VA | U.S. Department of Veterans Affairs

Clinical Pearls to Manage Chronic Insomnia

A Quick Reference Guide (2014)

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VA Academic Detailing Service Email Group:
PharmacyAcademicDetailingProgram@va.gov

VA Academic Detailing Service SharePoint Site:
https://vaww.portal2.va.gov/sites/ad

Potential Causes of Insomnia

Medications/Substances that Interfere with Sleep[1,2]		
Alcohol	Caffeine	Thyroid Hormone
Phenytoin	CNS Stimulants	Nicotine
Anticholinesterase Inhibitors	Decongestants (e.g. pseudoephedrine)	SSRIs/SNRIs
Bupropion	Diuretics	Theophylline

SSRI = Selective Serotonin Reuptake Inhibitor; SNRI = Serotonin-Norepinephrine Reuptake Inhibitor; CNS = Central Nervous System

Co-morbid Conditions that Interfere with Sleep[1]			
Medical			
Angina	Chronic Pain Disorders	Hyperthyroidism	Restless Legs Syndrome
Arthritis	COPD	Irritable Bowel Syndrome	Nocturia
Asthma	Emphysema	Parkinson's Disease	Sleep Apnea
Congestive Heart Failure	Epilepsy	GERD	
Psychiatric Disorders			
Substance Use	Anxiety Disorders	Depression	PTSD

COPD = Chronic Obstructive Pulmonary Disease; GERD = Gastroesophageal Reflux Disease; PTSD = Posttraumatic Stress Disorder

Insomnia Severity Index	
Please Rate the *CURRENT (i.e., last 2 weeks) SEVERITY* of Your Insomnia Problem(s)	
1	Difficulty falling asleep? 0 = None ; 1 = Mild ; 2 = Moderate ; 3 = Severe ; 4 = Very Severe
2	Difficulty staying asleep? 0 = None ; 1 = Mild ; 2 = Moderate ; 3 = Severe ; 4 = Very Severe
3	Problem waking up too early? 0 = None ; 1 = Mild ; 2 = Moderate ; 3 = Severe ; 4 = Very Severe
4	How satisfied/dissatisfied are you with your CURRENT sleep pattern? 0 = Very Satisfied ; 1 = Satisfied ; 2 = Moderately Satisfied ; 3 = Dissatisfied ; 4 = Very Dissatisfied
5	How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life? 0 = Not at all Noticeable ; 1 = A Little ; 2 = Somewhat ; 3 = Much ; 4 = Very Much Noticeable
6	How WORRIED/DISTRESSED are you about your current sleep problem? 0 = Not at all Worried ; 1 = A Little ; 2 = Somewhat ; 3 = Much ; 4 = Very Much Worried
7	To what extent do you consider your sleep problem to INTERFERE with your CURRENT daily functioning (e.g., daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.)? 0 = Not at all Interfering ; 1 = A Little ; 2 = Somewhat ; 3 = Much ; 4 = Very Much Interfering

Guidelines for Scoring/Interpretation *(add up scores for questions 1–7)*	
Total	**Category**
0–7	**No clinically significant insomnia**
8–14	**Subthreshold insomnia**
15–21	**Clinical insomnia (moderate)**
22–28	**Clinical insomnia (severe)**

Adapted from printable patient form available at: **https://vaww.portal.va.gov/sites/OMHS/cbt_insomnia/assessment/Insomnia%20Severity%20Index.docx**

Insomnia Pharmacotherapy

If the patient has been offered CBT-I and basic principles of sleep hygiene but is still suffering from insomnia, medications may be an option.

FDA Approved Agents for Insomnia[3,4]		Off-label Agents for Insomnia
Formulary	**Not Currently on VA National Formulary**	**Formulary**
Doxepin Temazepam Zolpidem IR Diphenhydramine	Doxylamine* Ramelteon Zolpidem CR Zaleplon Eszopiclone	Amitriptyline Gabapentin Hydroxyzine Mirtazapine Trazodone Prazosin (nightmares)

*OTC, not available through VA

Insomnia Pharmacotherapy

Pharmacologic Agents to Consider by Comorbidity				
Substance Use Disorder	**PTSD or Anxiety Disorder**	**No Comorbidities**	**Depression**	**Pain**
Gabapentin	Prazosin (if nightmares)	Doxepin	Mirtazapine	Gabapentin
Doxepin	Mirtazapine	Zolpidem	Doxepin	Amitriptyline
Trazodone	Doxepin	Temazepam	Trazodone	Doxepin
Mirtazapine	Trazodone	Ramelteon*	Amitriptyline	Ramelteon*
Amitriptyline	Amitriptyline	Trazodone	Ramelteon*	Trazodone
Ramelteon*	Ramelteon*	Mirtazapine	Antihistamines	Mirtazapine
Antihistamines	Zolpidem	Amitriptyline		Antihistamines
	Antihistamines	Antihistamines		

Medications listed may not be approved or strongly supported by evidence. Recommendations are guided by clinical experience and based on risks vs benefits analysis; * = not currently on VA National Formulary; PTSD = Posttraumatic Stress Disorder

Recommended Dosing[3–5,8]

Class	Agent	Usual Hypnotic Dose	Sedation Onset	Half-Life	Guidance in Special Populations		
					Geriatric (dosage range)	Renal	Hepatic
Tricyclic Antidepressant	Doxepin	3–6 mg	~30 min*	~15 hrs	Initial: 3 mg Max: 6 mg	N/A	Max: 3 mg
	Amitriptyline	10–25 mg	Not specified	9–27 hr	Caution in elderly pts	N/A	Begin low and increase as tolerated
Anticonvulsant	Gabapentin	600–900 mg	Not specified	5–7 hr anuria: 132 hr	N/A	CrCl <60 ml/min use caution	N/A
Antidepressant	Trazodone	25–100 mg	1–3 hr*	7–8 hr	Caution in elderly pts	N/A	N/A
	Mirtazapine	7.5–30 mg	Not specified	20–40 hr	Titrate slowly	CrCl <40 ml/min use caution	Titrate slowly
Antihistamine	Diphenhydramine	25–50 mg	1–3 hr	2–10 hr	Caution in elderly pts	bedtime dosing ok	N/A
	Doxylamine†	25 mg	~30 min	10–13 hr	Caution in elderly pts	N/A	N/A
	Hydroxyzine	50–100 mg	15–30 min	~20 hrs	Initiate at low doses	GFR <50ml/min: ↓ dose 50%	N/A
Melatonin Agonist	Ramelteon‡	8 mg	~30 min*	1–3 hr	N/A	N/A	Mild: use caution Severe: not recommended

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continued

Recommended Dosing[3–5,8]							
Class	Agent	Usual Hypnotic Dose	Sedation Onset	Half-Life	Guidance in Special Populations		
					Geriatric (dosage range)	Renal	Hepatic
Alpha-1 Antagonist	Prazosin (trauma nightmares)	Initial: 1 mg Average: 9–13 mg	Not specified	2–3 hr	Titrate slowly	N/A	N/A
Non-Benzodiazepines	Zolpidem IR	Women: 5 mg Men: 5–10 mg	~30 min*	2.5 hr	Max: 5 mg Avoid use >90d	N/A	5 mg
	Zolpidem CR†	Women: 6.25 mg Men: 6.25–12.5 mg	~30 min*	2.8 hr	Max: 6.25 mg Avoid use >90d	N/A	6.25 mg
	Eszopiclone‡	1–3 mg	Rapid (10 min* frequently cited)	6 hrs	2 mg	N/A	2 mg
	Zaleplon†	5–10 mg	~30 min*	~1 hr	Initial: 5 mg Max: 10 mg	N/A	Mild – Moderate Impairment: 5 mg Severe Impairment: not recommended

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Precautions and Contraindications[3–4]

Class	Agent	Contraindications	Precautions
Tricyclic Antidepressant	Doxepin	Narrow-angle glaucoma, severe urinary retention, MAOI within 14 days, acute recovery phase of MI	Risk of overdose: limit quantity prescribed in depressed patients
	Amitriptyline	Severe urinary retention, MAOI use within 14 days, acute recovery phase of MI, concurrent use of cisapride (↑ risk of arrhythmia)	- Risk of conduction abnormalities - Risk in respiratory disease: *not recommended in severe OSA*. - Risk of overdose: limit quantity prescribed in depressed patients - May ↓ seizure threshold: *avoid if seizure disorder, head trauma, alcoholism*.
Anticonvulsant	Gabapentin		- Poor renal function - ↓ Bioavailability at higher doses - Multiorgan hypersensitivity (rare)
Antidepressant	Trazodone	Coadministration with an MAOI, including linezolid or IV methylene blue, or use within 14 days of discontinuing an MAOI; increased risk of serotonin syndrome; concomitant use with saquinavir/ritonavir	- Priaprism: caution in sickle cell anemia, multiple myeloma, leukemia - QT prolongation, serotonin syndrome
	Mirtazapine	MAOI use within 14 days	- Akathisia, blood dyscrasias (neutropenia/agranulocytosis)
Antihistamine	Diphenhydramine	Acute asthma, breastfeeding, or early pregnancy	- Asthma, glaucoma, thyroid dysfunction - Cardiovascular disease* - BPH/urinary or pyloroduodenal obstruction
	Doxylamine		
	Hydroxyzine		

Disclaimer: This is a quick reference guide. For complete prescribing information please see package insert. *Cardiovascular Disease = Previous MI, stroke, tachycardia, or conduction abnormalities. MI = Myocardial Infarction, MAOI = Monoamine Oxidase Inhibitor, OSA = Obstructive Sleep Apnea

continued

Precautions and Contraindications[3–4]			
Class	**Agent**	**Contraindications**	**Precautions**
Melatonin Agonist	Ramelteon	History of angioedema with previous ramelteon therapy (do not rechallenge); concurrent fluvoxamine use	- Menses disruption, ↓ libido, respiratory depression - Hypersensitivity reactions
Alpha-1 Antagonist	Prazosin (trauma nightmares)	Hypersensitivity to quinazolines (e.g. doxazosin, terazosin)	- Angina: *discontinue if occurs* - Hypotension: *titrate slowly; use caution with other antihypertensives*
Non-Benzodiazepines	Zolpidem	**Zolpidem**: Canadian labeling: Significant OSA and acute or severe respiratory impairment; myasthenia gravis; severe hepatic impairment; personal or family history of sleepwalking	- Anaphylaxis and/or angioedema may occur with first or subsequent doses - CNS depression/impairment may not be reliably detected by routine exam; risk increases in the debilitated and elderly, patients with less than a full night of sleep (7 to 8 hours), higher doses, and concomitant use of other CNS depressants or use of drugs causing increased blood - Abnormal thinking/behavioral changes (including depression and suicide) - Complex sleep-related activities: *consider discontinuation* - **The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated.**
	Eszopiclone		
	Zaleplon		

Disclaimer: This is a quick reference guide. For complete prescribing information please see package insert. OSA = Obstructive Sleep Apnea

Adverse Effects with Insomnia Agents[3–5]

Class	Agent	Adverse Effects
Tricyclic Antidepressant	Doxepin	- Orthostatic hypotension, anticholinergic - Serious: cardiac conduction delay, agranulocytosis, anemia, leukopenia, thrombocytopenia, nephrotoxicity, suicidal thoughts
	Amitriptyline	- Orthostatic hypotension, anticholinergic, headache, weight gain - Serious: cardiac conduction delay, hepatotoxicity, agranulocytosis, NMS, seizure, suicidal thoughts
Anticonvulsant	Gabapentin	- Peripheral edema, nausea, vomiting, viral disease, dizziness, nystagmus - Serious: Stevens-Johnson syndrome, drug hypersensitivity syndrome, drug induced coma, seizures, suicidal thoughts
Antidepressant	Trazodone	- Constipation, diarrhea, nausea/vomiting, xerostomia, backache, dizziness, headache, blurred vision, dream disorder - Serious: cardiac dysrhythmia, prolonged QT, hypotension, seizure, priaprism, suicidal thoughts
	Mirtazapine	- ↑ appetite, weight gain, ↑ triglycerides, anticholinergic, dizziness - Serious: agranulocytosis, neutropenia, seizures, liver cirrhosis, NMS, serotonin syndrome, suicidal thoughts
Antihistamine	Diphenhydramine	- Anticholinergic, dizziness, thick sputum - Serious: anaphylaxis
	Doxylamine	- Anticholinergic
	Hydroxyzine	- Anticholinergic, headache

Disclaimer: This is a quick reference guide. For complete prescribing information please see package insert. NMS = Neuroleptic Malignant Syndrome

continued

Adverse Effects with Insomnia Agents[3–5]		
Class	**Agent**	**Adverse Effects**
Melatonin Agonist	Ramelteon	- Nausea, dizziness - Serious: worsening depression, hallucinations, mania, angioedema
Alpha-1 Antagonist	Prazosin	- First dose hypotension, palpitations, nausea, asthenia, headache, nasal congestion, edema
Non-Benzodiazepines	Zolpidem	- Dizziness, nausea, diarrhea, headache, visual disturbance - Serious: chest pain, tachycardia, hepatic encephalopathy, angioedema (rare), anaphylaxis (rare), depression, suicidal thoughts, next-morning impairment
	Eszopiclone	- Disorder of taste, headache, dizziness, vomiting, dry mouth, respiratory tract infection - Serious: angioedema (rare), next-morning impairment
	Zaleplon	- Headache, dizziness, nausea, weakness - Serious: anaphylaxis (rare), angioedema (rare), abnormal behavior, depression, suicidal thoughts/behaviors

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Non-Benzodiazepine Sedative-Hypnotics[5–7]

- Some studies suggest ↓ rates of tolerance and dependence compared to benzodiazepines
- Rebound insomnia can occur with both
- Consider intermittent (3–5 nights/week) dosing to further reduce these risks*

General Guidelines for Prescribing Sedative-Hypnotics[8]
1. Use the lowest effective dose
2. Consider intermittent dosing (alternate nights or less) if possible*
3. Prescribe for short-term use (≤4 weeks) in the majority of cases
4. Consider tapering when discontinuing as dependence may have developed
5. Be alert for rebound insomnia and other withdrawal symptoms
6. Advise patients of the interaction with alcohol and other sedating drugs

FDA Labeling and Dosing Changes for Zolpidem and Eszopiclone[†,9,10]

- Dosing recommendations changed due to risk of next-morning impairment.
- Levels can remain high enough to impair mental alertness the day after use. Advise these patients not to drive or engage in activities that require complete mental alertness the day after use (see package inserts for specific recommendations).
- Use the lowest dose capable of treating the patients' insomnia symptoms; higher dose is more likely to impair next-morning driving and other activities that require full alertness.

*Only zolpidem has been studied with intermittent dosing at this time

†Recommended dosing found on page 6 of pocket cards; please see respective package inserts for full prescribing information

Sleep Guidelines[11]

1. Wake-up at the same time every day whether you have a good or poor sleep on any particular night.
2. Go to bed when you are sleepy, but not too early (example: not before _____pm). Long periods of time in bed will lead to shallow, broken sleep. You should spend only the amount of time in bed that you actually need for sleep. Sticking to the suggested bedtime and waketime will help you overcome your sleep problem.
3. Get up when you can't sleep. When you are unable to sleep, get up and go to another room until you feel sleepy enough to fall asleep quickly before returning to bed. Get up again if sleep does not come on quickly.
4. Use the bed only for sleeping. Do not read, eat, watch TV, etc. in bed. Sex is the only exception.
5. Avoid daytime napping. Napping, particularly in the late afternoon or early evening may interfere with your night's sleep.
6. Create a buffer zone. The "buffer zone" is a quiet time prior to bed time. During this time, you should do things that are enjoyable on their own rather than activities that are taken as a means to an end.
7. Don't worry, plan, etc., in bed. If you are worrying, planning or can't shut off your thoughts, get up and stay up until you can return to bed without these mental activities interfering with your sleep.

Other Helpful Practices

1. Turn the clock around
2. Limit caffeine and consume before noon
3. Limit alcohol and do not consume within 3 hours of bedtime
4. Exercise regularly but not close to bedtime
5. Keep bedroom quiet, dark, and cool
6. Do not eat a heavy meal close to bedtime (a light bedtime snack such as milk, peanut butter, or cheese is OK)

References

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This reference guide was created to be used as a tool for VA providers and is available to use from the Academic Detailing SharePoint. These are general recommendations only; specific clinical decisions should be made by the treating provider based on an individual patient's clinical condition.

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