

VA



U.S. Department
of Veterans Affairs

Chronic Insomnia

VA Clinician's Guide to Managing Insomnia (2014)



*Real Provider Resources
Real Patient Results*

Chronic Insomnia

A VA Clinician's Guide to Managing Insomnia (2014)



VA Academic Detailing Service Real Provider Resources Real Patient Results

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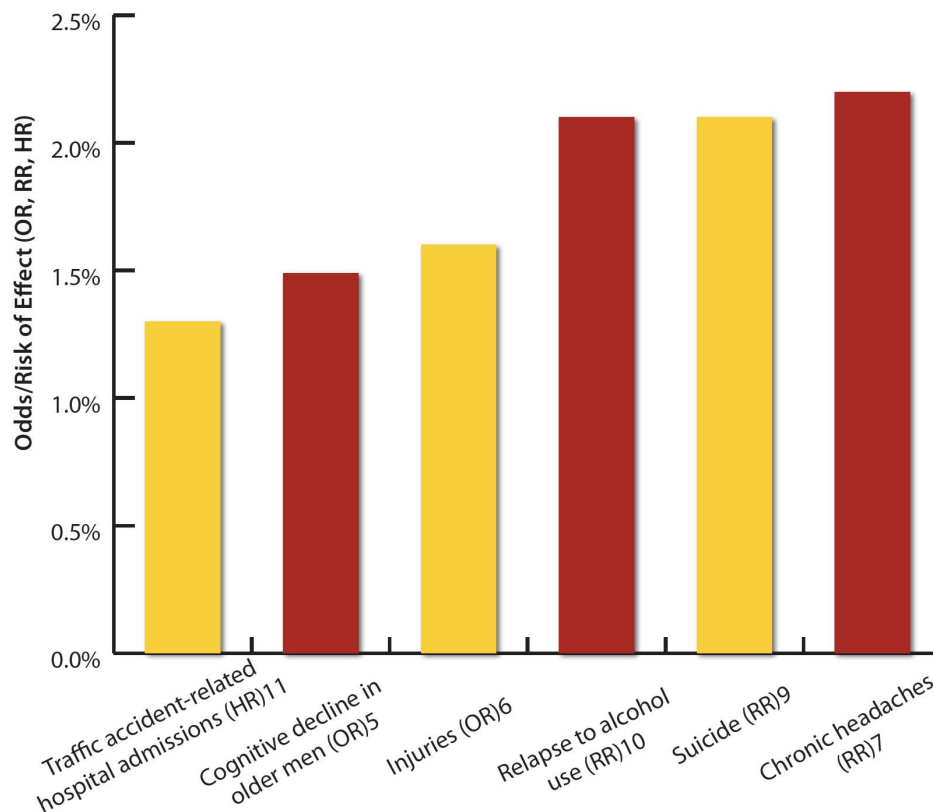
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Chronic Insomnia

Symptoms of insomnia are reported in 1 in 3 adults and are more prevalent in women.¹ The rate of diagnosed insomnia in soldiers has increased 10-fold between 2001 and 2009.² Disrupted sleep has been shown to reduce productivity, increase healthcare costs, and increase the risk of various medical and psychiatric disorders.³⁻¹⁰

Risks Associated with Insomnia^{5-7,9-11}



11. 59,940 patients ≥ 20 yo with primary insomnia and 119,880 controls. Accident-related admission rates were 49 per 10,000 person-years with sleep disorders and 37 per 10,000 person-years without sleep disorders (HR 1.3, 95% CI 1.17-1.45); 5. 6,444 community-dwelling men and women age ≥ 65 who had ≤ 1 error on the Short Portable Mental Status Questionnaire at baseline. Cognitive decline was defined as ≥ 2 errors on the Questionnaire at the 3rd follow-up. Adjusted OR for cognitive decline was 1.49 (95% CI 1.03-2.14) in nondepressed men; 6. Telephone survey in national sample of 4,991 employed health plan subscribers reporting any sleep problems on the America Insomnia Survey who answered self-report questions regarding injuries. Insomnia was significantly associated with workplace and nonworkplace injuries (OR 1.8 and 1.5) among workers having no comorbid conditions; 10. Included 172 men and women receiving treatment for alcohol dependence who completed a sleep questionnaire. Among the 74 who were followed for an average of 5 months after treatment, 60% with baseline insomnia vs 30% without baseline insomnia relapsed to any use of alcohol ($p=0.02$); 9. Chart review of 381 Veteran suicide decedents (173 with a clinician-documented sleep disturbance) who had a VA visit in the last year of life. Difficulty maintaining sleep was associated with suicide (RR 2.1, 95% CI 1.1-3.9); 7. Headache-free subjects ≥ 20 yo who answered the insomnia-related questions in the first survey ($n=15,060$) and completed the headache section of both were selected for this analysis. Those with insomnia were more likely to develop chronic headaches (RR 2.5, 95% CI 1.2-5.4).

OR = Odds Ratio; RR = Relative Risk; HR = Hazard Ratio

It is important to identify and manage sleep disturbances in our Veteran population.

Evaluation

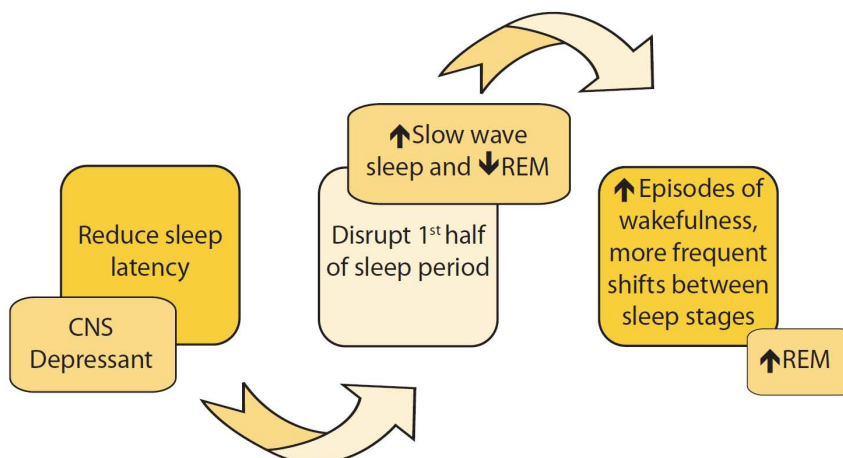
Find out if the Veteran is having a difficult time getting to sleep, maintaining sleep, suffering from early-morning awakening, having poor quality sleep, trauma-related nightmares, or excessive daytime sleepiness. In addition, all medical, psychiatric, drug, environmental, and social causes of insomnia should be evaluated and addressed if possible.

Questions to Rule-Out Other Sleep Disorders ^{12,13}	
1	Do you nap during the day, when, and for how long? (hypersomnia)
2	Do you snore? Does the bed partner observe episodes of where you stop breathing? (sleep apnea)
3	When you are in bed, do you have an irresistible urge to move your legs? (restless leg syndrome) OR Does your bed partner report that you kick or jerk your legs frequently during the night?
4	Do you eat at night?
5	Do you take any medications or over-the-counter preparations, herbal remedies, or psychoactive substances to assist with sleep?
6	Where do you sleep, and what surrounds you in your place of sleep, (e.g., computer, television, paperwork, room lighting, and outside noise)?
7	Do you drink coffee, tea, alcohol, or caffeinated colas? How much? How long before you go to bed?
8	How has your mood been recently? Are you still able to enjoy social/family activities? (depression)
9	Have you been told that you act strangely during your sleep? (parasomnias)

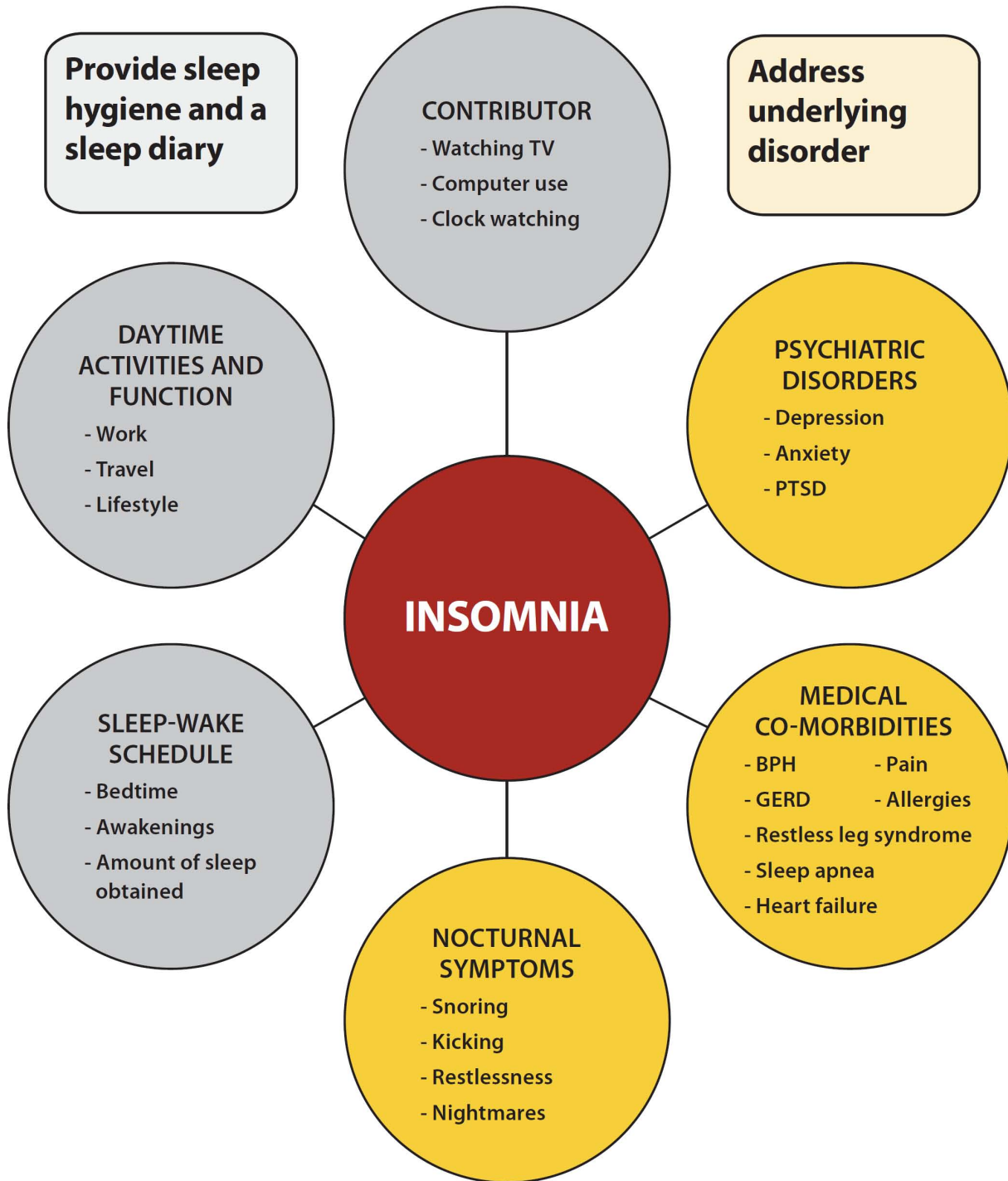
It is important to ask patients about their alcohol use as this can contribute to their insomnia.

Self-medicating with Alcohol¹⁴

→ Over time, the initial effect on sleep latency diminishes while the sleep disruption persists.



Possible Contributors to Insomnia^{1,12,13,15}



Identify and Modify Contributing Factors

- Assess current medications
 - ❖ Switch to non-stimulating medications
 - ❖ Adjust dosing schedule of stimulating medications (example: bupropion)
- Discuss caffeine, alcohol, or illicit drug effects on sleep¹⁵
- Educate the patient on proper sleep hygiene

Medications/Substances that Interfere with Sleep ^{13,15}		
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

Insomnia Severity Index

The Insomnia Severity Index (ISI) can be used to assess the nature, severity, and impact of insomnia on the Veteran as well as to monitor the Veteran's response to treatment.

The tool consists of 7 items intended to assess the patient's insomnia over the past 2 weeks. Patients are asked to rate their responses on a scale of 0–4.

Insomnia Severity Index*	
Please rate the <i>CURRENT</i> (e.g. <i>LAST 2 WEEKS</i>) <i>SEVERITY</i> 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 <i>CURRENT</i> 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 pattern? 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 daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) <i>CURRENTLY</i> ? 0 = Not at all Interfering 1 = A Little 2 = Somewhat 3 = Much 4 = Very Much Interfering

*This tool is available in My HealthVet and will soon be available via Mental Health Assistant in CPRS.

Adapted from Printable Patient form available at: https://vawww.portal.va.gov/sites/OMHS/cbt_insomnia/assessment/Insomnia%20Severity%20Index.docx

Total Score Categories:

0–7 = No clinically significant insomnia

8–14 = Subthreshold insomnia

15–21 = Clinical insomnia (moderate severity)

22–28 = Clinical insomnia (severe)

Thoroughly evaluate the Veteran’s complaint of insomnia and rule out or manage underlying causes of sleep disturbances.

Treatment

GOALS OF TREATMENT:

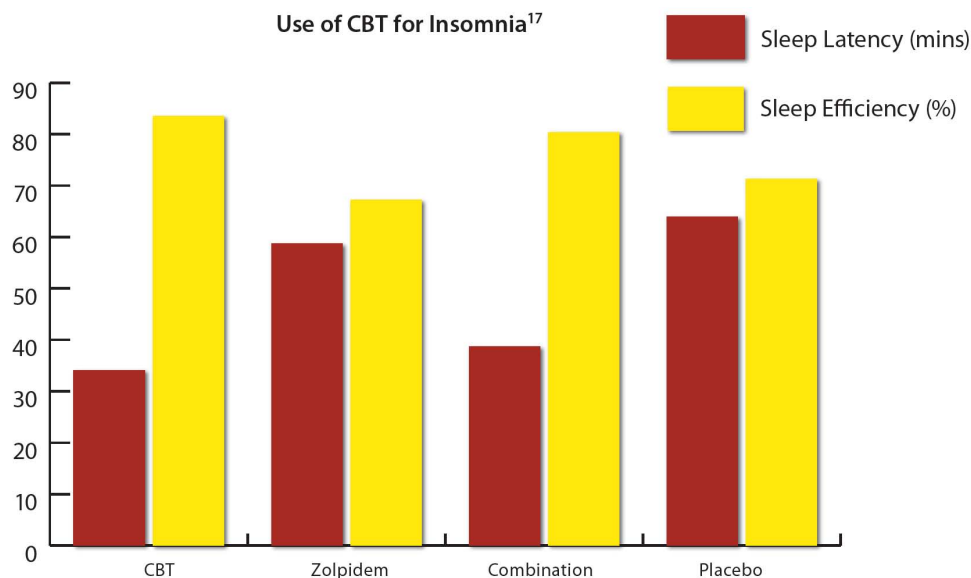
- Improve sleep quality and quantity
- Enhance associated daytime function



Treatment

Non-pharmacological Treatment Options

Evidence suggests that the lack of knowledge about non-pharmacological treatment options often contributes to the use of non-evidence-based long-term pharmacotherapy to treat chronic insomnia.¹⁶ Patients often develop behaviors (clock watching, remaining in bed awake for long periods of time, etc.) that can lead to further wakefulness, negative expectations, and distorted beliefs about their insomnia. The use of non-pharmacological treatment options such as **psychological and behavioral therapies can target negative learned responses that may be perpetuating the patient's insomnia**. Cognitive behavioral therapy for insomnia (CBT-I) is the most widely used and most studied non-pharmacological treatment.^{4,15}



CBT (Four 30 minute face-to-face sessions and 1 telephone session) was the most sleep effective intervention. It produced the greatest changes in sleep-onset latency and sleep efficiency and the largest number of normal sleepers after an 8 week treatment period. The combination of CBT and pharmacotherapy was no more effective than CBT alone.

Medication management of insomnia may not be necessary when referring a Veteran to CBT-I. If medications are needed for acute management of insomnia in lieu of CBT-I completion, consider providing a low dose and limited quantity.

Psychological and behavioral interventions are effective and should be recommended 1st line for the treatment of insomnia.¹⁵

Treatment

Pharmacological Options

If the patient has completed CBT-I and basic principles of sleep hygiene but is still suffering from insomnia, medications may be an option. Be sure to consider the Veteran's co-morbidities when selecting a medication to treat insomnia. The table below provides recommendations for treatment of common co-morbidities in patients also suffering from insomnia.

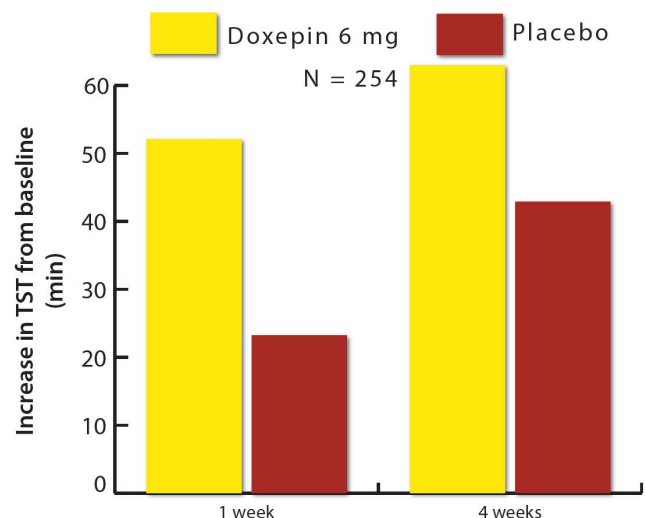
Sedating Treatment Options for Common Comorbidities					
	Pain	Depression	Anxiety Disorders	PTSD	Substance Use
Insomnia	Gabapentin	Mirtazapine	Mirtazapine	Prazosin (for trauma-associated nightmares)	Gabapentin
	Amitriptyline	Doxepin	Doxepin	Mirtazapine	
	Doxepin	Trazodone	Trazodone	Doxepin	
		Amitriptyline	Amitriptyline	Trazodone	
			Hydroxyzine	Amitriptyline	
			Temazepam	Hydroxyzine	

FDA APPROVED MEDICATIONS FOR SLEEP

→ Doxepin

- ❖ Tricyclic antidepressant (TCA) recently FDA approved at low doses for treatment of insomnia (sleep maintenance)
- ❖ Acts primarily as an H1 antagonist and has a side effect profile comparable to placebo at low doses¹⁸⁻²²
 - ⦿ Does not appear to cause tolerance or rebound insomnia²¹⁻²³
- ❖ Use caution in patients at high risk for suicide due to risk of toxicity in overdose.

Doxepin in Elderly Patients



This randomized double-blind, placebo-controlled trial in 254 elderly outpatients found that low dose doxepin significantly improved total sleep time, wake time after sleep onset, sleep quality, and CGI and ISI scores (all p-values <0.05) compared to placebo. Baseline TST (total sleep time) was 283.1 minutes for doxepin vs 293.5 minutes for placebo. Doxepin was also shown to be well-tolerated with a side effect profile comparable to placebo (27% incidence of adverse events with placebo vs 31% for doxepin).²¹

Low dose doxepin is a reasonable option for treatment of insomnia.

Treatment

→ Antihistamines (Diphenhydramine, Doxylamine, Hydroxyzine)

- ❖ Hydroxyzine may have more profound acute effects on sleep than OTC antihistamines¹²
- ❖ Associated with anticholinergic side effects (avoid in elderly patients)²⁴

→ Ramelteon

- ❖ Melatonin agonist (M1 and M2)
- ❖ Helps decrease sleep latency but has not been shown to have significant effects on sleep maintenance^{15,23}
- ❖ Does not appear to produce rebound insomnia or symptoms of withdrawal with prolonged use²⁵

→ Sedative-Hypnotics

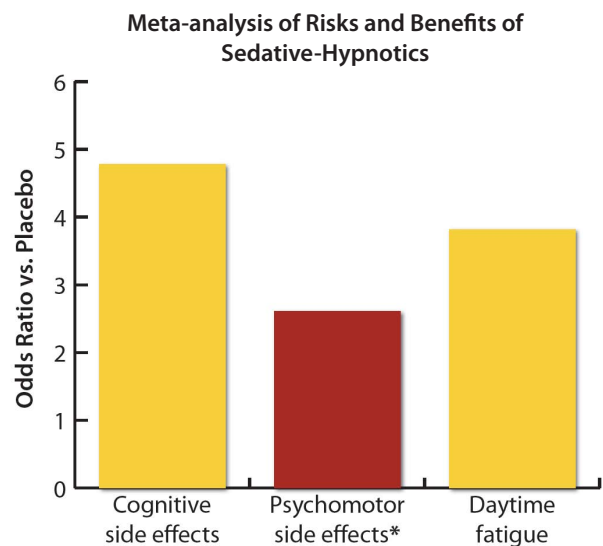
- ❖ Recommended by The American Academy of Sleep Medicine as first line agents with evaluation of agent 2–4 weeks after initiation¹⁵
- ❖ Should be used at the lowest effective dose then tapered and discontinued when possible¹⁵
- ❖ If long-term treatment is required, follow-up visits should be scheduled at least every 6 months to assess safety and efficacy
- ❖ Associated with many risks/side effects^{26,27}

→ Motor vehicle accidents

→ Psychomotor impairment (e.g., falls)

→ Cognitive impairment (e.g., anterograde amnesia, next-day sedation)

→ Dangerous interactions with other CNS depressants such as alcohol and opioids



A total of 830 subjects treated with a benzodiazepine, 609 with zaleplon, 384 with zolpidem, 106 with zopiclone[†], 14 with diphenhydramine and 468 with placebo were reviewed in this meta-analysis. The NNT for improved sleep quality was 13 and NNH for any adverse event was 6. Adverse events were >2x more likely than enhanced quality of sleep. In the studies comparing benzodiazepines vs non-benzodiazepine sedative-hypnotics, no significant difference in sleep quality (p=1.0) or adverse effects was seen (p=0.75).²⁸

*Not statistically significant; [†]Note zopiclone is not available in U.S.

Treatment

Non-Benzodiazepine sedative-hypnotics

- Some studies suggest lower rates of tolerance, dependence, and side effects with non-benzodiazepine sedative-hypnotics compared to benzodiazepines¹²
- Rebound insomnia still possible with non-benzodiazepine sedative-hypnotics^{4,12}
- Consider intermittent (3–5 nights/week) dosing of zolpidem to reduce risks of tolerance, dependence, and side effects^{4,12,29}

Benzodiazepines

- Tolerance often quickly develops to the sleep inducing and prolonging effects²⁶
- Commonly cause rebound insomnia upon discontinuation²⁶
 - ❖ Can occur after only 1–2 weeks of treatment^{26,30}
- Not recommended for long-term use
- Are commonly associated with accidental overdose deaths when used in combination with other CNS depressants

Consider avoiding benzodiazepines if the patient:

- Has PTSD
- Has a substance use disorder (alcohol or sedatives)
- Has a chronic respiratory disease (e.g., sleep apnea)
- Has a history of traumatic brain injury
- Has dementia
- Is elderly
- Is receiving other CNS depressants such as opioids

The risks of sedative-hypnotics outweigh the benefits in some patients. Consider alternative strategies to reduce risk.

Risk Reduction Strategies ³¹	
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

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

Agents Commonly Used for Sleep

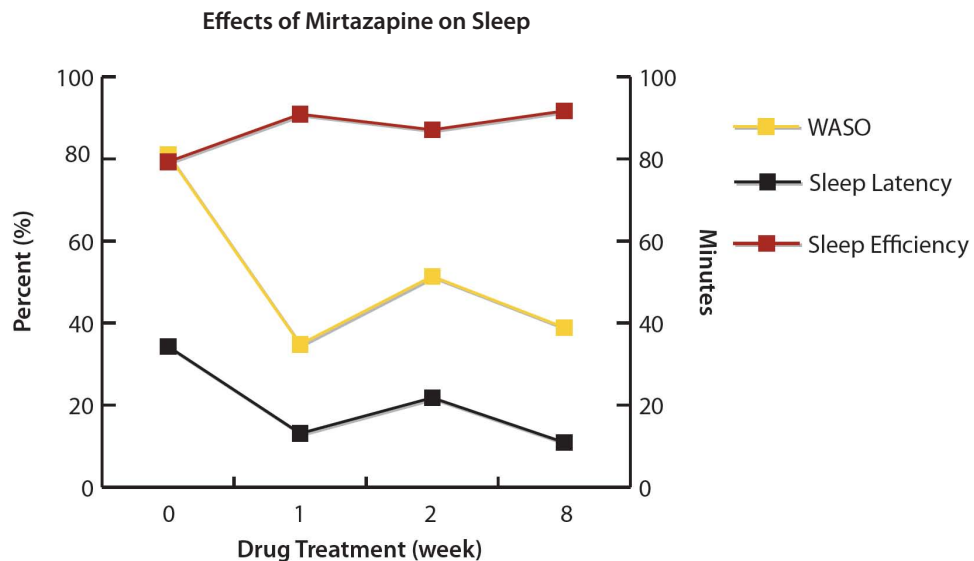
Many medications are used “off-label” for sleep due to their sedating side effects. However, many agents have side effects or other risks that may outweigh the benefits in some patients. It is important to weigh the risks and benefits before selecting an agent.

Trazodone

- Is an FDA-approved antidepressant, but when used at low doses it primarily acts at alpha-1, H1, and serotonin-2C & -2A receptors²³
- Is an effective sleep aid when used in conjunction with an antidepressant in patients with depressive disorders^{15,30}

Mirtazapine

- At low doses (7.5–15 mg), mirtazapine causes sedation primarily by acting as an H1 antagonist³²
- When titrated to therapeutic doses (15–45 mg) mirtazapine has been shown to produce changes in sleep comparable to zolpidem and zaleplon by blocking serotonin-2 receptors³³



Compared with baseline assessments, patients receiving mirtazapine (up to 45 mg) demonstrated significant reductions in sleep latency ($p=0.0015$) and wake time after sleep onset (WASO, $p=0.0008$) and significant increases in sleep efficiency ($p=0.0004$) and total sleep time (0.044).³³

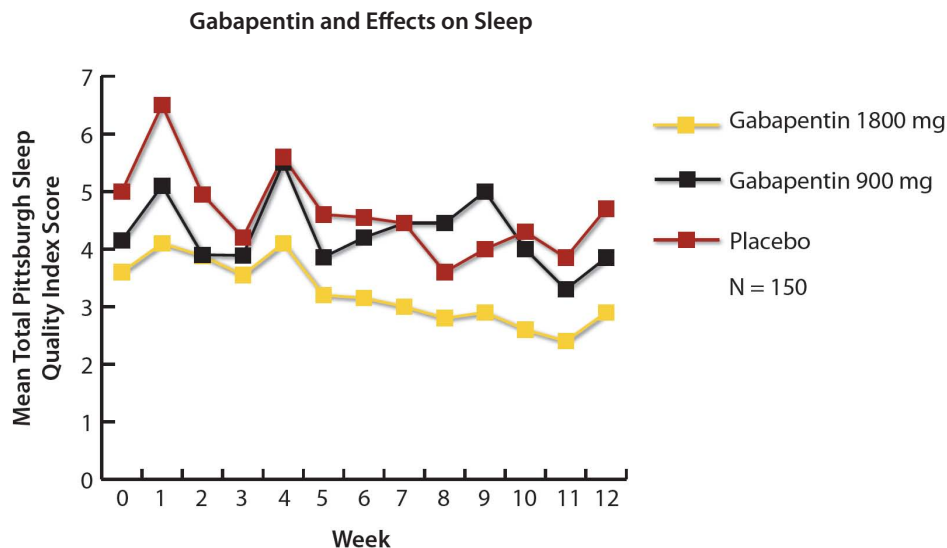
Amitriptyline

- Antidepressant commonly used at low doses for sleep due to H1, M1, and serotonin-2C antagonist activity
- May be preferred in patients with concomitant pain or headaches
- Use caution in patients at risk for suicide due to risk of toxicity in overdose
- Associated with anticholinergic side effects (avoid in elderly patients)²⁴

Agents Commonly Used for Sleep

Gabapentin

- Has been shown to increase slow-wave sleep (deep sleep), reduce sleep latency, and reduce arousals³⁴
- May be used to reduce drinking and improve sleep in patients with alcohol use disorders³⁵⁻³⁸



According to a 12-week, double-blind, placebo-controlled randomized dose-ranging trial looking at the effects of gabapentin on drinking outcomes and alcohol-related insomnia, gabapentin significantly improved abstinence rates, no heavy drinking, and sleep vs placebo. Significant dose dependent reductions were seen in the Pittsburgh Sleep Quality Index total score (gabapentin 1800 mg/day vs placebo: -1.5, $p < 0.001$).³⁵

Medications Used for Sleep ^{3,4,12,25,30-32,39}			
Generic Name	Dose (mg)	Half-Life (hrs)	Adverse Effects
Amitriptyline	10-25	9-27	Anticholinergic side effects, orthostasis
Doxepin*	3-6	~15	Sedation
Diphenhydramine	25-50	2-10	Dry mouth, dizziness, drowsiness
Doxylamine [†]	25	10-13	Dizziness, drowsiness; may cause more residual effects than diphenhydramine
Gabapentin	600-900	5-7	Dizziness, ataxia, tremor, nystagmus
Hydroxyzine [‡]	50-100	~20	Dry mouth, headache, somnolence
Mirtazapine	7.5-30	20-40	↑ Cholesterol, ↑ appetite, weight gain, dream disorder
Ramelteon	8	1-3	Headache, dizziness
Trazodone [§]	25-100	7-8	Orthostasis, dry mouth, headache, dream disorder

*Can be toxic in overdose, therefore avoid use in patients at high risk for suicide. FDA-approved dose for insomnia is 3-6 mg at bedtime; [†]Currently not on VA National Formulary; [‡]Approved for sedation, adjunct; [§]Time to peak serum concentration may be delayed with food.

Medications Used for Sleep ^{3,4,12,25,30-32,39}			
Generic Name	Dose (mg)	Half-Life (hrs)	Adverse Effects
Non-Benzodiazepines			
Zolpidem IR ^{*,†}	5-10	2.5	Dizziness, headache, ↓ appetite; next-morning impairment
Zolpidem CR ^{*,†,‡,§}	6.25-12.5	2.8	
Eszopiclone ^{*,‡,§}	1-3	6	Headache, unpleasant taste, next-morning impairment
Zaleplon [‡]	5-10	~1	Headache, dizziness, nausea
Benzodiazepines			
Temazepam	7.5-30	8-18	Confusion, dizziness, headache
Triazolam [‡]	0.125-0.25	2-6	Headache, dizziness, nausea/vomiting

Sedative-hypnotics have a risk of severe allergic reactions (angioedema, anaphylaxis) and complex sleep-related behaviors; *New dose recommendations suggest patients should not drive or engage in other activities that require complete mental alertness the day after taking the drug because drug levels can remain high enough the next day to impair these activities; †Lower initial dose recommended for females; ‡Currently not on VA National Formulary; §Max dose reduced for certain populations (see package insert for details).

Quetiapine

➔ Minimal evidence currently available to support use in insomnia⁴⁰⁻⁴³

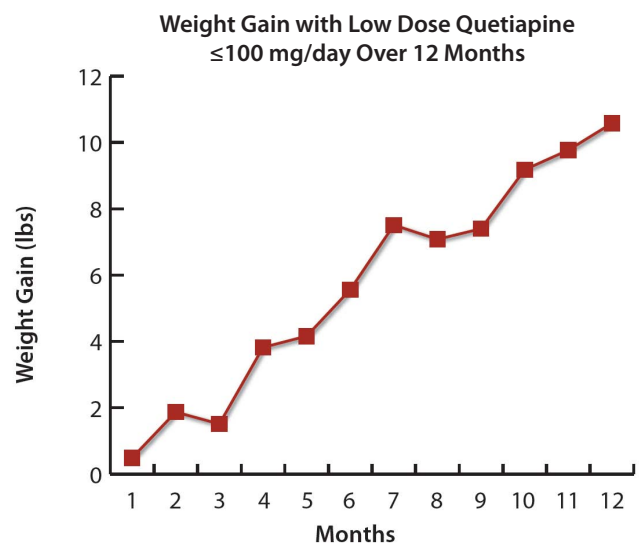
- ❖ Limited by small sample sizes and poor study design
- ❖ Questionable clinical significance

➔ Risk of serious side effects⁴³

- ❖ Cardiometabolic effects
 - ⊙ Significant weight gain even at low doses⁴⁴

❖ Tardive dyskinesia, orthostasis, constipation, dry mouth

❖ Case studies report somnambulism, periodic leg movements, lack of REM sleep and nighttime combativeness^{42,44,45}



At 6 and 12 months of treatment with quetiapine ≤100 mg/day, there was a significant increase in weight compared to baseline values ($p < 0.001$ for both time points).⁴⁴

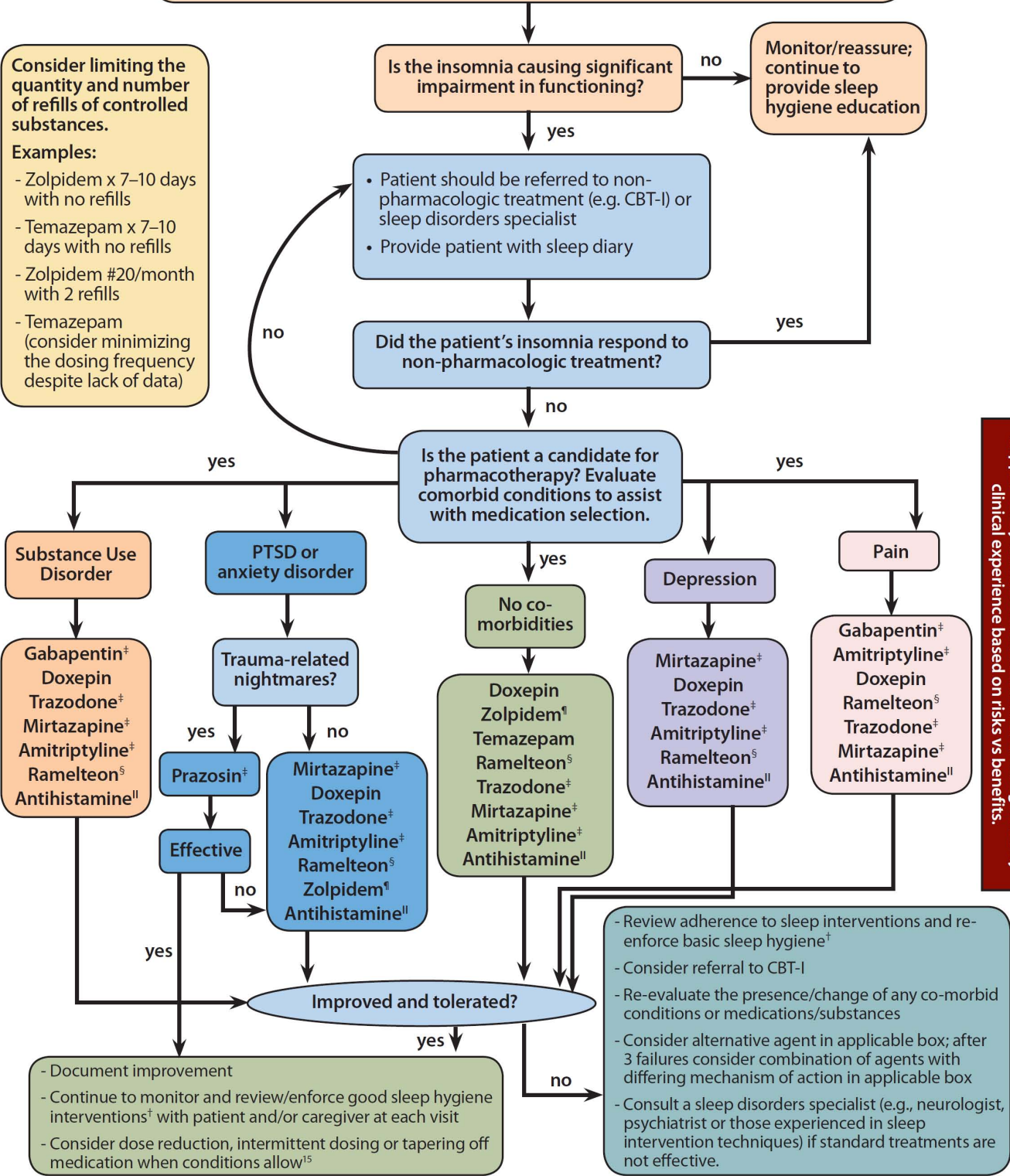
Quetiapine may help with sleep when given at therapeutic doses (150–800 mg day) in patients with approved indications for antipsychotic use and concomitant insomnia.

Use of low-dose antipsychotics for sleep is not recommended at this time due to lack of evidence and the risk of serious side effects.⁴⁶

Options for Managing Insomnia*

- Assess the nature, severity, and impact of insomnia on the Veteran (Consider use of Insomnia Severity Index (see pocket cards))
- Evaluate **co-morbid conditions, drug use or withdrawal** and/or attempt to **adjust any medications/substances** that could interfere with sleep
- Review the basic principles of sleep hygiene†

Consider limiting the quantity and number of refills of controlled substances.
Examples:
 - Zolpidem x 7-10 days with no refills
 - Temazepam x 7-10 days with no refills
 - Zolpidem #20/month with 2 refills
 - Temazepam (consider minimizing the dosing frequency despite lack of data)



Medications listed may not be approved or strongly supported by evidence. Recommendations are guided by clinical experience based on risks vs benefits.

*Situational causes of insomnia may not be addressed using this algorithm; †See pocket cards for more information; ‡Not FDA-approved for insomnia/sedation; §Not currently on VA National Formulary; ¶Antihistamines include: hydroxyzine, diphenhydramine, doxylamine; ¶Other z-hypnotics (non-benzodiazepine sedative hypnotics) include: zaleplon, eszopiclone.

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*Real Provider Resources
Real Patient Results*

U.S. Department of Veterans Affairs

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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VA Sharepoint Site
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