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Insomnia

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Abstract

Key Clinical Question—How does one diagnose and treat insomnia in adults?

Evidence Review—Summary of meta-analyses of chronic insomnia treatments.

Bottom Line—Insomnia is a common clinical condition characterized by difficulty initiating or maintaining sleep, accompanied by symptoms such as irritability or fatigue during wakefulness. The prevalence of insomnia disorder is approximately 10-20%, with approximately 50% having a chronic course. Insomnia is a risk factor for impaired function, the development of other medical and mental disorders, and increased health care costs. The etiology and pathophysiology of insomnia involve genetic, environmental, behavioral, and physiological factors culminating in hyperarousal. Efficacious treatments for insomnia include behavioral, cognitive, and pharmacologic interventions. Simple behavioral interventions are feasible in primary care settings, but lack of training in these techniques limits their use. Among pharmacologic interventions, the most evidence exists for benzodiazepine receptor agonist drugs, although persistent concerns focus on their safety relative to modest efficacy. Behavioral treatments should be used whenever possible, and medications should be limited to the lowest necessary dose and shortest necessary duration.

Dr. Ship

Ms. J is a 51-year-old woman with insomnia, which began at age 35 when her infant daughter had very disrupted sleep. By the age of 7, her daughter's sleep was improved, but Ms. J's was not. She was able to fall asleep, but was unable to stay asleep after about 3 in the morning. Ms. J tried several medications with variable success and side effects. She currently takes gabapentin, which is working well. She is very attentive to "sleep hygiene," and maintains a regular bedtime and waking time. M.s J's past medical history is notable for mild depression, Raynaud's Syndrome and myelodysplasia/myelofibrosis. Ms. J works as an educational consultant. She lives with her husband and two teenage children. She exercises regularly by swimming, cycling, and running. She does not use tobacco and has 1/2 glass of wine 3 nights per week. Current medications include escitalopram 20 mg daily, gabapentin 1200 mg qhs, and nifedipine SR 60 mg daily in cold weather. Ms. J has no drug allergies. On physical examination, Ms. J is healthy and fit. Weight is 121 pounds, blood pressure 119/64, and pulse 68 beats per minute.

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Ms. J: Her view

My insomnia began when I became a parent. I had an infant who never slept, nursed every hour and a half around the clock, and was just a difficult sleeper. I never knew when she would go to sleep, when or how many times she would wake up during the night, or if she would be up at 4:00 in the morning. My sleep got very disrupted and that continued until she was 7 years old. She finally slept, but then I could not sleep. I was exhausted and could have fallen asleep standing up, but I could not stay asleep. I would wake up between 2:00 and 3:00 in the morning and that would be it for the night. Benadryl initially worked, but over time I needed to take more and more and then it became completely ineffective, or it would finally kick in when I needed to get up. I would be very groggy. It made me very irritable. It affected my mood.

I tried melatonin. Trazodone was fairly effective but I woke up groggy and I had really wild dreams. Even if I slept through the night I often would wake up exhausted. I liked being able to sleep but I did not like the side effects. I took Ambien once and I was up the entire night. I had severe anxiety, felt very unsettled, and just was not happy. I was not willing to even try it a second night. Neurontin has been very effective in helping me to get more sleep, but I would not say that my sleep is reliable.

Not much has made my insomnia better or worse; there haven't been stress factors, work factors, family factors. I am not consciously thinking about things that prevent me from falling asleep, or thinking about falling asleep or staying asleep and saying, "Oh, I wish I could sleep." Are there other medications that I might consider, or medications in concert with the Neurontin that might help me to more consistently sleep? I need a good night's sleep for emotional, intellectual and physical consistency.

AT THE CROSSROADS: QUESTIONS FOR DR BUYSSE

What is the definition of insomnia? What are the subtypes? How is a diagnosis of insomnia made, and what evaluations should be undertaken? What treatments do you recommend? What are the indications, contraindications, and side effects for specific medications? Can medications be used indefinitely? When should a patient with insomnia be seen by a sleep specialist? What do you recommend for Ms. J?

Dr. Buysse

Definition of insomnia and subtypes—Insomnia is a patient-reported complaint of difficulty falling asleep or difficulty maintaining sleep, i.e., frequent awakenings, difficulty returning to sleep after awakenings, or awakening too early with inability to return to sleep. Although non-restorative sleep is often included as a symptom of insomnia, it has different epidemiological and functional correlates than other insomnia symptoms, including higher prevalence in young adults and a greater degree of daytime impairments such as sleepiness and fatigue.[2]{11363} The clinical disorder or syndrome of insomnia (Box 1) additionally specifies adequate opportunity and circumstances for sleep, and significant distress or symptoms during wakefulness. Adequate opportunity for sleep distinguishes insomnia from sleep deprivation, which has different causes and consequences. Ms. J clearly qualifies for an insomnia diagnosis.

Insomnia is not defined by a specific sleep amount; individuals with other sleep disorders and voluntary sleep restriction may also report short sleep. Individuals with insomnia are reliably distinguished from good sleepers by self-reported sleep symptoms, such as sleep latency (time to fall asleep) or wakefulness after sleep onset (WASO) >30 minutes.[3] Objective sleep measures derived from polysomnography or actigraphy show considerably

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more overlap between individuals with insomnia and good sleepers, making these methods less sensitive and specific than self-reports for identifying insomnia.[4] Furthermore, many patients with insomnia overestimate sleep latency and WASO and underestimate sleep duration in comparison to polysomnographic measures.[5] Thus, insomnia often involves altered perception of sleep.

Although insomnia is considered a sleep disorder, its pathophysiology suggests hyperarousal during sleep and wakefulness[6]. Evidence of hyperarousal in insomnia includes elevated whole-body metabolic rate during sleep and wakefulness, elevated cortisol and adrenocorticotropic hormone during the early sleep period, reduced parasympathetic tone in heart rate variability, and increased high-frequency electroencephalographic activity during non-rapid eye movement sleep. Functional imaging studies demonstrate smaller wake-sleep differences in regional brain metabolism in individuals with insomnia compared to good sleepers[7] (online supplement eFigure 1).

Insomnia is often subtyped by the predominant symptom, i.e., sleep onset vs. sleep maintenance. In epidemiological studies sleep maintenance symptoms are most prevalent among individuals with insomnia (approximately 50-70%), followed by difficulty initiating sleep (35-60%) and non-restorative sleep (20-25%).[8] However, multiple sleep symptoms are more common than any single symptom, both cross-sectionally and longitudinally.[9]

Insomnia disorders have also been categorized as primary and secondary, depending on whether the sleep problem is judged to be caused by another medical or mental disorder or medication/substance use. In practice, it is often difficult to determine whether a concurrent condition actually causes insomnia.[10] Furthermore, insomnia is a risk factor for many of the disorders with which it coexists, including coronary heart disease and depression.[11;12] For these reasons, the term “comorbid insomnia” has been recommended as preferable to “secondary insomnia.”[13] Although sleep medicine specialists have defined subtypes of “primary” insomnia,[1] the reliability and validity of primary insomnia and its subtypes is modest at best.[14]

The annual prevalence of insomnia *symptoms* in the general adult population ranges from 35-50%,[15] and the prevalence of insomnia *disorder* from 12-20%.[8;16] Risk factors include depression, female sex, older age, lower socioeconomic status, concurrent medical and mental disorders, marital status (greater risk in divorced/separated vs. married or never married individuals), and race (greater risk in African American vs. white race).[17] Insomnia follows a chronic course in 40-70% of individuals over 1-20 years.[18;19] Functional consequences of insomnia including reduced productivity, increased absenteeism, and increased health care costs.[20;21] Insomnia is also a risk factor for mental disorders; the risk ratio for incident depression among individuals with insomnia is estimated at 2.10 (95% confidence interval: 1.86-2.38).[12] Insomnia is associated with worse short and long-term treatment outcomes in depression and alcohol dependence and with increased risk of metabolic syndrome,[22] hypertension,[23] and coronary heart disease.[11] Insomnia with short sleep duration may be associated with higher risk than insomnia or short sleep duration alone.[23]

How is a diagnosis of insomnia made? What work-up is needed for patients with insomnia?—The evaluation and diagnosis of insomnia rest on a careful clinical history of the sleep problem and relevant comorbidites. The “3-P” model is a useful heuristic framework for assessment.[24] *Predisposing factors* increase the risk for developing insomnia, and include a family history and a lifelong propensity for stress-related poor sleep. *Precipitating factors* are medical, environmental, or psychosocial stressors that initiate a pattern of poor sleep. Her daughter’s irregular sleep served as a precipitating factor for Ms.

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J's insomnia. *Perpetuating factors* are behaviors and other factors that lead to a vicious cycle of continued sleep disturbance. For instance, many individuals with insomnia spend more time in bed trying to "catch up" on sleep. Increased time in bed and increased attention and effort to sleep fuel hyperarousal and perpetuate insomnia.[25;26] Ms. J's experience illustrates that insomnia often persists after resolution of the original stressor.

Key elements of the assessment include the patient's sleep characteristics, daytime behaviors, medical-psychiatric history, symptoms of other sleep disorders, and medications (Box 2).[27] Clinicians can also use several tools to help assess insomnia. Most important are prospective sleep-wake diaries, which evaluate the timing and variability of sleep,[28] and may identify targets for behavioral interventions (online supplement eFigure 2).

The differential diagnosis of insomnia includes other sleep and medical disorders (Box 2). Up to 50% of adults with obstructive sleep apnea (OSA) also complain of insomnia. The presence of loud snoring, witnessed apneas, obesity, and narrow upper airway all suggest OSA. Circadian rhythm sleep disorders, such as delayed sleep phase disorder and shift work disorder, include symptoms of difficulty falling asleep or waking too early. Abnormal sleep timing, i.e., going to bed and waking at very late times, distinguish these conditions from insomnia disorder. Restless legs syndrome often results in difficulty falling asleep, but is accompanied by an urge to move the extremities and dysesthesias. A separate insomnia diagnosis is not needed for all patients with medical, psychiatric, or other sleep disorders who have insomnia symptoms, and should be made only if the symptoms are severe or constitute an independent focus of clinical attention.

Recommended treatments, indications and contraindications, side effects, and duration of use—The goals of insomnia treatment are to improve quantitative and qualitative aspects of sleep, to reduce the distress and anxiety associated with poor sleep, and to improve daytime function.[27] Insomnia treatment includes two broad categories: Cognitive-behavioral treatments and medication treatment. Patients often prefer non-pharmacologic approaches,[29] but two-thirds of patients taking hypnotics report at least moderate satisfaction.[30] Patients often try self-help strategies including reading, relaxation, and "sleep hygiene," and over-the-counter remedies such as alcohol, antihistamines, and herbal preparations.[8]

Cognitive-behavioral treatments: Maladaptive behaviors, thoughts, and beliefs regarding sleep can serve as perpetuating factors for insomnia disorders, and are the targets of cognitive and behavioral treatments summarized in Table 1. These treatments include several common elements: The use of sleep diaries to identify baseline patterns and clinical changes; the importance of patient investment in changing behaviors; and the use of voluntary waking behaviors to influence sleep, which is a largely involuntary process. Behavioral treatments are indicated for primary and comorbid insomnia.

Cognitive-behavioral treatment of insomnia (CBT-I) is the most widely-used and widely-studied non-drug treatment. The efficacy of CBT-I has been demonstrated for chronic primary and comorbid insomnia in younger and older adults; Table 2 summarizes meta-analyses of efficacy studies. The acute effects of CBT-I over 6-10 weeks are comparable or superior to those of hypnotic medications,[31] and are maintained for up to 3 years of follow-up. Behavioral treatments are efficacious in patients taking hypnotics,[32] and help patients reduce medication use.[33] Initial combined behavioral and pharmacotherapy, followed by CBT-I alone, may produce the best long-term outcomes.[34] CBT-I is typically delivered in 6-8 individual sessions, but the efficacy of brief versions[35] and internet delivery[36] have also been demonstrated.

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Pharmacologic treatments: FDA-approved hypnotic agents include benzodiazepine receptor agonists (BzRA), antihistamine drugs (e.g., hydroxyzine, diphenhydramine), a tricyclic drug (doxepin), and a melatonin receptor agonist (ramelteon). Barbiturates (secobarbital, butalbital), related drugs (ethchlorvynol), and chloral hydrate are FDA-approved, but are not recommended because of their potential toxicity. Physicians also prescribe a number of drugs without an FDA indication for insomnia, including anxiolytic benzodiazepines, sedating antidepressants, sedating antipsychotics, and anticonvulsants. Approximately 15-20 million prescriptions are written for BzRA hypnotics annually in the US, and approximately 6-10% of the population reports having used a hypnotic.[8;37] Commercial claims and patient encounter data show that several of the most widely-prescribed drugs are not FDA-approved for treatment of insomnia.[38]

Hypnotics are indicated for the treatment of primary and comorbid insomnia disorder. Certain medical/psychiatric conditions constitute relative contraindications for specific hypnotic agents. Conversely specific treatment for comorbid disorders is essential when treating patiens with hypnotics. Patients with acute or situational insomnia symptoms such as those associated with travel or psychosocial stress, are often prescribed hypnotics as well.

Benzodiazepine receptor agonist drugs (BzRA) (Table 3): BzRA drugs include benzodiazepine (e.g., temazepam, triazolam) and “non-benzodiazepine” drugs (e.g., zolpidem, zaleplon, eszopiclone). BzRA drugs share a common mechanism of action, binding to a specific recognition site on gamma aminobutyric acid type A (GABA-A) receptors. BzRA drugs produce sedative/hypnotic, amnestic, anxiolytic, myorelaxant, and anticonvulsant effects, but different GABA-A receptors subtypes are responsible for these effects, and BzRAs vary in their specificity for these receptor subtypes.[39] For instance, zolpidem and zaleplon are relatively specific for GABA-A α1 receptors and have greater specificity for hypnotic vs. other effects.

The short-term efficacy of BzRA is well-established in clinical trials that demonstrate statistically significant improvements in sleep quality and sleep latency; WASO, sleep time, and sleep efficiency also improve depending on the drug’s duration of action (Table 2).[40] Additional double-blind placebo-controlled studies support the efficacy of BzRA for up to 6 months of nightly[41] or intermittent[42] use, and up to 12 months in open-label studies.[43]

BzRA drugs have inconsistent effects on sleep stages, and the clinical relevance of sleep stage effects is uncertain. Clinically important differences between specific BzRAs result from their pharmacokinetic properties. Most hypnotic BzRAs have rapid absorption and onset of action. More slowly absorbed BzRAs (e.g., oxazepam, clorazepate) are less useful for insomnia. Elimination half-lives of hypnotic BzRA vary widely, with predictable clinical effects. For example, zaleplon, with a half-life of one hour, reduces sleep latency but has no significant effect on WASO; flurazepam and its metabolite have half-lives up to 120 hours, resulting in reduced WASO as well as increased daytime sleepiness. Pharmacokinetic differences can be used to clinical advantage. Patients with sleep onset difficulties or morning sedation from hypnotics may benefit from a short half-life drug, and patients with sleep maintenance difficulties may benefit from a longer half-life drug.

Although some BzRA are FDA-approved for insomnia and others for anxiety, they have similar pharmacodynamic properties. Thus, clonazepam and lorazepam are sometimes used as hypnotics when they have the desired pharmacokinetic profile. Conversely, using multiple BzRA agents (e.g., lorazepam for anxiety, temazepam for insomnia) can lead to additive effects rather than distinct effects on different symptoms. Relative contraindications to BzRA use include alcohol or sedative abuse/dependence, use of other sedative drugs, severe pulmonary failure or untreated sleep apnea, hepatic failure, and hypersensitivity to

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the drug class. BzRA should be used with caution in patients with depression and in older adults.

Adverse effects of BzRA hypnotics include morning sedation, anterograde amnesia, anxiety (clearly noted by Ms. J), impaired balance, increased falls and hip fractures, and complex sleep-related behaviors such as sleepwalking, sleep-related eating, driving, and sexual behavior.[44] Most of these adverse effects are dose-related, and some (e.g., morning sedation) are related to pharmacokinetic properties of specific agents. Other risk factors for adverse events include increasing age, use of other sedating drugs and alcohol, a history of parasomnias, and the presence of insomnia itself. A meta-analysis of BzRA efficacy and adverse events in older adults concluded that beneficial effects are outweighed by adverse effects.[45] Because of concerns regarding complex sleep-related behaviors, the FDA in 2007 required additional warning language for all hypnotics.

Additional concerns regarding BzRA include rebound insomnia, withdrawal, and dependence. Rebound insomnia refers to an increase in sleep symptoms beyond baseline levels, and is commonly observed during abrupt discontinuation, particularly for shorter-acting drugs.[44] Although several early studies suggested lower potential for rebound with non-benzodiazepine drugs compared to benzodiazepines, rebound can occur with both.[46] Rebound can be minimized by gradual dose reduction over weeks-months. Withdrawal symptoms, i.e., symptoms other than the initial complaint upon discontinuation of the drug, can last for several weeks. Among individuals with no substance use history, BzRA self-administration represents therapy-seeking rather than drug-seeking behavior.[47] However, abuse can occur with benzodiazepine and non-benzodiazepine hypnotics, particularly in individuals with a history of alcohol or other sedative abuse.[46;48]

BzRA hypnotics are commonly used in drug overdoses but are rarely fatal by themselves, due to a high LD_{50}. However, they are frequently taken in combination with alcohol, opiates, and other drugs, leading to increased toxicity and mortality. Increased mortality risk has been associated with even therapeutic use of BzRA hypnotics,[37] although confounding by indication and the effects of comorbidities may influence these findings.

Other medications used to treat insomnia: (Table 4) Ramelteon is a melatonin MT_1 and MT_2 receptor agonist that has similar properties to endogenous melatonin. Clinical trials demonstrate significant effects on sleep latency and sleep duration, but not inconsistent effects on WASO.[49] Ramelteon, like melatonin, can also shift the timing of circadian rhythms, depending on the time of administration.[50] Ramelteon is generally well-tolerated with few side effects other than sedation.

Doxepin, a tricyclic compound, is FDA-approved for depression at doses of 100-200 mg, and for insomnia at doses of 3-6 mg. At antidepressant doses, doxepin has effects on multiple central nervous system neurotransmitters (Table 4). At hypnotic doses, doxepin is selective for H_1 receptors, which may account for its sedative effect without the typical anticholinergic side effects seen at higher doses (e.g., dry mouth, blurred vision, constipation). Clinical trials demonstrate reduced WASO, increased sleep efficiency and total sleep time for up to 5 weeks, with little effect on sleep latency.[51;52] Doxepin affects WASO and sleep efficiency across the entire night, whereas short half-life BzRA have limited effect in the final third of the night.

A variety of “natural” and over-the-counter drugs are used as hypnotics, despite a lack of controlled clinical trials to support their use. *Melatonin* is a hormone typically secreted during the night, which in humans corresponds to the major sleep period. Melatonin has been evaluated as a hypnotic in doses of 0.3 – 80 mg, showing a small but significant effect

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on sleep latency, but not other sleep measures.[53] *Valerian* derivatives are the most widely-used herbal treatments for insomnia. The heterogeneity among specific valerian preparations, doses, and study methods precludes any definitive statement regarding their efficacy.[54] *Diphenhydramine, doxylamine, hydroxyzine* and other antihistamine drugs are commonly used to treat insomnia. Antihistamine drugs also antagonize muscarinic cholinergic receptors, which can lead to side effects including cognitive impairment and urinary retention. Few empirical data are available to support their efficacy or safety.[55] Antihistamines are frequently used in combination with analgesics in OTC preparations targeted at nighttime relief of sleep and pain complaints. Ms. J's experience with diphenhydramine is consistent with limited efficacy and side effects of grogginess and irritability.

Other prescription medications are also used to treat insomnia, but none have been systematically evaluated for their efficacy and safety. *Trazodone* is widely-prescribed in doses of 25-100 mg. The largest study of trazodone showed effects comparable to zolpidem on sleep latency and sleep efficiency, but effects were nonsignificant at week 2.[56] Although trazodone has a relatively short half-life, morning sedation is a common side effect, as Ms. J described. *Gabapentin* and *pregabalin* are often used to treat chronic pain conditions with comorbid insomnia, including fibromyalgia. Self-reported sleep outcomes in these trials generally support positive effects on outcomes such as sleep latency and WASO, and polysomnographic studies have shown increased deep sleep.[57;58] These effects may have contributed to Ms. J's favorable response to gabapentin. *Sedating antipsychotic drugs*, such as olanzapine, quetiapine, and risperidone, are also used off-label to treat insomnia. Self-report outcomes and a small number of polysomnographic studies suggest their efficacy, but the potential for serious adverse effects, including weight gain and cardiometabolic effects, argue against their use except in patients with serious mental disorders.

Referral to a sleep specialist—Most patients with chronic insomnia are treated by primary care physicians, which is appropriate given the prevalence of insomnia and its interactions with comorbid conditions and medications. Evaluation and treatment by a sleep specialist are appropriate when the patient has symptoms or clinical features of another sleep disorder, such as excessive daytime sleepiness (narcolepsy, apnea) loud snoring or witnessed apneas (sleep-related breathing disorders), pronounced alteration of sleep timing (circadian rhythm sleep disorder), or unusual sleep behaviors or injury (parasomnia). Patients seeking a formal course of CBT-I or who fail to respond to hypnotic medications may also be appropriate for referral.

What do you recommend for Ms. J?—Ms. J presents features typical of chronic insomnia including a mix of sleep maintenance and sleep onset problems; a variety of daytime symptoms and sequelae; a precipitating factor for insomnia with persistent symptoms even after resolution; and trials of multiple behavioral, OTC, and prescription treatments. The least typical aspect of her presentation is the absence of significant worry or cognitive arousal with insomnia.

More detailed information regarding sleep should be gathered, including symptoms of other sleep disorders such as sleep apnea, and additional history regarding sleep timing and duration. A sleep diary and wrist actigraphy would more accurately portray day-to-day variability and time in bed.

This information could reveal additional targets for specific behavioral and cognitive interventions, such as reduction of time in bed to increase homeostatic sleep drive, or cognitive techniques to address arousal and unhelpful beliefs and attitudes about sleep. Training in relaxation strategies may be a useful adjunct to Ms. J's exercise regimen.

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Additional medication strategies include a trial of doxepin (3-6 mg), given the history of predominantly sleep maintenance symptoms. Middle-of-the-night dosing with sublingual zolpidem could provide a useful as-needed treatment. Finally, combination treatment with low doses of a short-acting BzRA (e.g., zaleplon) and doxepin or trazodone could achieve some of the benefits of each drug class while minimizing adverse effects.

QUESTIONS AND DISCUSSION

QUESTION

What do you do with patients who say they never sleep?

DR BUYSSE

Patients with insomnia generally report less sleep than we measure with polysomnography, but some have an extreme degree of mismatch, called paradoxical insomnia. The usual treatments for insomnia are indicated, but may be less efficacious. One small study suggested that individuals with extreme sleep misperception can be taught to more accurately perceive sleep by reviewing polysomnography results. Medications and sleep restriction may also reduce activity in brain systems that relate to altered perception of sleep.

QUESTION

What do you do with patients who take a sleeping pill every night over long periods of time, like 10 years?

DR. BUYSSE

Prior to 2005, FDA labeling for hypnotics discouraged use for longer than one month; since 2005, labeling for new hypnotics does not specify a duration. This change reflects placebo-controlled data showing efficacy of hypnotics for 6-12 months of nightly use. Hypnotic medications should be used in the lowest effective dose for the shortest necessary duration. However, because insomnia is often a chronic problem, short-term use of hypnotics is unlikely to solve the problem. I aim for intermittent, non-nightly dosing when possible, combined with behavioral treatment. For some patients, chronic nightly treatment is reasonable. Discuss the potential risks and benefits of long-term use, involve patients in decision-making, and regularly re-evaluate efficacy and side effects.

QUESTION

Can you comment specifically about medication alternatives in older adults?

DR BUYSSE

Behavioral measures are particularly important in older adults with insomnia, given the potential adverse effects of hypnotics. The key to behavioral treatment for *sleep* in the elderly is to plan activities to keep the person engaged and involved during *wakefulness* in order to reduce time in bed. There are no clear alternatives to BzRA hypnotics for the elderly, since the alternative drugs also have significant side effects, including impaired cognition and balance, and increased falls. Try to keep medication doses low, carefully monitor the patient, provide good education, and use behavioral interventions when possible.

QUESTION

Do you prescribe light therapy?

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DR BUYSSE

Bright white light and blue light can help insomnia by changing the timing of the biological clock. The effects of light depend on the time of administration. In older adults the biological clock is often advanced to an earlier time; light in the evening hours pushes the biological clock—and sleep—to a later time. For patients who have difficulty falling asleep at night and difficulty waking up in the morning due to a delayed biological clock, bright light treatment in the morning advances sleep to an earlier time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1

International Classification of Sleep Disorders, Second Edition Criteria for General Insomnia Disorder[1]

1. A complaint of difficulty initiating sleep, difficulty maintaining sleep, or waking up too early or sleep that is chronically unrestorative or poor in quality. In children, the sleep difficulty is often reported by the caretaker and may consist of observed bedtime resistance or inability to sleep independently.
2. The above sleep difficulty occurs despite adequate opportunity and circumstances for sleep.
3. At least one of the following forms of daytime impairment related to the nighttime sleep difficulty is reported by the patient:
    - **a.** fatigue or malaise
    - **b.** attention, concentration or memory impairment
    - **c.** social or vocational dysfunction or poor school performance
    - **d.** mood disturbance or irritability
    - **e.** daytime sleepiness
    - **f.** motivation, energy, or initiative reduction
    - **g.** proneness for errors or accidents at work or while driving
    - **h.** tension, headaches, or gastrointestinal symptoms in response to sleep loss
    - **i.** concerns or worries about sleep.

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Box 2

Evaluati on of Insomnia

Sleep History

The evaluation of insomnia rests on a careful clinical history. The clinician should evaluate the nature, frequency, and duration of insomnia symptoms, their chronology, and response to treatment. The patient's symptoms should be considered across the entire 24-hour day: Sleep and wakefulness affect each other in complex ways, and patients often seek treatment because of daytime symptoms and distress related to their sleep problems. Key elements of the sleep history include:

- *Temporal* aspects of sleep: Times at which patient goes to bed, attempts to sleep, wakes up, gets out of bed
- *Quantitative* aspects of sleep: Sleep latency (time it takes to fall asleep); number and duration of awakenings; wakefulness after sleep onset; total sleep time
- *Qualitative* aspects of sleep: Subjective sleep quality, satisfaction
- *Behavioral and environmental factors*: Non-sleep activities in bed (phone, computer, TV); environment (temperature, light, sound); bedpartners and pets; perceived causes of awakening
- Symptoms of *other sleep disorders*: Obstructive sleep apnea (snoring, breathing pauses); restless legs syndrome (urge to move the extremities); parasomnias (unusual sleep behaviors); circadian rhythm disorders (unusual sleep timing)
- *Daytime causes and consequences* of disturbed sleep: Napping; exercise; work and activities; social and family stressors; use of caffeine, alcohol, and tobacco

Medical and psychiatric history

Insomnia evaluation should include a medical/ psychiatric history and physical examination to identify comorbid conditions that can exacerbate, or be exacerbated by, insomnia.

- *Medical disorders*: Neurologic (stroke, migraine); Pulmonary (COPD, asthma); Chronic pain (arthritis, fibromyalgia); Endocrine (hypo-, hyperthyroidism); Gastroespohageal reflux; Cardiovascular (CHF)
- *Psychiatric disorders*: Depression; Bipolar disorder; Anxiety disorders; Substance use disorders
- *Medications*: Antidepressants; other sedatives; antihypertensives; steroids; decongestants and antihistamines; adrenergic agonists

Other tools and tests

- *Sleep-wake diary*: Prospective record of sleep-wake timing, quantity, and quality; may identify patterns that are useful targets for behavioral treatment
- *Wrist actigraphy*: Measure and store movement data for up to 28 days; rest-activity patterns correlate with sleep-wakefulness
- *Polysomnography (sleep study)*: Not recommended for routine assessment of insomnia, but appropriate to evaluate suspected sleep apnea or parasomnias

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Table 1

Cognitive-Behavioral Interventions for Insomnia*

Intervention	General description	Specific techniques
Sleep hygiene education	Recommendations promoting behaviors that help sleep, discouraging behaviors that interfere with sleep	• Don't try to sleep • Avoid stimulants (caffeine, nicotine) • Limit alcohol intake • Maintain a regular sleep schedule 7 nights a week • Avoid naps • Get regular exercise, at least 6 hours before sleep • Keep the bedroom dark and quiet
Stimulus control	Based on operant and classical conditioning principles: Non-sleep activities and the bedroom environment can serve as stimuli that interfere with sleep. Treatment prescribes behaviors that strengthen associations between the environment and sleep.	• Go to bed only when sleepy. • Use the bed and bedroom for sleep only. Do not read, watch television, talk on the phone, worry, or plan activities in the bedroom. • If unable to fall asleep within 10-20 minutes, leave the bed and the bedroom. Return only when felling sleepy again. • Set the alarm and wake up at a regular time every day. • Do not snooze. Do not nap during the day.
Sleep restriction therapy	Based on experimental evidence that sleep is regulated by circadian and homeostatic processes. Treatment increases homeostatic sleep drive by reducing time in bed, and maintaining a consistent wake time in the morning to reinforce circadian rhythms.	• Restrict time awake in bed using by setting strict bedtime and rising schedules limited to the average number of hours of actual sleep reported in one night. • Increase time in bed by advancing bedtime by 15-30 minutes when the time spent asleep is >85% of time in bed. • Keep a fixed wake-up time, regardless of actual sleep duration. • If after 10 days, sleep efficiency is lower that 85%, further restrict bedtime by 15-30 minutes.
Relaxation training	Muscular tension and cognitive arousal are incompatible with sleep. Relaxation decreases waking arousal, and facilitates sleep at night.	Specific techniques may include: • Progressive muscle relaxation • Guided imagery • Paced breathing
Cognitive therapy	Identify, challenge, and replace dysfunctional beliefs and attitudes regarding sleep and sleep loss. These beliefs increase arousal and tension, which impede sleep and further reinforce the dysfunctional beliefs.	• Challenge unhelpful beliefs and fears about sleep, e.g.: ○ Overestimation of numbers of hours of sleep necessary to be rested. ○ Apprehensive expectation that sleep cannot be controlled. ○ Fear of missing opportunities for sleep. • Thought journaling to reduce rumination • Design behavioral ―experiments‖ to test beliefs about sleep
Cognitive Behavioral Treatment of Insomnia (CBT-I)	Multi-modal treatment combining elements of above techniques	• Sleep education • Stimulus control techniques • Sleep restriction techniques • Cognitive therapy techniques • May include relaxation training

Intervention	General description	Specific techniques
Brief Behavioral Treatment of Insomnia[35]	Core techniques from Stimulus Control, Sleep Restriction therapies	• Limit time in bed to actual sleep time + 30 minutes • Establish regular wake time every day, regardless of prior night's sleep duration • Do not go to bed until sleepy • Do not stay in bed if awake

*See[59-61] for further details of each therapy.

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Table 2

Quantitative Reviews of Treatment Efficacy in Chronic Insomnia1

Source	Studies Reviewed	Major Findings
Psychological and Behavioral Treatments		
Morin et al., 1994[62]	• 59 controlled studies of psychologicalbehavioral treatments • Total n = 2102	• Moderate to large effect sizes (d = 0.42 – 0.88) for short-term outcomes of sleep latency, wake after sleep onset, number of awakenings, total sleep time • Effects sizes maintained at follow-up
Murtagh and Greenwood, 1995[63]	• 66 outcome studies • Total n = 1907	• Moderate to large effect sizes (d = 0.49 – 0.94) for short-term outcomes of sleep latency, total sleep time, number of awakenings, sleep quality • Effects maintained at long-term follow-up
Pallesen et al., 1998[64]	• 13 studies • Participants with minimum age 50 years and group mean age >60 years • Total n = 388	• Small to moderate effect sizes (d = 0.15 – 0.61) for post-treatment outcomes of sleep latency, wake after sleep onset, number of awakenings, total sleep time • Moderate effect sizes (0.37 – 0.66) for long-term outcomes
Smith et al., 2002[65]	• 21 studies • 8 pharmacologic RCTs, total n = 220 participants • 14 behavioral RCTs, total n=250	• Moderate to large effect sizes (d = 0.46 – 1.44) for outcomes of sleep latency, wake after sleep onset, total sleep time, sleep quality • Effect size for sleep latency was larger in behavioral than pharmacological treatment studies
Irwin et al., 2006[66]	• 23 RCTs of behavioral treatments for chronic insomnia • Younger and older adult samples • Total n not indicated	• Small effect sizes for total sleep time • Moderate to large effect sizes (0.50 – 0.79) for sleep quality, latency, efficiency, wake after sleep onset • Equivalent effects in younger and older adults except for total sleep time (smaller effect size in older adults)
Montgomery and Dennis, 2009[67]	• 6 RCTs of CBT-I • Adults > 60 years old with primary insomnia • Total n = 224	• Significant mean differences pre-post treatment for wake after sleep onset (self-report and PSG), sleep efficiency (PSG) • Mean differences not statistically significant for sleep latency, total sleep time (self-report and PSG), sleep efficiency (self-report)
Van Straten and Cuijpers, 2009[68]	• 10 controlled trials of self-help interventions (e.g., books, internet, audiotapes) vs. controls and in-person treatment • Total n = 1000	• Effect sizes small to moderate (d = 0.02 – 0.44) for total sleep time, sleep efficiency, sleep latency, wake after sleep onset, sleep quality in self-help vs. wait-list control • Effect sizes small to moderate (d = 0.02 – −0.50) favoring in-person treatment vs. self-help
Okajima et al., 2011[69]	• 14 RCTs of CBT-I vs. control treatments • Total n = 958	• Self-report outcomes: Effect sizes small for total sleep time (d = 0.00), moderate-large for sleep latency, wake after sleep onset, total wake time, sleep efficiency (d = 0.44 – 0.86) • Objective outcomes: Effect sizes small for sleep latency, total sleep time (d = 0.13-0.24), moderate for wake after sleep onset, total wake time, sleep efficiency (d = 0.42 – 0.73) • Effects generally maintained with 3-12 month follow-up

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Source	Studies Reviewed	Major Findings
Cheng and Dizon, 2012[70]	• 6 RCTs of computerized CBT-I vs. wait-list or active control • Total n = 228	• Small to large effect sizes (d = 0.22 – 0.86) for sleep latency, number of awakenings, sleep efficiency, sleep quality, Insomnia Severity Index • Non-significant effect size for wake after sleep onset (d = −0.18) • Average NNT in 4 studies ranges from 2.91 – 3.59
Pharmacologic Treatments		
Nowell et al., 1997[71]	• 22 RCTs of BzRA hypnotics • Adults younger than 65 years • N = 1894	• Moderate effect sizes (d = 0.56 – 0.71) for self-reported outcomes of sleep latency, total sleep time, number of awakenings, sleep quality • Z scores for effect sizes range from 0.71 – 0.76
Holbrook et al., 2000[72]	• 45 RCTs of benzodiazepine hypnotics compared to placebo or other active treatments • N = 2672	• Self-report outcomes: Significant difference favoring benzodiazepines vs. placebo for sleep latency, total sleep time • PSG outcomes: Significant difference favoring benzodiazepines vs. placebo for total sleep time • Side effects (drowsiness, dizziness, lightheadedness): Significantly more likely in patients taking benzodiazepines vs. placebo
Smith et al., 2002[65]	• 21 studies • 8 pharmacologic RCTs, total n = 220 participants • 14 behavioral RCTs, total n=250	• Moderate to large effect sizes (d = 0.45 – 1.20) for sleep latency, wake after sleep onset, total sleep time, sleep quality • Effect size for sleep latency larger in behavioral vs. pharmacological treatment studies
Dundar et al., 2004[73]	• 24 RCTs comparing benzodiazepine to non-benzodiazepine BzRA drugs • Total n = 3909	• Equivalent efficacy of benzodiazepine and non-benzodiazepine hypnotics on most outcomes • Shorter sleep latency for zolpidem vs. temazepam, zopiclone; and zaleplon vs. zolpidem
Glass et al., 2007[45]	• 24 RCTs of BzRA vs. placebo • Adults aged 60 or over • Total n = 2417	• Sleep quality: d = 0.13, number needed to treat = 13 • Total sleep time: mean difference = 25.2 minutes (95% C.I.: 12.8 – 37.8) • Number of awakenings: Mean difference = −0.63 (95% C.I.: −0.48 - −0.77) • All adverse events: Number needed to harm = 6 • Significantly greater risk of cognitive, fatigue, performance adverse effects, but not psychomotor adverse events (dizziness, loss of balance), with active drugs vs. placebo
Buscemi et al., 2007[74]	• 105 RCTs of BzRA and antidepressant drugs in chronic insomnia • Total n = 13986	• Significant difference for all drugs vs. placebo on polysomnographic sleep latency (weighted mean difference −7.0 - −12.8 minutes) and sleep diary sleep latency (weighted mean difference −12.2- −19.6 minutes) • BZRA: Significant effects on polysomnographic sleep efficiency; and on sleep diary wakefulness after sleep onset, sleep efficiency, total sleep time, sleep quality • Antidepressants: Significant effects on polysomnographic wake after sleep onset, sleep efficiency, total sleep time; and on sleep diary rating of sleep quality

Source	Studies Reviewed	Major Findings
		• Adverse events significantly greater for BzRA and antidepressants vs. placebo

Abbreviations: CBT-I = cognitive Behavioral Therapy for Insomnia; PSG = Polysomnography; RCT = Randomized Controlled Trial; BzRA = Benzodiazepine receptor agonist drug. The studies summarized in Table 2 are the product of a systematic literature review described in the on-line supplement (eMethods).

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Table 3

Benzodiazepine Receptor Agonist (BzRA) Drugs[1]

Class/Drug	TMax (hours)	Elimination Half Life (hours)	Usual Hypnotic Dose (mg)	Approved for Insomnia	Comments
Benzodiazepine					
Triazolam	1 – 2	2 – 6	0.125 – 0.25	Yes	Early reports of adverse effects were likely dose-related
Temazepam	1 – 2	8 – 22	15 – 30	Yes	Metabolized mainly by conjugation (no CYP-related drug interactions)
Estazolam	1.5 – 2	10 – 24	1 – 2	Yes	Triazolo ring structure similar to triazolam
Quazepam	2 – 3	48 – 120	7.5 – 15	Yes	Active metabolite (Ndesalkylflurazepam) accumulates with repeated dosing
Flurazepam	1.5 – 4.5	48 – 120	15 – 30	Yes	Active metabolite (Ndesalkylflurazepam) accumulates with repeated dosing
Alprazolam	0.6 – 1.4	6 – 20		No	Often noted for significant withdrawal
Lorazepam	0.7 – 1	10 – 20	1 – 4	No	Metabolized by conjugation (no CYP-related drug interactions)
Clonazepam	1 – 2.5	20 – 40	0.5 – 3	No	Often used for other sleep disorders including RLS, parasomnias
Non-Benzodiazepine					
Zaleplon	1 (0.5 – 2)	1 (0.8 – 1.3)	5 – 20	Yes	Shortest-acting BzRA
Eszopiclone	1.5 (0.5 – 2)	6 (5 – 8)	1 – 3	Yes	~30% may have unpleasant taste or side-effects
Zolpidem – Oral tablet	1.6 (0.5 – 1.5)	2.5 (1.4 – 4.5)	5 – 10	Yes	Most widely-prescribed hypnotic
Zolpidem: Extended Release (Ambien CR®)	1.5 (1.5 – 2.0)	2.8 (1.6 – 4.5)	6.25 – 12.5	Yes	Higher concentrations 3-8 hours post dose than traditional zolpidem
Zolpidem: Sublingual (Intermezzo®)	0.6 (0.6 – 1.3)	2.5 (1.4 – 3.6)	1.75 – 3.5	Yes	Buffer permits increased buccal absorption, lower dose
Zolpidem: Sublingual (Edluar®)	1.4 (0.5 – 3.0)	2.7 (1.5 – 6.7)	10	Yes	Mainly absorbed via GI tract
Zolpidem: Oral Spray (Zolpimist®)	0.9	2.8 (1.7 – 8.4)	10	Yes	Bioequivalent to tablets in terms of $C_{max,}$ $T_{max,}$ $t_{1/2}$

[1] Sources: FDA-approved prescribing information and sources[39;75]. Published pharmacokinetic data are not consistently reported for all drugs.

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Table 4

Other Drugs Commonly Used as Hypnotics[1]

Class/Drug	T_{Max} (hours)	Half Life (hours)	Mechanism[2]	Usual Hypnotic Dose (mg)	FDA Approved Indication	Comments, Side Effects
Melatonin agonist drugs						
Melatonin	0.3 – 1	0.6 – 1	MT_1, MT_2 agonist	0.5 – 3	No FDA approval	FDA defined as a dietary supplement
Ramelteon	0.75 (0.5 – 1.5)	1 – 2.6	MT_1, MT_2 agonist	8	Insomnia	Main effect on sleep latency
Sedating antidepressant drugs						
Doxepin	3.5 (1.5 – 4)	15 (10 – 30)	Low dose: H1 antagonist Higher doses: $5HT_2$, α_1, M_1, antagonist; NE, 5HT reuptake inhibitor	3 – 6 (Silenor®) 10 – 100 (generic)	Insomnia Depression Anxiety	3-6 mg dose approved for insomnia; Side effects at higher doses: orthostatic hypotension, anticholinergic, cardiac conduction delay
Amitriptyline	2 – 5	30 (5 – 45)	$5HT_2$, α_1, M_1 antagonist; NE, 5HT reuptake inhibitor	10 – 100	Depression	Side effects at higher doses: orthostatic hypotension, anticholinergic, cardiac conduction delay
Trazodone	1 – 2	9 (7 – 15)	$5HT_2$, α_1, H_1 antagonist; 5HT reuptake inhibitor	25 – 150	Depression	Side effects: dizziness, risk of priapism
Mirtazapine	2 (1 – 3)	30 (20 – 40)	$5HT_{2\text{-}3}$, $\alpha_{1\text{-}2}$, H_1, M_1 antagonist; 5HT reuptake inhibitor	7.5 – 30	Depression	Increased appetite, weight gain, anticholinergic
Sedating antipsychotic drugs						
Olanzapine	4 – 6	20 – 54	$5HT_2$, $D_{1\text{-}4}$, α_1, H_1, $M_{1\text{-}5}$ antagonist	2.5 – 20	Schizophrenia Bipolar Disorder	Hypotension weight gain, akathisia, dizziness
Quetiapine	1 – 2	6	$5HT_{1\text{-}2}$, $D_{1\text{-}2}$, $\alpha_{1\text{-}2}$, H_1 antagonist	25 – 50	Schizophrenia Bipolar Disorder	Dry mouth, constipation, weight gain, asthenia, headache
Antihistamine drugs						
Diphenhydramine	1 – 4	4 – 8	H_1, M_1 antagonist	25 – 50	Allergic reactions, motion sickness, Parkinsonism	Anticholinergic
Doxylamine	2 – 3	10	H_1, M_1 antagonist	25 mg	Allergies, hypersensitivity, insomnia	Anticholinergic; Dystonic reaction
Anticonvulsant drugs						
Gabapentin	1.6 – 3	5 – 9	Uncertain. GABA analog, but does not have activity at GABA receptors. Possible $alpha_2$-delta receptor ligand	100 – 900	Post herpetic neuralgia; epilepsy	Renal excretion, non-linear pharmacokinetics (reduced bioavailability at higher doses); izziness, ataxia, fatigue

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Class/Drug	T_{Max} (hours)	Half Life (hours)	Mechanism[2]	Usual Hypnotic Dose (mg)	FDA Approved Indication	Comments, Side Effects
Pregabalin	1.5	6.3	$alpha_2$-delta receptor ligand. GABA analog, but does not have activity at GABA receptors.	50 – 300	Diabetic peripheral neuropathy; Post herpetic neuralgia; Adjunct for partial seizures; Fibromyalgia	Renal excretion; dizziness, headache, weight gain, dry mouth

[1] Sources: FDA-approved prescribing information and sources[57;58]. Published pharmacokinetic data are not consistently reported for all drugs.

[2] MT = Melatonin receptor; H = Histamine receptor; 5HT = Serotonin; M = Muscarinic cholinergic receptor; α = alpha adrenergic receptor; D = Dopamine receptor; GABA = Gamma-aminobutyric acid