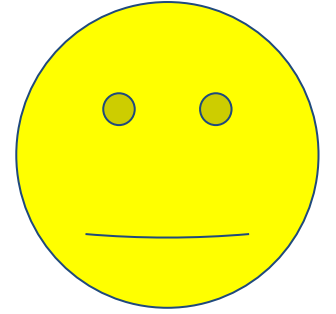
PHARMACOLOGIC: OFF-LABEL MEDICATIONS

Generic	Brand Name	Drug Class	Receptor(s)	Onset (mins)	Dose (mg)	Sleep Indication
Gabapentin	Neurontin	Anticonvulsant	α -2- δ -1 Ca^{2+} antagonism	120 - 180	100 - 900	Initiation/Maintenance?
Quetiapine	Seroquel	Atypical Antipsychotic	H_1 , α_1 , 5-HT_{2a} antagonism	30 - 90	25 - 100	Initiation/Maintenance?
Trazodone	Desyrel	Atypical Antidepressant	H_1 , α -1, 5-HT_{2a} antagonism	30 - 60	25 - 150	Initiation/Maintenance?
Mirtazapine	Remeron	Atypical Antidepressant	H_1 , 5-HT_{2a} antagonism	30 - 90	7.5 - 45	Initiation/Maintenance?

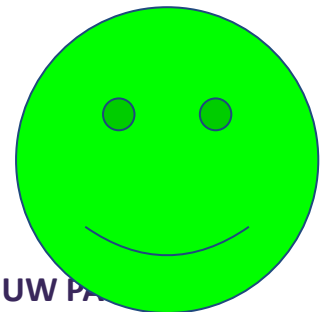
CLASS: BENZODIAZEPINES

- Medications: Quazepam, Estazolam, Flurazepam, Temazepam, Triazolam
- FDA Approval: Yes
- Mechanism of Action:
 - Sedation: Positive allosteric modulator of GABA_A
 - Bind as positive allosteric modulators to potentiate the GABA_A receptor by increasing channel opening *frequency*
 - Bind non selectively to α -subunits, 1, 2, 3, and 5
- Considerations:
 - Black Box: Risk of dependence, tolerance, withdrawal, and misuse
 - Risk for delirium, sedation, complex sleep-related behaviors, and impaired balance/falls.
 - Found to suppress deep sleep, which can compromise the restorative effects of sleep.⁷
 - No strong correlation has been found between dose and sleep latency/duration.⁷
 - Consider using the FDA approved benzodiazepines for insomnia as opposed to commonly used agents such as lorazepam, clonazepam, alprazolam, and diazepam

CLASS: BENZODIAZEPINES



- Prescribe (Yes/No):
 - Yes or consider: acute, rapid, short-term use, 7-14 days
 - No or caution: alcohol/opioid use disorder, elderly, PTSD (relative contraindication), falls, delirium, dementia/cognitive impairment, pregnancy (teratogenic), sleep apnea, pulmonary disease
- Taper:
 - Chronic (> 6 months): 10% every 2-4 weeks
 - Acute (< 6 months): 25% every 1-2 weeks
- Agent Selection:
 - Triazolam (Halcion): initiation
 - Peak concentration: 1.3 hours
 - Half-life: average 2.2 hours
 - Temazepam (Restoril): maintenance/initiation
 - Peak concentration: 1.2 - 1.6 hours
 - Half-life: 3.5 - 18.4, average 8.8 hours



CLASS: NONBENZODIAZEPINE HYPNOTICS OR Z DRUGS

- Medications: Zolpidem, Eszopiclone, Zaleplon
- FDA Approval: Yes
- Mechanism of Action:
 - Sedation: Positive allosteric modulator of GABA_A
 - Bind as positive allosteric modulators to potentiate the GABA_A receptor by increasing channel opening *frequency*
 - Bind selectively to α -1 subunits; however, eszopiclone binds to non selectively to α -subunits, 1, 2, 3, and 5
- Considerations:
 - Similar efficacy and tolerability but lower rate of dependence and tolerance compared to benzodiazepines.⁷
 - Shares the same risks of benzodiazepines of sedation, anterograde amnesia, complex sleep-related behaviors, and impaired balance/falls.⁷
 - Selectivity to α -1 subunit and shorter half lives may be responsible for less next-day fatigue and neuropsychological dysfunction compared to benzodiazepines.⁷
 - Black Box: risk of rare but serious injuries or death from complex sleep behaviors

CLASS: NONBENZODIAZEPINE HYPNOTICS OR Z DRUGS



- Prescribe (Yes/No):
 - Yes or consider: typically acute use, 1-4 week(s) use
 - No or caution: elderly, falls, delirium, dementia/cognitive impairment, current/recent/historic complex sleep behaviors
- Taper:
 - Zolpidem: ~25% every 1-2 weeks
 - Eszopiclone less likely to have withdrawal; however, may consider tapering
 - Zalepon is not known to have withdrawal so no need for taper
- Agent Selection:
 - All z-drugs are great for the FDA indications and align with appropriate peak plasma levels and half-life
 - While not proven, may consider other Z-drugs compared to eszopiclone given less selectivity to α -1 subunits

CLASS: BARBITURATES



- Medications: Butabarbital, Secobarbital
- FDA Approval: Yes
- Mechanism of Action:
 - Sedation: Positive allosteric modulator of GABA_A
 - Bind as positive allosteric modulators to potentiate the GABA_A receptor by increasing channel opening *duration*
 - Bind to α - and β -subunits
- Considerations:
 - Barbiturates are more potent and dangerous, as they can directly activate receptors and suppress respiration at higher doses, whereas benzodiazepines rely on GABA presence
- Prescribe (Yes/No): NO!
- Taper:
 - No need to taper given medication is only given for ~2 weeks and because the half-life is quite long
 - Butabarbital: ~100 hours
 - Secobarbital: ~28 hours

CLASS: DUAL OREXIN RECEPTOR ANTAGONISTS



- Medications: Suvorexant, Lemborexant, Daridorexant
- FDA Approval: Yes
- Mechanism of Action:
 - Sedation: orexin antagonism
 - Block the binding of wake-promoting neuropeptides (orexin A and B) at OX1R and OX2R receptors, inhibiting the brain's arousal system, impacting the "master switch" for wakefulness, and inhibiting neurotransmitters like histamine and acetylcholine
- Considerations:
 - No notable daytime fatigue or “hangover” effect reported
 - Does not disrupt NREM and REM sleep
- Prescribe (Yes/No):
 - Yes or consider: sleep maintenance/initiation
 - No or caution: severe hepatic dysfunction, narcolepsy, active/worsening depression (may trigger SI)
- Taper:
 - No need to taper; no physical dependence

CLASS: FIRST GENERATION ANTIHISTAMINE



- Medications: Diphenhydramine, Doxylamine
- FDA Approval: Yes, OTC
- Mechanism of Action:
 - Sedation: H₁ antagonism
 - H₁ antagonism: acts in the central nervous system, particularly in wakefulness-regulating regions such as the posterior hypothalamus, thereby inhibiting histamine's wake-promoting effects, reducing alertness, shortening sleep latency, and increasing slow-wave sleep.
 - M₁ antagonism: anticholinergic (relatively high affinity)
- Considerations:
 - Significant anticholinergic activity
 - This is a major pathway for many off-label medications
- Prescribe (Yes/No):
 - Yes or consider: itching
 - No or caution: elderly, most cases
- Taper:
 - No need to taper medications from a sleep perspective
 - Consider decreasing by 25-50% every 1-2 weeks at high doses to prevent anticholinergic withdrawal

MEDICATION: DOXEPIN



- Class: Tricyclic Antidepressant, H₁ antagonism
- FDA Approval: Yes
- Mechanism of Action:
 - Sedation: H₁ antagonism (high affinity at low dosages)
 - M₁, α-1, NET, SERT antagonism: minimal to no activity at low sleep dosages
- Considerations:
 - More selective/pure histamine blockade compared to doxylamine and diphenhydramine at low dosages
 - Often challenging to find/prescribe 3-6mg, reasonable to prescribe 10mg
- Prescribe (Yes/No):
 - Yes or consider: sleep maintenance, long-term use, depression, anxiety
 - No or caution: untreated narrow-angle glaucoma, urinary retention, elderly, history of suicide attempts (overdose), MAO-I use (current or in last 2 weeks)
- Taper:
 - No need to taper at low sleep dose

MEDICATION: RAMELTEON



- Class: Melatonin agonist
- FDA Approval: Yes
- Mechanism of Action:
 - Sedation: Melatonin agonist
 - Bind to and activate melatonin receptors (MT1/MT2), mimicking the effects of the natural hormone to modulate neuronal activity and stabilize circadian rhythms
 - About 17x more potent at the MT1/MT2 receptors than melatonin.
- Consideration:
 - Relatively good side effect profile
 - Minimal drug-drug interactions
 - Monitor for parasomnias (rare), worsening of psychiatric symptoms (depression, anxiety), increased prolactin, and rebound insomnia
- Prescribe (Yes/No):
 - Yes or consider: Difficulties with sleep initiation only, sleep augmentation
 - No or caution: active or worsening psychiatric symptoms
- Taper:
 - Does not required to be tapered (usually only a single 8mg dose)

MEDICATION: AMITRIPTYLINE

- Class: Tricyclic Antidepressant
- FDA Approval: No
- Mechanism of Action:
 - Sedation: H₁ and α-1 antagonism (high affinity even at low dosages)
 - M₁ antagonism: anticholinergic (high affinity even at low dosages)
 - NET >>> SERT antagonism: neuropathic pain, anxiety, and depression
- Evidence:
 - Systematic review/meta-analysis: No indication of RCT-level evidence for amitriptyline for insomnia; evidence base is low quality.⁹
 - Controlled trials (new):
 - Amitriptyline not clinically meaningful vs placebo beyond short term.¹⁰
 - Non-inferior to CBT-I by margin, but less effective in achieving meaningful improvements and with more side effects.¹¹

MEDICATION: AMITRIPTYLINE



- Considerations:
 - High lethality when used in suicide attempts given Na⁺ channel blockage (arrhythmias, bundle-branch blocks, etc.)
 - Blockade of α -1 receptors can lead to significant orthostasis and falls
- Prescribe (Yes/No):
 - Yes or consider: Neuropathic pain, anxiety, depression
 - No or caution: elderly (anti-cholinergic, falls), cardiac co-morbidities, history of suicide attempts (overdose), combining with other sleep aids, bipolar disorder, MAO-I use (current or in last 2 weeks)
- Taper:
 - Chronic (> 6 months): 10% every 2 weeks
 - Acute (< 6 months): 25% every 1-2 weeks

MEDICATION: NORTRIPTYLINE

- Class: Tricyclic Antidepressant
- FDA Approval: No
- Mechanism of Action:
 - Sedation: H₁ and α-1 antagonism (much less than amitriptyline)
 - M₁ antagonism (much less than amitriptyline): anticholinergic
 - NET >>> SERT antagonism: neuropathic pain, anxiety, and depression
- Evidence:
 - Systematic review/meta-analysis: No indication of RCT-level evidence for amitriptyline for insomnia; evidence base is low quality.⁹
 - Less studies when compared to amitriptyline

MEDICATION: NORTRIPTYLINE



- Considerations:
 - Less anticholinergic activity compared to amitriptyline
 - High lethality when used in suicide attempts given Na⁺ channel blockage (arrhythmias, bundle-branch blocks, etc.)
 - Blockade of α -1 receptors can lead to significant orthostasis and falls
- Prescribe (Yes/No):
 - Yes or consider: Neuropathic pain, anxiety, depression
 - No or caution: elderly (anti-cholinergic, falls), cardiac co-morbidities, history of suicide attempts, combining with other sleep aids, bipolar disorder, MAO-I use (current or in last 2 weeks)
- Taper:
 - Chronic (> 6 months): 10% every 2 weeks
 - Acute (< 6 months): 25% every 1-2 weeks

MEDICATION: TRAZODONE

- Class: Atypical Antidepressant
- FDA Approval: No
- Mechanism of Action:
 - Sedation: H₁, α-1, and 5-HT_{2a} antagonism (low doses)
 - 5-HT_{2a} antagonism: improving sleep quality by increasing slow-wave sleep
 - 5-HT_{2c} antagonism: increased appetite, possible mood/anxiety
 - SERT antagonism (higher doses): depression, anxiety
- Evidence:
 - Broad Systematic Review & Meta-Analysis (CNS Drugs) of 44 randomized controlled trials (n≈3,935) covering subjective and objective sleep outcomes (2024).¹²
 - No significant change in subjective total sleep time (TST) though mild improvement in objective TST and sleep efficiency
 - Improved subjective sleep quality (moderate effect) and fewer nocturnal awakenings and reduced wake after sleep onset (WASO).
 - Systematic review and meta-analysis (2026) showed trazodone improved total sleep time and sleep efficiency.¹³
 - Adverse effects like dizziness, sedation, headache, nausea, and somnolence.

MEDICATION: TRAZODONE



- Considerations:
 - Expert consensus to not use trazodone as a 1st line insomnia agent
 - Monitor for priapism (rare), rebound insomnia, dizziness/falls, and daytime sedation
- Prescribe (Yes/No):
 - Yes or consider: sleep maintenance/initiation, short period of time
 - No or caution: falls, history of priapism, MAO-I use (current or in last 2 weeks)
- Taper:
 - Reduction by 10-25% every 1-2 weeks

MEDICATION: QUETIAPINE

- Class: Atypical Antipsychotic
- FDA Approval: No
- Mechanism of Action:
 - Sedation: H₁, α₁, and 5-HT_{2a} antagonism (low doses)
 - D₂ antagonism (high doses): psychosis
 - M₁, M₃, M₅ antagonism: anticholinergic, hyperglycemia
 - NET and 5-HT_{1a} antagonism: depression, anxiety
- Evidence:
 - Quetiapine was associated with improved subjective sleep quality and total sleep time (48 minutes more) compared with placebo.¹⁴
 - Sleep improvements were most evident in people with generalized anxiety disorder and major depressive disorder
 - No robust, primary insomnia RCTs showing clear or any benefit.

MEDICATION: QUETIAPINE



- Considerations:
 - Expert consensus is to not use for sleep
 - Poses many medical risks including glucose dysregulation, weight gain, tardive dyskinesia, and increased risk of stroke in those with dementia.
- Prescribe (Yes/No):
 - Yes or consider: schizophrenia, bipolar disorder, MDD, GAD
 - No or caution: elderly, dementia, metabolic syndrome, type II diabetes, obesity, combining with other sleep aids, MAO-I use (current or in last 2 weeks)
 - Not a 1st line insomnia agent given significant side effect profile
- Taper:
 - Reduction by 25% every 1-2 weeks

MEDICATION: MIRTAZAPINE

- Class: Tetracyclic antidepressant
- FDA Approval: No
- Mechanism of Action:
 - Sedation: H_1 , $5-HT_{2a}$
 - Theoretically:
 - Lower doses have a higher affinity to antagonize H_1 leading to greater sedating effects
 - Higher doses, antihistamine activity is offset by increased noradrenergic transmission which reduces sedation.
 - Inhibits central α -2 adrenergic receptors leading to increased serotonin and norepinephrine.
 - Selective for presynaptic/central α -2
 - $5HT_{2C}$ antagonism: increased appetite, possible mood/anxiety
 - $5HT_3$ antagonism: decrease vomiting/nausea
 - $5HT_{1A}$ agonism: may increase prefrontal cortex dopamine

MEDICATION: MIRTAZAPINE

- Evidence:

- Systematic review and meta-analysis (2026) showed mirtazapine significantly improved objective sleep parameters such as total sleep time, slow-wave sleep %, and sleep efficiency, and reduced wake after sleep onset, compared with baseline or control conditions. Subjective sleep quality also improved.¹³
 - Adverse effects like sedation and weight gain were common
- MIRAGE Trial (2025): double-blind, placebo-controlled randomized trial in adults ≥ 65 years with chronic insomnia.¹⁵
 - Mirtazapine significantly reduced insomnia severity (Insomnia Severity Index), improved total sleep time and sleep efficiency, and decreased subjective wakefulness after sleep onset compared with placebo after 28 days of treatment.
 - Significantly improved objective sleep parameters such as total sleep time, slow-wave sleep %, and sleep efficiency, and reduced wake after sleep onset, compared with baseline or control conditions.
- DREAMING (2025): double-blind, placebo-controlled study in adults (18-85 yrs) with insomnia disorder.¹⁰
 - Findings at 6 weeks: Mirtazapine produced a clinically meaningful reduction in insomnia severity scores compared to placebo at 6 weeks.
 - Longer term: No significant differences were seen beyond 6 weeks.

MEDICATION: MIRTAZAPINE



- Considerations:
 - In the above studies, adverse side effects, most notably sedation and weight gain, were somewhat common
 - Weight gain is appetite mediated
 - Out performed both amitriptyline and trazodone in the systematic review and meta-analysis
- Prescribe (Yes/No):
 - Yes or consider: anxiety, depression, appetite stimulation, nausea, cancer population, elderly
 - No or caution: obesity, hyperphagia, MAO-I use (current or in last 2 weeks)
- Taper:
 - Reduce by 7.5 - 15mg every 1-2 weeks

MEDICATION: GABAPENTIN

- Class: Anticonvulsant
- FDA Approval: No
- Mechanism of Action:
 - Sedation: α -2- δ -1 Ca^{2+} antagonism
 - α -2- δ -1 Ca^{2+} antagonism: High affinity for binding sites throughout the brain corresponding to the presence of the voltage-gated calcium channels, especially α -2- δ -1, which seems to inhibit the release of excitatory neurotransmitters, such as glutamate and monoamines, in the presynaptic area
 - Has a cyclohexyl group added to the structure of GABA, but does not bind to GABA receptors or influence synthesis or uptake of GABA
- Evidence:
 - Gabapentin showed improvement in increased total sleep time and slow-wave sleep while, reducing sleep latency and awakenings in chronic illnesses.¹⁶
 - RLS, neuropathic pain, alcohol dependence, hot flashes in menopause, fibromyalgia, phantom limb pain, HIV-associated sensory neuropathies
 - A polysomnographic study has shown gabapentin enhances slow-wave sleep in patients with primary insomnia, improves sleep quality by increasing sleep efficiency and decreasing spontaneous arousal.¹⁷

MEDICATION: GABAPENTIN



- Considerations:
 - Rarely can contribute to or cause suicidality, depression, Steven-Johnson syndrome, or rhabdomyolysis
 - Needs to be renally adjusted
 - Most helpful with insomnia secondary to another medical illness
- Prescribe (Yes/No):
 - Yes or consider: restless leg syndrome, neuropathic pain, alcohol cravings, hot flashes, anxiety
 - No or caution: elderly, cognitive impairment, falls, CKD
- Taper:
 - Reduction by 10-25% OR 300mg every 1-2 weeks

MEDICATION: HYDROXYZINE



- Class: H1 antagonism
- FDA Approval: No
- Mechanism of Action:
 - Sedation: H1 antagonism
 - α -1, M1, 5-HT2a antagonism: minimal to no clinically significant activity; only considered in overdose
- Evidence:
 - A systematic review, only 5 studies (total \approx 207 patients) with doses ranging from 25 mg to 100 mg at bedtime.¹⁸
 - Results were mixed: some studies suggested improvements in sleep onset or subjective sleep quality, but effects on sleep maintenance and objective measures were inconsistent.
 - Hydroxyzine might be considered for short-term use in adults when other treatments are ineffective or not tolerated, but the evidence is limited and inconclusive.
- Considerations:
 - Similar histaminergic binding but no clinically significant anticholinergic binding when compared to diphenhydramine and doxylamine
- Prescribe (Yes/No):
 - Yes or consider: sleep initiation, short-term
 - No or caution: elderly
- Taper:
 - No taper needed

MEDICATION: PRAZOSIN

- Class: α_1 antagonism
- FDA Approval: No
- Mechanism of Action:
 - Sedation: α_1 antagonism
 - Blocks α_1 activity in the CNS reducing sympathetic activity
 - Blocks α_1 peripherally with vascular smooth muscle, causing vasodilation, and reducing blood pressure
- Evidence:
 - Recent meta-analysis suggests improvement in insomnia symptoms and sleep disturbance, though older analyses had mixed findings on sleep quality specifically.^{19,20}
 - There is reasonable evidence that prazosin reduces PTSD-related nightmares, with multiple meta-analyses showing statistically significant effects versus placebo.^{21,22}

MEDICATION: PRAZOSIN

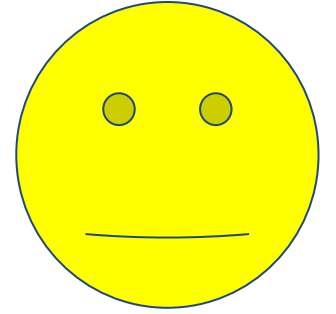


- Consideration:
 - There are many medications (tamsulosin, doxazosin, terazosin, carvedilol, etc.) with α_1 activity, review prior to prescribing this medication
- Prescribe (Yes/No):
 - Yes or consider: PTSD, nightmares, vivid dreams, arousal symptoms
 - No or caution: falls, orthostatic hypotension, current use of other α_1 antagonists
- Taper:
 - Reduction by 1-2mg every 1-2 weeks

SUPPLEMENT: MELATONIN

- Class: Melatonin
- FDA Approval: No
- Mechanism of Action:
 - Sedation: MT1/2 inhibition
 - Binds to MT1 and MT2 receptors in the suprachiasmatic nucleus of the hypothalamus, reducing neural firing to lower body temperature and decrease alertness
 - MT1 receptors inhibition induces sleepiness and MT2 Receptors inhibition helps to shift the phase of circadian rhythms.
- Evidence:
 - A meta-analysis showed that melatonin can reduce time to fall asleep (~5–10 minutes) and slightly improving sleep efficiency, especially in older adults.²³
 - Effects on total sleep time or staying asleep are small and inconsistent.

SUPPLEMENT: MELATONIN



- Consideration:
 - Dosing typically 1-3mg
 - Not regulated, unclear what you are actually getting
 - Generally well tolerated with minimal adverse effects and no significant medication interactions. Can be combined with other psychotropic agents for sleep.
 - Monitor for causing vivid dreams and/or nightmares
 - Evidence does not support melatonin as a broadly effective long-term insomnia treatment
 - In most cases, use ramelteon instead
- Prescribe (Yes/No):
 - Yes or consider: circadian cycle insomnia, sleep augmentation, maybe?
 - No or caution: chronic insomnia, current use of ramelteon

SUPPLEMENT: CANNABIS



- Class: CB1 agonist
- FDA Approval: No
- Mechanism of Action: CB1 agonism
 - CB1 agonism (THC): inhibits orexin secretion which increases total sleep time and slow-wave sleep while reducing REM sleep and sleep latency
- Evidence:
 - Meta-analysis of 6 randomized, placebo-controlled trials (1,077 adults) found that cannabinoid treatments significantly improved subjective sleep quality compared with placebo.²⁴
 - The effect on self-reported sleep quality was small to moderate overall (standardized mean difference ~0.53, $p = 0.04$).
 - CBD-only interventions did not show significant improvements.
 - A separate 2025 meta-analysis of polysomnographic studies found that cannabis does not consistently alter objective sleep measures such as total sleep time, latency, efficiency, or staging.²⁵
- Consideration:
 - Some evidence for subjective sleep quality improvement and no consistent improvements seen in polysomnographic parameters
 - Low doses of THC may promote sleep, while high doses may cause, or contribute to, fragmented sleep or daytime sleepiness.
 - Side effects include altered perception, increased appetite, impaired cognition/memory, sedation, anxiety, depressed mood, psychosis
- Recommend (Yes/No): No!

SUPPLEMENT: VALERIAN ROOT



- Class: GABA modulation
- FDA Approval: No
- Mechanism of Action:
 - Increases gamma-aminobutyric acid (GABA) levels and metabolites may inhibit GABA breakdown
 - Modulate GABAA receptors to induce sedation and reduce anxiety.
 - 5-HT1a antagonism (possibly): anxiety
- Evidence:
 - Valerian is generally safe with low risk of severe adverse effects.²⁶
 - Some meta-analyses show modest improvements in perceived sleep quality, but results are inconsistent across studies.²⁶
 - No consistent evidence that valerian significantly improves sleep latency, total sleep time, or sleep efficiency measured by polysomnography or actigraphy.²⁷
- Considerations:
 - Studies often use 160 to 600 mg of extract, often taken 1-2 hours before bedtime
 - Possibly more effective when taken consistently for 1-2 weeks.
 - Consider counseling against use if using multiple GABA or serotonin agents
- Recommend (Yes/No): No!

SUPPLEMENT: MAGNESIUM

- Class: GABA Modulation
- FDA Approval: No
- Mechanism of Action:
 - Enhancing GABAergic activity (promoting relaxation) and inhibiting NMDA receptors (reducing excitatory neurotransmission), lowering cortisol, and regulating melatonin, which together help modulate the central nervous system and reduce muscle tension.
- Evidence:28
 - Meta-analytic evidence supports a modest reduction (~17 min) in sleep onset latency with magnesium supplementation in older adults with insomnia.
 - Possible increase in total sleep time, but not consistently statistically significant across trials.
 - Some RCTs (e.g., with magnesium L-threonate) show improvements in objective sleep quality, REM sleep stages, as well as subjective measures.
 - Other pilot RCTs find modest subjective improvements in sleep severity scales.

SUPPLEMENT: MAGNESIUM



- Considerations:
 - Overall evidence is mixed and often low quality, especially for general populations. Trials are relatively small, vary in magnesium form/dose, and often lack long durations.
 - Magnesium may modestly improve sleep onset and aspects of sleep quality, especially in older adults or people with insomnia symptoms; the effects are generally small.
 - Common formulations include: magnesium glycinate (most common), L-threonate, and taurate
 - Would not use magnesium citrate given laxative effect
- Recommend (Yes/No): No, probably not. Though would be less likely to have patient discontinue.



SUMMARY

- Insomnia diagnosis/treatment is important because it impacts mental/medical health, quality of life, safety, and economic issues.
- CBT-insomnia is the gold-standard, first-line intervention for insomnia management.
- Pharmacologic treatment depends on the sleep problem and comorbidities.
- FDA-approved classes include certain benzodiazepines, Z-drugs, ramelteon, doxepin, doxylamine, diphenhydramine, and DORAs.
- Quetiapine and trazodone are not 1st line sleep agents and should not be used in most/many cases.
- May consider mirtazapine, gabapentin, hydroxyzine, and prazosin in specific cases for sleep impairment.
- Melatonin, cannabis, magnesium, and valerian root have limited/mixed research or benefit on insomnia.

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THANK YOU!

QUESTIONS?