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Review Article

Insomnia and its management: A systematic review

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ABSTRACT

Insomnia Disorder is one of the most prevalent sleep disorders, and it involves both sleep complications and daytime complaints. Adequate quality sleep is crucial for good health and high quality of life. Despite this, the high prevalence and burden of insomnia disorder, which may be acute (short-term) or chronic, is growing globally. This systemic review focuses on insomnia and its management. The main causes and risk factors for insomnia are discussed, as well as the diagnostic criteria for a correct diagnosis. The treatment of insomnia, which is typically a mixture of cognitive-behavioral therapy and pharmacological treatment, is addressed, as well as the vital role pharmacists may play in not just treating insomnia but also determining the root cause/s of sleep disruptions.

1. Introduction

Sleep disorders are also one of the most common conditions for adults in primary care. They are associated with a decrease in physical wellbeing and a poor view of individual health, as well as negative personal and social effects. Insomnia is described as a symptom of a sleep disorder characterized by dissatisfaction with sleep quantity or quality and one or more of the following subjective complaints: trouble falling asleep, difficulty maintaining sleep, or early morning awakening with inability to return to sleep. Sleep deficiency is associated with heightened anxiety, physical pain and irritation, and cognitive deficits. It has been linked to increased morbidity, cardiovascular disease, rheumatic disease, respiratory disease, cerebrovascular disorders, and diabetes in the long term.[1]

It should be diagnosed using diagnostic criteria from the Diagnostic and Statistical Manual (DSM) of the American Psychiatric Association and the International Classification of Sleep Disorders (ICSD). Both have recently been revised. The fifth edition of the Diagnostic and Statistical Manual of Psychiatric Disorders (DSM-5) is targeted at primary care and general mental health services. Sleep disturbances must induce clinically relevant disturbance or impairment(s) of functioning (social, educational, occupational, behavioral, learning, or other) despite sufficient potential for sleep on at least three nights a week for at least three months to meet the criteria for insomnia disorder.[2]

Symptoms must not be primarily attributed to other sleep disturbances or present solely during the process of any sleep-wake disturbance (circadian rhythm disorder, breathing-related sleep disorder, narcolepsy); they must not be due to the hormonal impact of a substance, and they must not be clarified by coexisting psychiatric disorders or psychiatric problems to be diagnosed. Fatigue, mood instability, impaired cognitive control, and anxiety or interference with personal functioning are all signs of insomnia disorder. In their current and previous versions, all standards identify sleep-related complaints despite sufficient sleep opportunity paired with pain or dysfunction caused by the sleep difficulty. Until recently,

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medical guidelines categorized insomnia as either primary or comorbid, based on whether or not any disorders were present. However, both the DSM-5 and the ICSD-III now use the word "insomnia disease," obliterating the difference between main and secondary insomnia. In clinical practice, the distinction has dubious usefulness, and revisions illustrate this perception by prescribing an insomnia disorder diagnosis for patients who follow medical requirements, regardless of coexisting symptoms, unless the other condition causes the sleep issues.[3]

Depending on how insomnia is identified, prevalence rates vary from approximately 33% in an international survey of primary care patients to 17% of adults in the United States experiencing "regularly getting insomnia or difficulty sleeping in the past 12 months" to 6–10% of adults meeting specified diagnostic requirements. Insomnia is a sleep condition in which people have trouble falling asleep and maintaining sleep. Previous insomnia diagnosis guidelines did not prescribe a minimum period for sleep problems; chronic insomnia was used to characterize cases that extended weeks to months, and insomnia was listed as chronic in 40 to 70% of cases. In longitudinal trials, the length of chronic conditions such as insomnia disorder varies from 1 to 20 years.[4]

Insomnia is 1.4 times more common in females than it is in males. Insomnia is most prevalent in older adults; aging is often followed by changes in sleep habits (disrupted sleep, irregular awakening, early waking), which may lead to insomnia. Sleep deficiency is a frequent problem among the elderly. While certain cases of insomnia coexist with other conditions (particularly psychological diagnoses and pain disorders), existing diagnosis guidelines indicate that insomnia disorder encompasses sleep disturbances that are not clarified by another behavioral or medical issue.[5]

2. Insomnia

2.1. Classification of Insomnia

Insomnia may be divided into three classes based on the duration of symptoms.

1. **Transient insomnia** lasts one week or less and may be termed transient insomnia
2. **Short-term insomnia** lasts more than one week but resolves in less than three weeks
3. **Long-term or chronic insomnia** lasts more than three weeks.[6]

Insomnia can also be classified based on the reasons which are as follow sleep hygiene

1. Sleep disorders
2. Stress factors

2.1.1. Signs and symptoms of insomnia

Impairment of daytime functioning is the defining and the most common symptom of insomnia[7].

2.1.2. Other common symptoms include

1. Daytime fatigue
2. Daytime sleepiness
3. Mood changes
4. Poor attention and concentration
5. Lack of energy
6. Anxiety
7. Poor social function
8. Headache
9. Increased errors and mistake

2.2. Causes of Insomnia

Insomnia may be the only symptom, or it may be accompanied by other symptoms.

Chronic insomnia is commonly caused by fatigue, life activities, or sleep-disrupting habits. Insomnia can be resolved by treating the root cause, but it can often last for years.[8]

Common causes of chronic insomnia include:

2.2.1. Stress

Jobs, education, fitness, savings, or family concerns will keep your mind busy at night, making sleeping difficult. Insomnia may also be caused by stressful life experiences or depression, such as the death or injury of a loved one, divorce, or the loss of a career.

2.2.2. Travel or work schedule

Circadian rhythms serve as an internal clock, regulating sleep-wake cycles, metabolism, and body temperature. Insomnia can be caused by disrupting the body's circadian patterns. Jet lag from going through different time zones, working a late or early shift, or shifting shifts regularly are the causes.[9]

2.2.3. Poor sleep habits

An erratic bedtime routine, naps, relaxing activities before bed, an inconvenient sleep atmosphere, and using the bed for work, feeding, or watching TV are all examples of poor sleep patterns. Before going to bed, avoid using computers, televisions, video games, laptops, or other screens.

2.2.4. Eating too much late in the evening

It's good to have a small snack before bedtime, but eating too much will make you physically exhausted when you're lying down. Heartburn, or backflow of acid and food from the stomach into the esophagus after feeding, is common and will keep you awake.

Chronic insomnia may also be linked to medical issues or the use of such medications. Although treating the medical condition may assist in sleep recovery, insomnia may continue long after the medical condition has been resolved.[10]

2.2.5. Mental health disorders

Anxiety conditions, such as post-traumatic stress disorder, may make sleeping difficult. It's possible that waking up so early is a symptom of depression. Insomnia is often linked with other mental health problems.

2.2.6. Medications

Many prescription drugs, such as antidepressants and asthma or blood pressure medications, will interrupt sleep. Caffeine and other stimulants are present in many over-the-counter drugs, including pain relievers, cough and cold medications, and weight-loss products.[11]

2.2.7. Medical conditions

Chronic pain, diabetes, cancer, asthma, heart disorder, overactive thyroid, gastroesophageal reflux disease (GERD), Parkinson's disease, and Alzheimer's disease are all related to insomnia.

2.2.8. Sleep-related disorders

Sleep apnea is a condition in which you avoid breathing repeatedly during the night, disrupting your sleep. Restless legs syndrome induces painful leg sensations and an almost overwhelming urge to move them, making it impossible to fall asleep.

2.2.9. Caffeine, nicotine, and alcohol

Stimulants include coffee, tea, cola, and other caffeinated beverages. They will help you stay awake at night if you drink them late in the afternoon or evening. Nicotine, which is used in cigarette products, is another stimulant that can disrupt sleep. Although alcohol can help you fall asleep, it prevents you from sleeping deeper and often wakes you up in the middle of the night.[12]

2.3. Insomnia and aging

2.3.1. Changes in sleep patterns

When people become older, sleep becomes less restful, so noise or other environmental changes are more likely to wake them up. Since the internal clock progresses with age, elderly patients become exhausted early in the evening and awake earlier in the morning. However, older people need the same amount of sleep as younger people.

2.3.2. Changes in activity

Someone may become less physically or socially engaged. A lack of movement will make it tough to get a decent night's sleep. Additionally, the less involved you are, the more likely you are to take a daily nap, which will interrupt your sleep at night.

2.3.3. Changes in health

Sleep disorders may be caused by chronic discomfort from illnesses such as back problems or arthritis, as well as anxiety or depression. Sleep may be disrupted by issues that increase the need to urinate through the night, such as bladder or prostate problems. As people become older, sleep apnea and restless legs syndrome become more common.

2.3.4. More medications

Elderly adults prefer to take more prescription drugs than younger people, which raises the risk of medication-related insomnia.

2.4. Risk factor of insomnia

About everyone gets a sleepless night now and then. However, the chances of getting insomnia are higher if you[13]:

2.4.1. In the case of a woman

Hormonal changes during the menstrual cycle and menopause may play a role in the case of a woman. Night sweats and hot flashes are normal during menopause, and they can make it difficult to sleep. Insomnia is normal during pregnancy and breastfeeding as well.

2.4.2. Over the age of 60

Insomnia becomes more common as people become older due to improvements in sleep habits and wellbeing.

2.4.3. In case of a mental health disorder or physical health condition

Many problems that affect mental or physical health will interrupt sleep, particularly if you have a mental health problem or a physical health condition.

2.4.4. Anyone who is under a lot of pressure

Temporary insomnia may be triggered by traumatic periods and occurrences. Chronic insomnia may also be caused by major or long-term stress.

2.4.5. Irregular schedule

Changes in work shifts or travel, for example, may cause the sleep-wake cycle to be interrupted.

2.5. Complications of insomnia

1. Reduced response rate while driving and a greater risk of injuries
2. Mental health problems such as depression, anxiety, or drug misuse

3. Long-term illnesses or disorders, such as elevated blood pressure and heart disease, pose an elevated risk and severity
4. Preventative steps
5. Good sleeping habits will help you avoid insomnia and have a good night's sleep
6. Ensure a regular bedtime and wake time throughout the week, even weekends
7. Stay healthy — daily exercise promotes a restful night's sleep
8. Test the drugs to see if they may be affecting your insomnia
9. Limit or avoid naps
10. Don't use cigarettes and avoid or restrict caffeine and alcohol
11. Limit the intake to big meals and drinks before going to bed
12. Get your bedroom sleep-friendly and just use it for sex or sleep
13. Develop a calming bedtime routine, such as taking a warm bath, reading a book, or listening to soothing music [14]

Circadian rhythmicity and sleep control are related to several sleep-regulating drugs. Despite the oversimplification, we contend that endogenous molecules can be divided into two groups: wake-promoting/sleep-suppressing substances such as histamine, catecholamines, and orexin, and sleep-promoting/wake-suppressing substances such as serotonin, adenosine, melatonin, and prostaglandin D2, GABA.

Only a few biochemical experiments on insomnia have been performed, and they have focused on a small number of molecules, such as GABA and cortisol. The following is a list of research that has linked different molecules to insomnia. [15]

The findings are mixed across research, and no definite trend for a single type of molecule that shows whether it encourages sleep or wakefulness has emerged.

Despite contrary data, the hyperarousal hypothesis has largely been used to explain the findings. Increased and decreased GABA in the occipital cortex of insomnia patients, for example, have been reported to support the hyperarousal model of insomnia.

However, sleep regulatory molecules interrelate in complex ways, and many of their effects are dependent on the brain state's milieu; that is, they are state-dependent. Because of these reasons, it's extremely unlikely that all cases of insomnia are caused by variations in a particular form of the molecule such as hyperarousal-related. [16]

Chronic insomnia, according to a more advanced theory, is caused by the disintegration of the brain's alternating patterns of wake-promoting and sleep-regulatory molecules. Consistent routines, in-home PSG, and sleep deprivation studies, especially those that look at the wake- and sleep-promoting molecules or their mRNA and associated microRNA during various states over the 24-hour day, can be useful in understanding the molecular underpinnings of chronic insomnia. Furthermore, studies that relate this level of study to its genetic underpinnings are needed. [17]

3. Molecular mechanisms of Insomnia

Relevant brain structures with widespread projections in the brain produce many of the molecules involved in sleep-wake regulation. However, there is mounting evidence that certain sleep-regulating molecules have a local impact on neurons in the regions where they are made.

The aggregation of sleep-regulatory substances such as tumor necrosis factor- α and IL-1 β, which essentially derive from previous neuronal use, is thought to be responsible for local sleep tendency and slow-wave amplitude. [18]

Slow-wave activity is thought to spread from cortical columns to adjacent regions through humoral and electric interactions, gradually leading to a "global" sleep state in the entire organism.

In this viewpoint, insomnia might not be a "whole-brain" concern. During global sleep, an animal model of insomnia showed synchronized localized Fos activation in both sleep-promoting and wake-promoting areas [19].

In humans, spectral EEG methods have shown elevated regional electrical brain activity during non-rapid eye movement (NREM) sleep in patients with insomnia. Many patients with insomnia do not have objective sleep disturbance because discrete neuronal groups remain active during PSG-defined sleep, according to one hypothesis. Many patients with insomnia can interpret this brain dynamic as wakefulness, which is misclassified as "natural" sleep based on standard PSG guidelines [20].

To determine if insomnia is synonymous with a diffuse pattern of wakefulness at the neuronal level or is best identified by a region-specific persistence of wake-like brain activity during globally specified EEG sleep more compatible with the next level of study, advances in neuroimaging technology will be needed. Various electrophysiologic (EEG) and physiologic tests have been used to investigate hyperarousal during sleep and wakefulness. Increased high-frequency EEG activity (β and γ), reduced activity, and increased REM EEG arousals are all EEG markers of hyperarousal. [21]

4. Electrophysiologic and Physiologic Dysregulation in Insomnia

Various electrophysiologic (EEG) and physiologic tests have been used to investigate hyperarousal during sleep and wakefulness. Increased high-frequency EEG activity (β and γ), reduced δ activity, and increased REM EEG arousals are all EEG markers of hyperarousal. Increased body temperature, metabolic rate, skin resistance, and heart

rate, among other physiologic measures, will be discussed later.[22]

4.1. NREM Sleep Instability

According to the Neurocognitive Model of Insomnia, acute insomnia may be perpetuated by maladaptive behavioral coping mechanisms, and chronic insomnia may grow as a consequence of conditioned arousal. The repetitive correlation of sleep-related cues with wakefulness and/or arousal, which results in an arousal response when a sleep-related stimulus is introduced, is known as conditioned arousal. Cortical arousal, as measured by high-frequency EEG activity (β and γ, 16-50 Hz), is the cause causing chronic insomnia in the neurocognitive model. This EEG behavior is thought to arise at the time of sleep onset as a result of classic conditioning, which is a conditioned reaction to sleep-related cues.[23]

Data to back up this theory indicate that patients with insomnia have lower δ and higher high-frequency NREM EEG capacity, as well as a connection between high-frequency EEG activity and subjective sleep problems. The subjective-objective disparity that frequently characterizes insomnia can be exacerbated by high-frequency EEG, which improves sensory and knowledge processing. When it comes to insomnia-control variations in high-frequency EEG behavior during wakefulness, the evidence is mixed. High-frequency waking EEG activity, on the other hand, is related to high-frequency NREM EEG activity and self-reported hyperarousal symptoms. These results back up the idea that insomnia is correlated with high-frequency EEG control, which is a symptom of CNS hyperarousal.[24]

4.2. REM Sleep Instability

According to the REM sleep instability model, the subjective perception of insomnia is linked to lower REM sleep percent and higher REM EEG arousals. Arousals and awakenings during REM sleep were found to be more effective than NREM parameters in separating patients with insomnia from healthy sleepers in one study. In insomnia, fragmented REM sleep can lead to subjective-objective sleep disparities by promoting the impression of increased wakefulness and nonrestorative sleep.[25]

4.3. Physiologic Hyperarousal

Findings investigating different indicators of physiologic arousal in individuals with insomnia add to the evidence that hyperarousal plays a role in the pathophysiology of insomnia. Monroe found that weak sleepers had higher body temperatures, body movements, vasoconstrictions, and skin resistance than healthy sleepers as early as 1967. Also, elevated 24-hour metabolic rate (as determined by oxygen consumption), 24-hour adrenocorticotropic hormone and cortisol levels, and heart rate have been related to insomnia in several reports. Individuals with insomnia showed greater suppression of facial muscle activation and enhanced cardiac vagal tone in reaction to sleep-related emotional stimulus than good sleepers, according to several researchers. Others also looked directly at the sleep-onset cycle, showing that subjects with insomnia have a higher frontalis electromyogram, a higher heart rate, and a lower finger temperature than control subjects up to the point of sleep onset. Also, patients with insomnia showed sympathetic activity at sleep initiation, as demonstrated by consistently lower cardiac pre-ejection period (PEP) values as compared to healthy sleepers. The time period between the initiation of ventricular depolarization (marked by the onset of the QRS complex in the ECG) to the opening of the aortic valve is known as cardiac PEP. The duration of PEP is inversely proportional to the degree of β-adrenergic tone. As a result, lower PEP values suggest improved sympathetic nervous system activation.[26,27]

5. Self-report & Insomnia

In contrast to certain other sleep conditions, insomnia is diagnosed solely based on self-report; physiologic markers of sleep dysregulation (PSG) or hyperarousal are not commonly used to assess insomnia. Several organizations have created self-report measures to diagnose insomnia and evaluate insomnia-related experiences and impairments. Patients' subjective experiences with insomnia were collected in focus tests, which revealed the disorder's pervasiveness, the belief that others do not completely grasp the effects of insomnia, and the significance of daytime symptoms of insomnia. Presleep cognitive activity in insomnia patients focuses on rehearsal/planning, sleep and its consequences, and autonomic experiences, among other things, according to self-report measures developed to assess presleep thought content and sleep-related quality of life impairment in insomnia. Self-report symptom tests have also been seen to accurately distinguish between insomniacs and healthy sleepers in this research.[28]

While PSG frequently indicates abnormalities in sleep architecture and continuity in insomniacs, the extent of patient-control discrepancies is often minimal, and the severity of empirical results is often less than that of self-report. Nonetheless, variations in subjective and objective measurements among insomnia patients may have important clinical consequences. For instance, a meaningful difference between subjective and objective measurement of sleep is prevalent among patients with insomnia with objective normal sleep duration but not among patients with insomnia with objective short sleep. Furthermore, compared with patients with insomnia that have a regular average sleep period, patients with insomnia that have a limited clinically assessed sleep duration are more likely to experience unfavorable health effects such as diabetes, hypertension physiologic hyperarousal, cognitive problems, and even

mortality. The magnitude of the disparity between self-reported and clinically assessed sleep, as well as its night-to-night variability, could constitute a high-risk presentation that may help researchers better understand the etiology and pathophysiology of insomnia. As a result, objective sleep tests can be helpful adjunctive measures in predicting the biological severity and medical effects of insomnia, and cost-effective objective sleep measures may be used in the routine diagnostic protocol for insomnia to identify phenotypes.[29,30]

6. Diagnosis

Patients must have at least one of the following symptoms on at least three nights a week to be diagnosed with insomnia: difficulties inducing and/or managing sleep; inadequate quality sleep; difficulty sleeping despite ample opportunity and conditions for sleep; or getting up too early. Patients may often have at least one of the following daytime impairments linked to sleep difficulty: focus, concentrating, or memory impairment; fears or worries about sleep; daytime sleepiness; mistakes or injuries at work or when driving; exhaustion or malaise; stomach symptoms; loss of motivation; mood disorder or irritability; social or vocational instability.[31]

7. Treatment of Insomnia

The main aims of the treatment used to treat chronic insomnia are to increase sleep quality and quantity, as well as to improve daytime impairments.

At least one behavioral modification, such as stimulus management therapy or relaxation therapy, is normally used in the initial recovery plan.[32] Biofeedback therapy is also used. When pharmacotherapy is required, the following requirements should be used to guide the selection of a particular medication within a class:

1. Symptom pattern;
2. Treatment goals;
3. Past treatment responses;
4. Patient preference;
5. Cost;
6. The availability of other treatments;
7. Comorbid conditions;
8. Contraindications;
9. Concurrent medication interactions; and
10. Potential adverse effects[33]

The recommended sequence of medication trials is

Short- or intermediate-acting benzodiazepine receptor agonists (BzRAs) or the melatonin agonist ramelteon

1. If the first agent was unsuccessful, try other short- or intermediate-acting BzRAs or ramelteon
2. Antidepressants that induce sedation (e.g., trazodone, doxepin, amitriptyline, or mirtazapine)
3. Ramelteon in combination with a sedative antidepressant
4. Other sedatives, such as antiepileptic or atypical antipsychotic drugs.[21]

Prescription medicines licensed by the Food and Drug Administration (FDA), off-label remedies, over-the-counter products, and natural remedies for patients with insomnia would be discussed in the parts below.

7.1. Benzodiazepines receptor agonists (BzRAs)

Both benzodiazepine (BZD) and non-BZD agents are used in BzRAs. About the fact that both of these drugs bind to the gamma aminobutyric acid ($GABA_A$) receptor complex, their affinity for binding sites varies. Non-BZDs bind more selectively to the alpha 1 subunit, while BZDs have equal selectivity for alpha subunits 1, 2, 3, and 5. The sedative-hypnotic, muscle-relaxant, anxiolytic, and anticonvulsant actions of BzRAs are due to the different subunits of the $GABA_A$ receptors. Furthermore, non-BZDs are thought to have less toxic effects on the central nervous system (CNS) and a lower risk for abuse than BZDs due to their selectivity for the alpha 1 subunit.[34]

7.2. Benzodiazepines

Triazolam (Halcion, Pfizer), temazepam (Restoril, Mallinckrodt), estazolam (ProSom, Abbott), quazepam (Doral, Questcor), and flurazepam are the five forms of BZDs currently approved by the FDA for the treatment of insomnia.

Because of their capacity for misuse or dependency, all of these drugs are known as Schedule IV controlled substances. The key distinction between them is their duration of action they are involved. Triazolam is short-acting; estazolam and temazepam are intermediate-acting, and quazepam and flurazepam are long-acting. The most widely used BZD for insomnia is temazepam. The onset and time duration of a BZD should be considered when picking one. Patients' resistance to the sedative effects of BZDs has grown quickly; thus, long-term use of these medications is not advised. In addition to the potential for resistance and dependency, BZDs have been linked to psychomotor retardation, paradoxical suppression (e.g., heightened excitement, irritability, and impulsivity), memory failure, depression, and teratogenic symptoms in pregnant women, Because of the risk of cognitive dysfunction, delirium, falls, and injuries, BZDs should be discouraged in elderly patients.[35]

7.3. Nonbenzodiazepines

Non-BZDs, also known as "Z drugs," was developed to reduce the harmful consequences and abuse potential of BZDs. As compared to placebo, the commercially available

Z drugs— zaleplon, zolpidem, and eszopiclone—provided minor but statistically significant decreases in subjective and polysomnographic sleep latency, according to a meta-analysis of 13 trials involving over 4,000 participants. Sleep latency was lowered to a greater extent in trials with higher doses, longer treatment periods, and a higher percentage of younger and/or female patients.

Zolpidem: The first Z drug to be developed was zolpidem. It is widely available as immediate- and modified-release tablets (Ambien and Ambien CR [both Sanofi]), as well as sublingual tablets (Edluar) and Intermezzo Transcept Pharmaceuticals; oral spray (ZolpiMist). When pharmacokinetics of zolpidem sublingual tablets and oral spray were compared to those of immediate-release zolpidem tablets, the sublingual formulations preserved bioequivalence while providing a faster onset of operation. Since certain zolpidem formulations are only available as brand-name products, treatment costs should be considered[36].

Treatment-emergent adverse events including drowsiness, dizziness, fatigue, nightmares, and irritation have contributed to the drug's discontinuation in trials. Controlled-release and immediate-release formulations also have identical adverse-event profiles. In clinical trials, zolpidem had little effect on retrograde memory, which was a typical side effect of older BZD insomnia therapies. However, anterograde amnesia was seen in some patients. Controlled-release zolpidem may have a greater impact on anterograde amnesia due to its pharmacokinetic profile.

Drugs that have CNS depressant effects can enhance zolpidem's CNS depressant effects. Furthermore, the coadministration of cytochrome P450 3A4 (CYP3A4) inhibitors can increase zolpidem exposure. The medication should be treated with caution in combination with chlorpromazine, imipramine, ketoconazole, or rifampin.

Since recent research found that blood pressures in certain patients could be elevated enough the morning after use to affect behaviors that require alertness, such as driving, the FDA recommended that clinicians use lower doses of zolpidem in January 2013. The FDA advised manufacturers that the minimum zolpidem dosage for women should be reduced from 10 mg to 5 mg for immediate-release products (Edluar, Ambien, and ZolpiMist) and from 12.5 mg to 6.25 mg for extended-release products (Ambien CR). The FDA has advised manufacturers that the labeling for men should suggest that health care practitioners prescribe administering the lower doses of 5 mg for immediate-release products and 6.25 mg for extended-release products. The suggested doses of Intermezzo, a lower-dose zolpidem product approved for middle-of-the-night awakenings, did not change.[37]

Zaleplon: The second non-BZD to become available was Zaleplon (Sonata, Pfizer). Its quick initiation of action and slightly reduced time of action are helpful to patients who wake up in the middle of the night. Both zaleplon and zolpidem successfully shortened sleep latency and lengthened sleep period when administered at nighttime awakening in a randomized, double-blind, placebo-controlled trial. Zaleplon, on the other hand, has a shorter period of residual sedation than zolpidem.

In clinical trials of zaleplon, the most frequent side effects were headache and dizziness. The zaleplon and placebo classes had equal rates of patients' withdrawing from these trials due to adverse effects. Zaleplon is mainly metabolized by aldehyde oxidase, unlike the other non-BZDs, which are widely metabolized by CYP3A4. While the use of potent CYP3A4 inhibitors and inducers together will cause zaleplon levels to alter, routine dose adjustments are not usually required.

When zaleplon is taken with a high-fat or heavy meal, absorption is delayed by about two hours and decreased by about 35 percent. Zaleplon is a pregnancy type C drug that should be used with caution in pregnant women. For non-elderly patients, a normal dose range is 10 mg to 20 mg. For such groups, such as the elderly, debilitated, or hepatically affected, a 5-mg dosage is prescribed. Patients with the extreme hepatic disease do not take Zaleplon.[38]

Eszopiclone: Eszopiclone (Sunovion, Lunesta) is a non-BZD hypnotic used for long-term insomnia therapy. Eszopiclone was shown to be beneficial for the treatment of insomnia in a six-month, double-blind, placebo-controlled, parallel-group trial of approximately 800 patients, as measured by sleep delay, overall sleep time, and wake time after sleep onset. Eszopiclone can only be used in patients who can get at least seven to eight hours of sleep before the expected period of waking due to its longer half-life.

A bad taste, fever, somnolence, and dizziness are among the most frequent side effects of eszopiclone. There was no indication of resistance to eszopiclone during treatment or rebound insomnia after the treatment was stopped in a six-week sample of patients with primary insomnia.[39]

CYP3A4 is the enzyme that metabolizes eszopiclone. The use of potent inhibitors or inducers of CYP3A4 enzymes at the same time can influence drug exposure. In patients taking eszopiclone with a strong CYP3A4 inhibitor like ketoconazole, dose reductions are advised. Eszopiclone's effectiveness can be reduced when combined with CYP3A4 inducers like rifampin.

Eszopiclone is quickly absorbed, taking about an hour to reach full concentration. Eszopiclone absorption is slowed when taken with or directly after a heavy meal, resulting in a decrease in the drug's effect on sleep onset. Eszopiclone is classified as a pregnancy type C drug by the FDA and should be avoided by pregnant women. If clinically recommended, nonelderly adults may take a daily dose of 3 mg. In patients taking potent CYP3A4 inhibitors or in specific groups, such as the elderly, debilitated, or hepatically affected, the dosage does not exceed 2 mg.

The FDA released an alert in May 2014 about eszopiclone-related deficiency in driving and other behaviors the following day. As a result, the minimum starting dose at bedtime has been lowered to 1mg.[40]

7.4. Melatonin agonists

Ramelteon (Takeda, Rozerem) is the only melatonin (MT) agonist with this prescription for the treatment of insomnia marked by trouble falling asleep. Ramelteon has little affinity for GABA receptors as a targeted MT_1 and MT_2 receptor agonist, which eliminates the possibility of misuse. In studies, ramelteon has been shown to reduce both polysomnographic and subjective sleep latency in patients with chronic insomnia.

Dizziness, fatigue, and nausea are among the most frequent ramelteon side effects. Ramelteon, unlike zolpidem and eszopiclone, has little effect on patients' equilibrium, limiting the chance of falls. Furthermore, the medication has no neurological or psychomotor side effects.

Despite its rapid absorption, ramelteon has low bioavailability due to widespread first-pass metabolism. When ramelteon is taken with food, its absorption is slowed and decreased. Ramelteon should not be used to treat people who have trouble sleeping because of its short half-life (1.36 hours).

Several CYP enzymes are involved in the metabolism of Ramelteon. The use of ramelteon in combination with fluvoxamine, a potent CYP1A2 inhibitor, should be avoided. Ramelteon can also be used with caution in patients who are taking CYP2C9 inhibitors like fluconazole or CYP3A4 inhibitors like ketoconazole. Ramelteon's effectiveness can be decreased when paired with heavy CYP3A4 inducers like rifampin.

Ramelteon is listed as a pregnancy type C drug, which means it should be used with caution for pregnant women. Although the drug is cleared more slowly from older adults compared with younger ones, with a 70% greater area under the curve (AUC), no dose adjustments are required in the elderly. In those with a mild-to-moderate hepatic disability, Ramelteon can be used with caution, and it is contraindicated in those with extreme hepatic impairment.[41]

7.5. Tricyclic antidepressants

Doxepin (Pernix, Silenor Therapeutics) is a sedating tricyclic antidepressant with a high affinity for histamine (H1) receptors. It has been approved for the treatment of insomnia that is marked by difficulties regulating sleep. Doxepin is most often associated with headache and somnolence as side effects. When compared to the higher doses used for depression, the lower doses accepted for sleep have little to no side effects.

Low-dose doxepin offered minor gains in sleep maintenance and duration but had little effect on sleep initiation, according to a study of nine randomized, placebo-controlled trials. There were no major sedative effects recorded the next day. Treatment with doxepin resulted in increased sleep duration and fewer awakenings after sleep initiation without inducing anticholinergic side reactions or memory damage in a four-week, randomized, double-blind, placebo-controlled trial involving 254 elderly participants. When doxepin is taken after a high-fat meal, the absorption of the drug is increased by about 40%, and the time to peak plasma concentration is prolonged by about three hours. As a result, doxepin cannot be taken within three hours of consuming food.

Doxepin is classified as a pregnancy type C drug, which means it should be used with caution for pregnant women. CYP2C19 and CYP2D6 are the enzymes that break it down. As a result, taking doxepin with inhibitors of these enzymes at the same time can increase drug exposure. Adults under the age of 65 can take 6 mg 30 minutes before bedtime. In older patients, the starting dosage is 3 mg, which can be raised to 6 mg if clinically necessary. In patients with hepatic deficiency, the dosage does not exceed 3mg.[42]

7.6. Barbiturates

Barbiturates can induce CNS depression ranging from mild sedation to general anesthesia. Furthermore, these drugs' hypnotic doses will reduce sleep latency and the number of awakenings. Barbiturates are a class of medicines that have been approved by the FDA for the treatment of insomnia. However, because of their severe side effects, such as the risk of fatal toxicity, their poor therapeutic index, and the potential for resistance and dependency, they are not recommended for use in that environment.

7.7. Orexin receptor antagonist: Suvorexant

Suvorexant (Merck, Belsomra) is the first drug in a new family of insomnia medicines called orexin receptor antagonists. Orexins are neurotransmitters that regulate sleep and wakefulness. Suvorexant was approved in August 2014 for the treatment of insomnia marked by sleep onset and/or management difficulties. It is a controlled drug classified as Schedule IV.

Suvorexant is classified as a maternity type C medicine. Patients of hepatic or renal dysfunction do not require dose changes. Individuals over 65 years of age demonstrated no clinically meaningful discrepancies in safety and effectiveness as compared to younger, stable participants. Suvorexant is mostly metabolized by the CYP3A enzyme, but it cannot be taken with potent CYP3A inhibitors. These drugs can significantly decrease suvorexant levels, thus reducing the drug's efficacy. Suvorexant's initial dosage should be decreased to 5 mg as used with mild CYP3A inhibitors, and then increased to 10 mg when tolerated.

Suvorexant may have a lower risk of misuse and adverse effects than BzRAs, according to clinical trial results and the drug's mode of action. Suvorexant's higher price and the availability of less costly generic substitutes, on the other hand, would undoubtedly restrict its use.[39]

7.8. Off-Label Treatments for Insomnia

7.8.1. Antidepressants

Trazodone: Trazodone, which was approved by the FDA more than 30 years ago, is used to treat depression in elevated doses. The drug is also used off-label as a hypnotic at low doses due to its modulating effect on serotonin (5-HT_A) receptors. At levels as low as 10 mg, trazodone activates nearly half of the 5-HT_A receptors in the brain, according to studies. A starting dosage of 25 to 50 mg at bedtime is prescribed for patients with insomnia. As suggested, this can be titrated to a dose of 100 mg per night. Higher doses can cause anticholinergic side effects and orthostatic hypotension, which may raise the risk of falling and injury.

Mirtazapine: Mirtazapine (Merck, Remeron) belongs to the piperazinoazepine class of medications, which has sedative effects that may aid patients with insomnia. The drug's potent antagonistic actions on histamine (H_1) receptors induce sedation. Only for the treatment of the major depressive disorder is mirtazapine currently approved. In insomnia patients, a daily dose of 30 mg is normally prescribed; higher doses can reduce the drug's sleep-inducing effects. Mirtazapine has been linked to anticholinergic effects and may interfere with triglyceride therapy.[40]

Other TCAs: Some sedating TCAs (such as nortriptyline, amitriptyline, and imipramine) have been used off-label to treat insomnia patients, but doxepin is FDA-approved for the treatment of insomnia marked by difficulties with sleep maintenance. However, these medications' broad neurotransmitter effects raise the probability of anticholinergic effects, orthostatic hypotension, and slowed heart conduction, and safer medication methods have reduced their usefulness. TCAs have been labeled as potentially harmful to elderly people.[43]

Atypical Antipsychotics: Atypical antipsychotic drugs like olanzapine, quetiapine, and risperidone are widely used for sleep disorders, even though they are not FDA-approved. The antagonistic effects of these drugs on multiple neurotransmitter systems, especially serotonin (5-HT_2) and histamine (H_1) receptors, trigger sedation. The most widely used antipsychotic for insomnia is quetiapine.

Antipsychotics effects on sleep have been observed in individuals with comorbid disorders including addiction and psychosis, but they have not been tested in people who have primary insomnia. These medications are less attractive than FDA-approved agents for this indication due to serious side effects such as metabolic syndrome and extrapyramidal effects.[44]

7.9. Over the counter medications

7.9.1. Antihistamines

The first-generation antihistamines diphenhydramine and doxylamine are used over the counter as sleep aids due to their sedative properties. Benadryl, Unisom Sleep Gels, and other products contain diphenhydramine, while Unisom Sleep Tabs contain doxylamine. There isn't enough evidence to back up the use of these drugs in clinical trials as insomnia treatments. Diphenhydramine and doxylamine are only minimally effective in inducing sleep, can decrease sleep quality, and may induce residual drowsiness, according to reports. As a consequence, these medicines should not be used by insomniacs. Antihistamines have also been linked to anticholinergic side effects including constipation, dry mouth, and confusion. Antihistamines can be used by the elderly because they are more susceptible to these side effects.[43]

7.9.2. Melatonin

Melatonin is a pineal-gland hormone involved in sleep control, is sold over-the-counter as a dietary aid, and although it's often used to treat insomnia caused by secondary factors including jet lag and shift work. After three weeks of therapy in adults with primary insomnia, a prolonged-release formulation of melatonin was associated with developments in sleep and daytime parameters, including sleep latency, sleep efficiency, and morning alertness, in a randomized, double-blind, placebo-controlled trial. Several patients who received medication for six months sustained their improvements. In general, though, the research shows that melatonin is inadequate in treating most primary sleep conditions with short-term application because melatonin is not approved for the management of chronic insomnia owing to a lack of robust effectiveness and safety results.[45]

7.10. Herbal treatment

7.10.1. Valerian

Since ancient Greek and Roman times, valerian is herbal medicine made from the root of Valeriana officinalis, has been used to cure insomnia. It tends to interfere with GABA-ergic neurotransmission, resulting in sedation. While several studies have found valerian to be effective in the treatment of insomnia, others have found it to be ineffective. Interpretation of the available clinical data is complicated by small sample sizes, by the use of different amounts and sources of valerian, by the different outcomes measured, and by high withdrawal rates. Overall, the evidence for valerian as an insomnia medication is inconclusive, and its use in these patients is not recommended.

7.10.2. Kava

Kava, a sedative, anticonvulsive, antispasmodic, and core muscular-relaxant herbal substance originating from a shrub (Piper methysticum) cultivated in the Pacific islands, tends to function on both GABA and BZD binding sites. Anxiety, stress, and restlessness, which are all main causes of chronic insomnia, are treated with over-the-counter kava-containing drugs. Kava is not approved for the treatment of chronic insomnia, as is the case for other herbal substances, due to a lack of therapeutic effectiveness and safety results. The FDA issued a warning in 2002 that kava-containing products could cause serious liver damage.[46]

7.11. Treatment without medications

1. Position your desk next to a window: Our bodies use sunshine to set our circadian clock, so sunlight is the most important element you'll need to improve your sleep. So, during the day, strive to sit by a window to get some sunshine exposure.
2. Caffeine will help you sleep: This can seem counterintuitive. Coffee, on the other hand, will help set sleep schedules in the morning. However, avoid drinking coffee after 2 p.m. to allow your body to eliminate all caffeine from your bloodstream before bedtime.
3. Don't use electronics late at night: Blue light from an iPad or laptop disrupts normal sleep patterns. As previously mentioned, the secret to resetting the sleep cycle is light exposure.
4. Sleep nude: Sleeping naked not only lets you feel free and safe, but it also helps you sleep by lowering your body temperature, which is a significant sleep signal. Keep the temperature in the bed between 16 and 20 degrees Celsius, and wear loose clothing or sleep nude.
5. Avoid using a pillow: Lying on your back is the safest posture. A thick pillow will cause the spine to bend uncomfortably if you sleep with it. If you really must, use thin pillows. If you sleep on your back, avoid using a pillow under your head because it can uncomfortably stretch your neck. Instead, insert a pillow under your stomach and hips to relieve discomfort in your neck and back.
6. Exercise but not too late: Exercise is a perfect way to get the sleep schedule back on track. However, doing it late at night can cause you to become too energized. Exercising late raises your body temperature, and it takes your body at least 4-6 hours to calm off. If you have insomnia, work out first thing in the morning rather than later.
7. Use House Plants: Build a sanctuary in your space by keeping it tidy and calming. Adding any house plants is a smart way to do this. House plants, such as English Ivy, tend to purify the air in your home and create a calming environment.[39,47]

8. Conclusion

Insomnia is a significant problem that may have harmful effects on an individual's health. It has a negative impact on the quality of life of those who are afflicted and is linked to a variety of other illnesses. Insomnia is an underdiagnosed and undertreated condition, despite its high prevalence. Chronic insomnia has been linked to an increased risk of developing chronic diseases, so the root causes should be detected and treated. Pharmacological treatment, cognitive behavioral therapy, and treating comorbid disorders are all used to cure insomnia. The key aim of treatment is to increase sleep consistency and length, as well as daytime activity and anxiety reduction. Cognitive-behavioral therapy and pharmacological medication can be used separately or in combination, depending on the seriousness of insomnia, but behavioral therapy is normally recommended as the first line of treatment. There are several types of medications that are available for the treatment of insomnia, including BZD and non-BZD drugs, the melatonin agonist ramelteon, the sedating antidepressant doxepin, and the orexin receptor antagonist suvorexant. Also, several agents approved for other indications, such as the antidepressants trazodone and mirtazapine, are used in this setting. Over-the-counter alternative therapies include antihistamines, melatonin, and the herbal products valerian and kava which also belong to the FDA-approved insomnia treatments. When deciding on care choices, the patient's interests and beliefs should be taken into account. To prevent developing dependency and resistance, hypnotics can be used for the shortest time possible and at the lowest dosage possible. The pharmacist needs to provide guidance and counseling on the various treatments for insomnia, as well as any potential side effects. The pharmacist may also help determine the root causes of insomnia and provide helpful guidance about how to improve sleep patterns.

9. Conflicts of Interest

All contributing authors declare no conflicts of interest.

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None.

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