Insomnia: A Current Review

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Insomnia is a widely prevalent disorder with pervasive effects on quality of life.

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Abstract

Insomnia is a prevalent sleep disorder with pervasive effects on quality of life. The deleterious effects of insomnia are largely preventable with appropriate therapeutic interventions. Pharmacotherapy should be initiated in patients with inadequate response to CBT-I and tailored to comorbidities. Referral to a sleep medicine specialist should be considered in patients with a suboptimal response.

Introduction

Insomnia is a prevalent sleep disorder that is frequently underdiagnosed or undertreated. It is clinically characterized by subjective difficulty falling asleep or staying asleep which must be present for at least three days a week for three months to meet ICSD-3 diagnostic criteria.[1] Importantly insomnia occurs despite adequate opportunities to sleep and is accompanied by daytime symptoms. Similar criteria have been proposed and established by the DSM-5 and ICD-10.[2,3]

In adults, daytime effects can range from fatigue, trouble focusing, reduced motivation, and irritability to memory impairment. Affected individuals may report dissatisfaction or anxiety about the quality of their sleep. In children, insomnia is typically reported by parents or caregivers as resistance to going to bed and poor academic performance.

Types of insomnia

Insomnia is classified based on the duration of symptoms. Chronic insomnia is defined by symptoms occurring at least three times a week for at least three months. Short-term insomnia is distinguished by symptoms that last less than three months. It is often seen in association with acute stressors and disappears with resolution of the stressor but can evolve into chronic insomnia when perpetuating factors are present.

Epidemiology and Pathophysiology

Estimates of the prevalence of insomnia in the adult population vary from 10% to as high as 40%.[4] This uncertainty stems from lack of awareness and the complexity of diagnostic criteria required to make a definite diagnosis.[5] Contributing factors for insomnia are defined by Spielman's three-factor model which classifies them as predisposing, precipitating, and perpetuating factors.[6]

Predisposing factors include advanced age, female gender, depressed mood, increased levels of perceived stress, hypnotic use, substance abuse, and a positive family history of insomnia.[7] Lower socioeconomic status has been associated with insomnia, although racial and ethnic minorities are less likely to report it possibly because of perceived implications for employment.[8,9] Insomnia has been linked with many chronic

medical conditions including heart disease, cancer, neurologic disease, chronic urinary and gastrointestinal disorders, and chronic pain.[10-12] Up to 40% of affected individuals are diagnosed with psychiatric disorders such as depression, anxiety, and post-traumatic stress disorder.[12]

Precipitating factors include stressful life events, medical or psychiatric illness, and medications like steroids that can cause insomnia.

Perpetuating factors include maladaptive responses such as daytime napping and increasing anxiety that sustain this process, eventually culminating in chronic insomnia.

Aside from its biological effects, insomnia has economic implications for society. Insomnia can cause chronic absenteeism with a propensity to self-medicate with over-the-counter medications and alcohol. Indirect cost to the economy is estimated at over $60 billion per year, excluding direct healthcare costs.[13] These costs are largely preventable by timely diagnosis and institution of appropriate therapeutic interventions.

Treatment of Insomnia

Treatment of insomnia is broadly grouped into non-pharmacologic and pharmacologic interventions.

Non-pharmacologic Interventions

These interventions constitute the cornerstone of management and should be applied before attempting pharmacotherapy. Moreover, they should be continued while the patient receives pharmacotherapy for effective treatment with the lowest possible medication. This minimizes the risk of medication side-effects and improves sustainability of the therapeutic strategy.[14]

Cognitive Behavioral Therapy (CBT)

CBT is a psychotherapeutic technique focusing on identifying and eliminating intrusive thoughts with negative effects on behavior and emotion.[15] CBT for insomnia (CBT-I) is specifically tailored to insomnia and combines educational and behavioral interventions with cognitive techniques. Educational intervention is centered around sleep hygiene, which includes maintaining a regular sleep schedule, avoiding screen time 30 minutes prior to bedtime, maintaining a cool and dark sleeping environment, avoidance of caffeine after lunch, and minimizing daytime naps. Behavioral interventions include stimulus control, sleep restriction, and relaxation techniques. Cognitive interventions include thought-stopping, constructive worry exercise, cognitive restructuring, cognitive defusion, and paradoxical intention.[14,16,17] While best delivered by psychologists, online versions are available.

Pharmacologic Interventions

Available interventions include numerous FDA-regulated agents spanning prescription medications approved for insomnia, prescription medications used off-label for insomnia, and over-the-counter drugs. Additionally, we will review unregulated supplements and recreational agents like alcohol that are frequently used for self-medication by persons suffering from insomnia as they have implications for pharmacotherapy of insomnia.

FDA-Approved Pharmacotherapy for Insomnia

Several pharmacotherapeutic agents are approved by the FDA for use in insomnia. These agents can exert their effects through the $GABA_A$ receptor (benzodiazepines, and non-benzodiazepine Z drugs), orexin receptor (DORAs), or melatonin receptor (ramelteon).

Drugs Acting Via the $GABA_A$ Teceptor

They include benzodiazepines and non-benzodiazepine benzodiazepine receptor agonists (BZRAs) also known as 'Z' drugs. They have a rapid onset of action and increased total sleep time making them effective in sleep-onset and sleep maintenance insomnia.[18]

- ***Benzodiazepines***

Benzodiazepines (BZDs) are positive allosteric modulators of the $GABA_A$ receptor complex. Gamma amino butyric acid (GABA) is a sleep-promoting neurotransmitter in the central nervous system. BZDs exert their effect by increasing GABA binding to the $GABA_A$ receptor resulting

Table 1. Summary of available benzodiazepines including indication, dosing and half-lives.

BZD	Sleep-onset insomnia	Sleep maintenance insomnia	Dosing in adults<65 yr	Dosing in adults ≥65 yr	Half-life (hrs)
Estazolam	+	+	1-2 mg	0.5-1 mg	10-24
Flurazepam	+	+	15-30 mg	15 mg	48-120
Quazepam	+	+	7.5-15 mg	7.5 mg	48-120
Temazepam	+	+	7.5-30 mg	7.5 mg	8-22
Triazolam	+	-	0.125-0.5 mg	0.125-0.25 mg	2-4

in increased intracellular chloride, membrane hyperpolarization, and signal inhibition. This is accomplished by binding of BZD to the alpha subunit of the receptor complex. There are six subtypes of the alpha subunit that determine the downstream effects of GABA including muscle relaxation, anxiolysis, and sedation.[19] BZDs bind to subtypes 1, 2, 3, and 5.

The rapid onset of action of BZDs requires that they be dosed at bedtime and their long half-life necessitates that adequate time be allowed in bed and hazardous activities avoided after drug administration. Special precautions should be taken when prescribing these agents to older people and individuals with liver impairment.

Although generally well tolerated, BZDs can have side-effects ranging from daytime somnolence, dizziness, ataxia, and headaches to more serious conditions like anterograde amnesia and complex sleep behaviors like somnambulism.[19] They are also associated with rebound insomnia and withdrawal symptoms like anxiety and seizures when abruptly discontinued after prolonged use. Patients who receive these agents should be educated about the potential for such complications. Individual drugs are summarized. (Table 1).

- ***Non-benzodiazepine BZRAs (Z Drugs)***

These agents are pharmacodynamically similar to BZDs and also act on the alpha subunit of the $GABA_A$ receptor complex to enhance GABA binding. However, unlike BZDs, these drugs bind specifically to the alpha-1 subunit which mediates the sedative action of GABA. As a result, they have fewer "off-target" effects seen with BZDs and are better tolerated.[20] The majority of these drugs are long-acting; except zaleplon, which is short-acting and not associated with daytime somnolence. They carry the potential for excessive sedation in older and hepatically-impaired individuals. Additionally, zolpidem requires dose modification in women because of slower metabolism.[21] Z drugs have been linked with complex sleep behaviors that can lead to potentially fatal situations. Reports of such incidents led the FDA to issue a black box warning for these agents in April 2019.[22] Individual drugs in this category are summarized (Table 2).

- ***Dual Orexin Receptor Antagonists***

Dual orexin receptor antagonists (DORAs) act by blocking receptors to orexin peptides A and B. The orexin pathway promotes wakefulness and arousal.[23] Suvorexant, lemborexant, and daridorexant are currently approved in this class. They are effective in both sleep-onset and sleep-maintenance insomnia. They are long-acting and can cause daytime somnolence. These drugs have better safety profile in the elderly.[24] Despite a favorable benefit-risk profile, DORAs are not preferred over other FDA-approved drugs due to significant cost. The pharmacokinetic properties of these agents are summarized (Table 3).

Ramelteon

This is a synthetic analog of melatonin, which acts selectively on the MT1 receptors in

Table 2. Summary of available non-benzodiazepine BZRAs including indication, dosing and half-lives.

Non-BZD	Sleep-onset insomnia	Sleep maintenance insomnia	Dosing in adults <65 yr	Dosing in adults ≥65 yr	Half-life (hrs)
Zaleplon	+	-	5-20 mg	5 mg	1
Zolpidem IR	+	+	5-10 mg*	5 mg	1.4 – 4.5
Zolpidem oral liquid	+	+	5-10 mg* (5 mg/ spray)	5 mg	1.4 – 4.5
Zolpidem ER	+	+	6.25-12.5 mg†	6.25 mg	1.6 – 4
Zolpidem sublingual	-	+	3.5 mg‡	1.75 mg	1.4 – 4.5
Eszopiclone	+	+	1-3 mg	1-2 mg	6

*5 mg in females due to slow metabolism
†6.25 mg in females due to slow metabolism
‡1.75 mg in females due to slow metabolism

the suprachiasmatic nucleus to attenuate the circadian alerting signal and shorten sleep-onset latency. It is suitable for sleep-onset insomnia such as individuals with delayed circadian rhythm/sleep cycle. Ramelteon is not helpful for individuals with difficulty staying asleep. The clinical efficacy of ramelteon is relatively minor, but studies have reported subjective benefits extending up to a year.[25] Ramelteon dose is 8 mg once daily within 30 minutes of bedtime. It is a relatively safe drug, does not cause daytime sedation or withdrawal effects after cessation, and does not have abuse liability.

Doxepin (Low Dose)

Doxepin is a selective histamine receptor antagonist. At low doses of 3-6 mg, it acts selectively on H1 receptors and is effective for sleep maintenance because of its relatively long half-life. Although it can cause daytime somnolence, it has no abuse liability and there is no limitation on duration of use.

Off-Label Use of Prescription Medications (FDA-Approved But Not for Insomnia)

Many medications produce sedation—including antidepressants, anticonvulsants, mood-stabilizing agents, and antipsychotics. Their sleep-promoting effects are mediated by suppression of wake-promoting neurotransmitters such as acetylcholine, dopamine, norepinephrine, serotonin, and histamine. These agents are typically not recommended as stand-alone therapy for insomnia. However, in patients with insomnia and concurrent psychiatric disorders requiring pharmacotherapy, the sedating properties of these drugs can be useful in alleviating insomnia.[26]

Antidepressants

Examples include trazodone and mirtazapine. Trazodone has a rapid onset of action that makes it helpful for sleep-onset disorders but a long half-life that can cause excessive daytime sedation. Additionally, trazodone is associated with serotonergic adverse effects including hypotension, sweating, arrhythmias, and serotonin syndrome. Because of these adverse effects, trazodone is not recommended as a standalone therapy for insomnia.[27] However, one review article suggests that trazodone may be used in low doses (25-100 mg) for insomnia.[28] Mirtazapine has similar sleep-promoting properties and is associated with

Table 3. Summary of available DORAs including dosing, half-lives and adverse effects.

DORA	Dose	Onset (mins)	Half-life (hrs)	Adverse effects (class effects)
Suvorexant	10-20 mg	30	12	• Daytime somnolence • Significant drug interaction (CYP3A4 dependent metabolism) • Sleep paralysis • Hypnagogic and hypnopompic hallucination • Cataplexy-like symptoms • Contraindicated in narcolepsy
Lemborexant	5-10 mg	15-20	17-19	
Daridorexant	25-50 mg	60	8	

anticholinergic adverse effects but does not cause cardiac and sexual dysfunction, unlike trazodone. Mirtazapine and trazodone are best considered in patients with comorbid depression with insomnia.[29]

Anticonvulsants

Gabapentin and pregabalin may be considered in patients with comorbid pain, seizure disorder, and alcohol use disorders. There are no randomized controlled data to support the use of these agents for insomnia in the absence of such conditions.[30]

Antipsychotics

They are considered in patients with comorbid psychosis and insomnia unresponsive to standard therapies: examples include quetiapine and olanzapine. Olanzapine has a prolonged half-life that can cause marked daytime sedation. They may be associated with significant toxicity and should not be used for insomnia in the absence of comorbid psychiatric indications.[31] Quetiapine for instance carries a black box warning for suicidal thoughts and both agents carry warnings about increased mortality in older individuals.[32]

Over-the-Counter Medications

Antihistamines

These medications do not require prescription and include agents like doxylamine and diphenhydramine. Despite their widespread use, accounting for an estimated 60% of all medications used for insomnia,[33] there is little to no high-quality evidence to support their use for this indication. They exert their sleep-promoting effects via postsynaptic histamine receptor blockade. They can cause anticholinergic side-effects like dry mouth, blurry vision, confusion, and urinary retention, as well as prolonged sedation and daytime sleepiness. These effects are magnified in older individuals and patients receiving other anticholinergic medications.[34] Given the potent anticholinergic effects of diphenhydramine (also available in combination with acetaminophen), its use is not recommended for insomnia. Moreover, the use of these agents is typically associated with rapid development of tolerance, which renders them ineffective for chronic insomnia.

Unregulated Supplements and Recreational Substances

Unregulated Supplements

Safety concerns apply to over-the-counter medicines and supplements. Examples include ashwagandha, chamomile flower extract, magnesium supplements, glycine, L-theanine, and valerian root with limited data to support their efficacy, safety, and quality control.[35] They

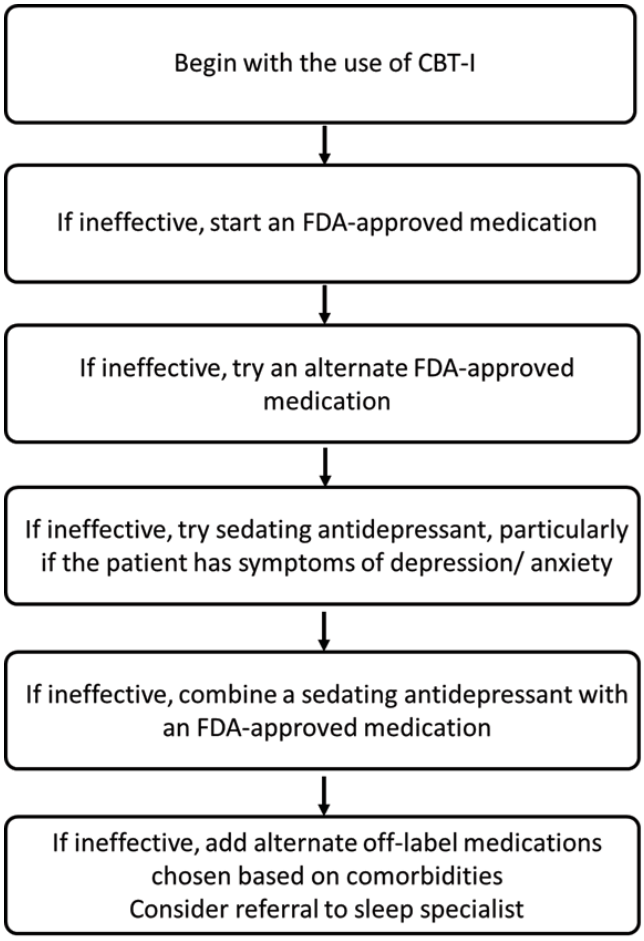

Figure 1. Simplified algorithm for initiating and/or combining pharmacological therapy.

are not regulated by the FDA, do not require a prescription, and their use is not supported by the American Academy of Sleep Medicine.[27]

Melatonin

Melatonin is a hormone secreted by the pineal gland. Melatonin levels are suppressed during the day, rise towards nightfall, plateau overnight, and then fall back to daytime concentrations by dawn.[36] The sleep-enhancing effects of melatonin are mediated by MT1 and MT2 receptors.[37] The circadian reinforcing effect of melatonin makes it suitable for patients with sleep-onset disorders.[38] Melatonin has been used in patients with Delayed Sleep Phase syndrome, who go to sleep later and may present as sleep-onset insomnia. This agent may be used in appropriate settings under the supervision of a clinician.

Recreational Substances

Acute ingestion of alcohol reduces sleep latency and improves quality and quantity of non-REM sleep during the first half of the night. However, there is disruption of sleep architecture in the second half.[39] Thus, alcohol use leads to diminished sleep quality, sleep disruption, and worsening insomnia. Insomnia is a prominent symptom of alcohol withdrawal leading to a vicious cycle of relapsing alcoholism as withdrawing patients use alcohol to control symptoms.[40] There is also a significant risk of extreme sedation if patients prescribed medications for insomnia consume alcohol. Therefore, it is imperative to obtain a careful history before starting pharmacotherapy for insomnia.[41]

Principles of Pharmacologic Therapy in Insomnia

When used appropriately, pharmacotherapy is effective in managing insomnia and produces quick symptom relief. However, pharmacotherapy can produce significant side-effects that potentially offset its benefits and it is important to use good judgment when prescribing such medications. These drugs should be used at the lowest effective dose to minimize risk of adverse effects and the maximum recommended dose should not be exceeded. They should be supplemented with CBT-I wherever possible to maximize benefit. In fact, CBT-I should always be the first line of treatment. Efforts should also be made to taper the dose with improvement in symptoms. The duration of pharmacotherapy for insomnia is not well established and should be individualized. For reference, it must be remembered that most clinical trials did not extend beyond 12 months of therapy. Limiting the use of these agents to a shorter duration reduces risk of dependence. However, such a strategy may not be feasible in patients with chronic comorbidities who require prolonged therapy.

Patients on these agents should be educated about the goals of treatment and potential safety issues including the risk of withdrawal and drug interactions with alcohol and other CNS

depressants. Patients must be regularly evaluated while on therapy to assess efficacy, ongoing needs, adverse effects, and new symptoms. Pharmacotherapy is not recommended in individuals below 18 years. On the other hand, although effective in older patients, these drugs must be used with caution and at lower doses to mitigate the risk of adverse events.

With a wide range of pharmacologic agents available, determining which medication is most likely safe and effective in an individual requires careful consideration of several factors including the pattern of symptoms (sleep-onset, sleep maintenance, or both), the effectiveness and tolerability of past treatment, access to non-pharmacologic therapy, medical comorbidities, side-effect profile of the medication being considered, potential interactions with the patient's other medications, cost of therapy and patient preference. Further complicating this process is the fact that some patients might not respond to single-agent therapy and thus require combination therapy. A simplified algorithm for initiating and/or combining pharmacological therapy is outlined (Figure 1).

Conclusion

Insomnia is a widely prevalent disorder with pervasive effects on quality of life. Effective management should begin with non-pharmacologic interventions such as CBT-I. Pharmacotherapy should be initiated in patients with inadequate response to CBT-I and tailored to comorbidities to maximize benefits and minimize side-effects. Combination therapy with two or more classes of medication may be needed in some individuals but should only be attempted under close medical supervision. Referral to a sleep medicine specialist should be considered in patients with suboptimal response to standard pharmacotherapy approaches outlined in this article.

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