Continuing Education

Insomnia: Overview and Treatment

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Insomnia: Overview and Treatment

Learning Objectives

1. List the categories of risk factors that may contribute to insomnia and provide examples of each.
2. Describe the physiology of sleep and how these normal processes can be interrupted to cause insomnia.
3. Discuss sleep hygiene and how proper attention to it can contribute to restful sleep.
4. List the pharmacological categories available for sleep medications and provide an example of each category.
5. Discuss the major advantages and disadvantages of the pharmacological categories of for sleep medications.

Introduction

Insomnia is characterized as difficulty falling asleep or maintaining sleep, and is the most common complaint in general medical practice. Individuals with insomnia may also experience poor quality sleep.[1-3] Insomnia disorder is defined as "sleep difficulties associated with daytime impairment or distress about difficulty sleeping".[4] Insomnia occurs in 33% to 55% of the adult population, usually beginning in early or middle adulthood. Insomnia is twice as prevalent in women than in men and much more common in the elderly.[1,5] Over the course of one year, approximately one-third of the population in the United States reported experiencing insomnia.[1,2,5] A diagnosis of chronic insomnia disorder in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 5th ed. includes that symptoms must cause clinically significant functional distress or impairment; be present for at least 3 nights per week for at least 3 months; and not be linked to other sleep, medical or mental disorders.[31] Insomnia can have a drastic effect on daily life, and individuals may experience loss in productivity at work, daytime fatigue, difficulty concentrating, and comorbid anxiety and depression.[1,5] It is common for patients who suffer from insomnia to have comorbid psychiatric or medical conditions, with 40% to 50% having a concurrent psychiatric disorder.[1-3,5] It is crucial that we recognize and treat insomnia to restore daily functioning because 10% to 20% of patients who suffer with insomnia will try to self medicate with alcohol or nonprescription drugs.[1] The National Sleep Foundation recently completed a study and has made recommendations for the amount of sleep needed for different age groups.[6]

Table 1

Recommended Sleep Duration for Age Groups[6]	
Age	**Recommended Sleep**
Newborns (0-3 months)	14 to 17 hours
Infants (4-11 months)	12 to 15 hours
Toddlers (1-2 years)	11 to 14 hours
Preschoolers (3-5 years)	10 to 13 hours
School-ages children (6-13 years)	9 to 11 hours
Teenagers (14-17 years)	8 to 10 hours
Young Adults (18-25 years)	7 to 9 hours
Adults (26-64 years)	7 to 9 hours
Older Adults (≥ 65 years)	7 to 8 hours

Risk Factors

The risk factors that can influence insomnia are expansive and include temperamental, environmental, genetic, physiological, and sleep hygiene factors (Table 2). In addition to these factors, sleep disturbances can precipitate in predisposed individuals who endure major life events and chronic daily stress. Other factors that need attention and can provoke persistent insomnia include poor sleep habits, inconsistent sleep schedules, and fear of lack of sleep.[5]

Table 2. Risk Factors for Insomnia[1,5,6]	
Temperamental	• Anxiety • Worry-prone personality or cognitive style • Inclination to repress emotions
Environmental	• Noise • Light • Uncomfortably high or low temperature • High altitudes • Jet lag or shift work
Genetic and Physiological	• Female gender • Advancing age • Disrupted sleep • Monozygotic twins > dizygotic twins
Sleep Modifiers	• Poor sleep hygiene
Comorbid Disease States	• Diabetes • Coronary heart disease • Chronic obstructive pulmonary disease • Arthritis • Fibromyalgia • Chronic pain conditions • Substance abuse • Mental disorders • Bipolar, depressive, and anxiety disorders
Medications	• Anticonvulsants • Central adrenergic blockers • Diuretics • SSRIs • Corticosteroids • Stimulants
Behaviors	• Excessive caffeine intake • Drinking alcohol before bedtime • Smoking cigarettes before bedtime • Excessive daytime napping • Irregular or continuously disrupted sleep-wake cycles

Pathophysiology

Normal sleep is divided into sleep stages that can be classified as non-rapid eye movement sleep (NREM) or rapid eye movement sleep (REM). The sleep stages and the subdivided stages within them serve a physiologic function while all major organ and regulatory systems continue to function during sleep.[2,6] The characteristics that help categorize the stages include patterns of brain waves, muscle tone, and eye movements.

NREM is divided into four stages that are differentiated based on the amount of time spent within them and the function they serve (Table 3).

Table 3. Non-Rapid Eye Movement Sleep[2]			
Stage	**Name**	**Function**	**Total Sleep Time (% of)**
1	Relaxed wakefulness	Initiate sleep	2-5
2	Rapid-wave (alpha)	Rest for muscles and brain by muscle atonia and low voltage brain wave activity	~50
3	Slow-wave (delta)	Restorative sleep	5
4			10-15

At sleep onset, the brain moves quickly from stage 1 to stage 2 while decreasing activity of both muscles and brain waves. Stages 3 and 4 occur approximately 1 to 3 hours after falling asleep following a brief REM period. Both the duration and quality of each stage is important to patients with or without insomnia, although quality of sleep may be more important than quantity. Arousability is prominent within the first two NREM stages and pose a large threat to insomnia patients, since they contain the majority of total sleep time. Serotonin, adenosine, cholecystokinin, IL-1, somatostatin, and growth hormone augment the last two stages, known as delta sleep. Delta sleep is seen mainly in young children and adults, decreasing in amount as age increases, and nearly nonexistent by age 75.[2]

REM sleep is described as an active period of sleep marked by intense brain activity.[6] While the purpose surrounding REM sleep is unknown, It can be characterized by a decrease in function of the body and brain stem. During this time, the neurochemical processes are still functional and dreaming occurs.[2] The physical aspects of REM sleep include rapid, irregular, and shallow breathing, with rapidly moving eyes and temporarily paralyzed limb muscles. Due to dreaming taking effect during this period, physiological aspects including increased heart rate and blood pressure occur. Although the need of REM sleep is unknown, it is required since a lack of REM sleep can result in an overall restless sleep. The goal is to achieve a restorative sleep that helps promote learning, memory, mood, and ability to concentrate.[6]

The amount of sleep needed varies between different age groups. Research shows that the average adult needs between 7 to 9 hours of sleep every night, while teenagers require approximately 9.5 hours per night. Although the amount of sleep is important, the mixture of REM and NREM sleep is equally important. According to the National Sleep foundation, a complete sleep cycle consists of "NREM and REM cycles that alternate every 90 to 110 minutes and is repeated four to six times a night". When these sleep cycles become impaired, sleep loss becomes impactful on physiological and cognitive functions such as memory, attention, complex thought, motor response and emotional control.[6]

Continuous interruption of the sleep cycle can be harmful on the endocrine system and contribute to the development of obesity, diabetes, and hypertension. During sleep the body secretes important hormones that affect growth, energy regulation, and metabolic and endocrine functions. Some hormones that are released during sleep include cortisol, growth hormone, follicle stimulating hormone, and other hormones that affect appetite and weight. Cortisol is an important hormone in the sleep cycle due to its ability to promote wakefulness and is usually released near the end of a sleep cycle.[6]

The brainstem, hypothalamus, and basal forebrain are the main neural structures that control the sleep-wake cycle. The neurochemicals associated with

these structures are as important as the sleep stages and their function. Wakefulness is attained through noradrenergic, histaminergic, and acetylcholine-containing neurons that are located within these structures. Other substances that contribute to wakefulness include glutamate, substance P, thyrotropin-releasing factor, and corticotropin-releasing factor. Sleepiness is promoted by decreases in dopamine, and increases in neurotransmitters that increase NREM sleep such as GABA and adenosine.[1]

Insomnia seems to stem from a variation in the sleep-wake cycles and can persist to deteriorate patient health and lifestyle.

Diagnosis and Classification

Insomnia is a disorder characterized by the principal complaint of dissatisfaction in the overall amount or quality of sleep obtained. This dissatisfaction is associated with the inability to initiate sleep (sleep-onset insomnia), maintain sleep (sleep-maintenance insomnia), or return to sleep following early awakening (late insomnia). Those with insomnia may experience any one, or combination, of these symptoms throughout the course of the disorder with the primary complaint often varying over time. The impaired sleep in these patients must be accompanied by significant distress or decline in functioning of any important aspect of daily life such as social, academic, or occupational in order to be diagnosed as insomnia. These events must also occur at least 3 nights per week with sufficient opportunity to sleep to be designated as insomnia. Insomnia may be further classified based on frequency and duration of symptoms. Acute or transient insomnia involves symptoms that last for a few days to a few weeks. Symptoms lasting for no less than 1 month and no longer than 3 months are specified as episodic insomnia. Insomnia is considered to be chronic if the symptoms persist longer than 3 months. Finally, those who experience two or more separate episodes of insomnia within the span of 1 year are considered as having recurrent insomnia. Insomnia is an extremely common comorbidity to various other pathologies. It is important to determine that the sleep complaints a patient is having are not attributable, or better explained by, any other potential cause. This includes other sleep or mental disorders, medical conditions, or from substance abuse such as medications, caffeine, or illegal substances. [5]

Goals of Therapy

Due to insomnia's ability to affect quality of life and daily functioning, it is crucial to administer proper treatment. The goal of insomnia therapy is to help patients fall asleep, stay asleep, and improve the quality of sleep so they can awaken feeling refreshed and rested.[1-3] By correcting the sleep complaint, an improvement in daytime functioning, such as improved ability to concentrate and increased productivity, should follow.[1,3]

Pharmacologic Treatment

The decision on how to treat and manage insomnia is based on the underlying cause and if it is transient, episodic, or chronic.[5] In all patients who present with insomnia, patient education is essential. Patients should be educated on sleep hygiene and stress management, and pharmacological therapy should only be utilized when necessary.[1,3] The most recent guidelines (American College of Physicians, 2016) recommend that all patients with chronic insomnia disorder receive cognitive behavioral therapy (CBT) as the initial therapy.[31] If use of pharmacologic therapy is indicated, it is recommended that the medication be used at the lowest dose and for the shortest time period possible.[1] For patients with chronic insomnia, short acting benzodiazepines, nonbenzodiazepine $GABA_A$ agonist, sedating antidepressants, and ramelteon are preferred. Over-the-counter antihistamines, such as diphenhydramine, and herbal supplements, such as valerian root and melatonin, are not recommended. The use of barbiturates, older drugs approved for insomnia, is no longer encouraged or recommended.[3] Sedative-hypnotics may be used carefully in transient, episodic, and chronic insomnia, though the choice of drug and duration will differ.[1] The most recent guidelines (American College of Physicians, 2016) do not offer a recommendation for pharmacologic therapy due to lack of evidence for efficacy or safety. However, if pharmacologic therapy is considered it should be used after CBT and for no more than 4 to 5 weeks.[31]

Table 4. Benzodiazepines[7]				
Benzodiazepine	**Onset of Action**	**Duration**	**Usual Hypnotic Dose**	**Elderly Dose**
Estazolam (ProSom®)	15-60 minutes	Intermediate	1-2 mg	0.5-1 mg
Flurazepam (Dalmane®)	10-30 minutes	Long	15-30 mg	15 mg
Temazepam (Restoril®)	30-60 minutes	Intermediate	15-30 mg	7.5-15 mg
Triazolam (Halcion®)	15-30 minutes	Short	0.125-0.25 mg	0.125-0.25 mg

Benzodiazepines

Benzodiazepines (BZD) are a class of sedative-hypnotics that help decrease sleep inactivity and increase the duration of the first two stages of sleep.[7,8] The medications within this class indicated for insomnia include estazolam (ProSom®) , flurazepam (Dalmane®) , temazepam (Restoril®), and triazolam (Halcion®) . These drugs differ based on duration of action, onset, and associate hypnotic dose.

Mechanistically, BZDs work by binding specifically to $GABA_A$ receptor subunits within the central nervous system and help promote sleep, while affecting cognitive, memory, and psychomotor functions.[6,8] Binding at this subunit increases the opening frequency of GABA-mediated chloride ion channels, resulting in enhanced membrane hyperpolarization, and a decrease in action potential firing. The actions of CNS sedation, anxiety relief, amnesia, hypnosis, coma, and respiratory depression are dose-dependent. Clinically, this class of drugs helps with acute anxiety states, insomnia and other sleep disorders, as well as muscle relaxation. The majority of BZDs are metabolized by CYP3A4, except lorazepam, oxazepam, and temazepam.[7] Hepatic metabolism is the major route of clearance for this class of drugs and poses the increased risk of interactions with drugs that are either inducers or inhibitors of CYP3A4.[7,8] Other risks for drug interactions include the use of CNS depressants and alcohol, which can further exacerbate CNS depression and other adverse effects. BZDs are schedule IV controlled substances (C-IV) and have increased risks of dependence of tolerance, abuse, and rebound insomnia. The adverse effects include impaired next-day performance, anterograde amnesia, and aggressive behavior. Within the elderly population, impaired coordination, increased incidence of falls and hip fractures, and weakness are common adverse effects that should be given consideration. These drugs (Table 4) have a pregnancy category X. While overdose with BZDs alone are uncommon, concurrent use with opioid analgesics, alcohol, or other CNS depressants, greatly increases the probability of overdose.[7]

Non-Benzodiazepine Receptor Agonists

The non-benzodiazepine receptor agonists were developed to provide effects similar to the benzodiazepines but with a more tolerable side effect profile due to receptor specificity; they include zolpidem tartrate (Ambien®), zaleplon (Sonata®), and eszopiclone (Lunesta®).[3,9-11] Unlike the benzodiazepines, however, they are only indicated for short-term relief of insomnia and should not be taken chronically. Tolerance may develop, decreasing overall efficacy and placing patients at risk for serious adverse events.[3,9] Patients using non-benzodiazepine receptor agonists have been reported to engage in complex activities while not fully awake, such as eating, driving, and holding conversations,[10,11]

Zolpidem produces its effects by binding centrally to the omega-1 subclass of benzodiazepine receptors. Zolpidem has little to no peripheral activity which gives it the benefit of having none of the muscle relaxant properties found in the benzodiazepines.[10,11] It has a very

rapid onset that is significantly delayed when taken with or immediately after meals and a relatively short half-life which reduces incidence of next-day sedation. Patients should be counseled to take zolpidem immediately before bed and only when they have at least 7 to 8 hours designated for sleep or at least 4 remaining hours if using the sublingual tablets. Common side effects include headache, fatigue, nausea, diarrhea, and drowsiness. More serious but rare side effects include changes in thoughts or behaviors, memory loss, angioedema, anaphylaxis, anxiety, and depression.[10,11]

Zaleplon also acts by selectively binding to omega-1 benzodiazepine receptors, but retains peripheral activity resulting in benzodiazepine-like muscle relaxation as well as hypnotic sedation.[10,11] Patients should be counseled to not take with or after meals as this will delay onset. Zaleplon has not been shown to increase total sleep time, therefore patients do not need a large amount of dedicated time for sleep nor do most patients experience next-day sedation.[9-11] Common side effects include dizziness, headache, abdominal pain, nausea, memory impairment, and amnesia. Rare but serious side effects include anaphylaxis, angioedema, changes in thoughts or behaviors, suicidal thoughts, new or worsening depression, memory loss or anxiety. Sudden discontinuation of zaleplon may result in rebound insomnia.[10,11]

Although not fully known, it is thought that **eszopiclone** also acts on the same benzodiazepine receptors as zolpidem and zaleplon.[10,11] Although not recommended for chronic use, eszopiclone sets itself apart from the other two agents by providing a longer possible duration of use. It has been shown effective up to 6 months as compared to around 35 days for the other two agents, making it an optimal choice in patients suffering from longer cases of insomnia.[9-11] It should not be given with or after meals as this will delay its onset. Patients should not use eszopiclone if they are unable to dedicate 7 to 8 hours to sleep. Common side effects include drowsiness, dizziness and headache. Rare or more serious side effects include angioedema, anaphylaxis, changes in thoughts or behaviors, fever, chills, body aches, and hallucinations.[10,11]

Table 5. Non-Benzodiazepines[3,9-11]

Non-Benzodiazepine	Available formulations	Indication	Maintenance dose
Zolpidem (Ambien®)	Immediate-release	Sleep-onset	Men- 5 to 10 mg Women- 5 mg
	Controlled-release	Sleep-onset Sleep-maintenance	Men- 6.25 to 12.5 mg Women- 6.25 mg
	Sublingual	Night-time awakening	Men- 3.5 mg Women-1.75 mg
Zaleplon (Sonata®)	Immediate-release	Sleep-onset Night-time awakening	10 to 20 mg
Eszopiclone (Lunesta®)	Immediate-release	Sleep-onset Sleep-maintenance	1 to 3 mg

Sedating Antidepressants

Trazodone (Oleptro®) is a sedating antidepressant that may be used to treat insomnia.[1-3,8,12,13] It is preferred when treating patients with comorbid depression, anxiety, or prone to substance abuse.[3] Trazodone can help individuals initiate sleep, stay asleep and improve the quality of sleep.[1] Trazodone is serotonin receptor modulator, serotonin reuptake inhibitor, and significantly blocks histamine (H1) and adrenergic (alpha1) receptors.[1,12,13] Trazodone should be taken 1 hour prior to bedtime in a dose of 50 to 100 mg, this dose is sufficient to treat insomnia but higher doses are needed to treat depression.[1,8,12,13] Onset of action is 1 to 3 hours for sedative effects.[12] Trazodone undergoes extensive hepatic metabolism predominantly through the cytochrome 3A4 system.[12,13] Common side effects include sedation, headache, dizziness, dry mouth, and nausea. Rare but serious side effects include hypotension, serotonin syndrome, priapism, and suicidal thoughts.[1,12,13,]

Other sedating antidepressants such as amitriptyline, nortriptyline, doxepin, and mirtazapine, may be used to treat insomnia and are effective at helping patients maintain sleep.[1,3] **Mirtazapine** is a tetracyclic antidepressant with sedative effects, however one disadvantage to mirtazapine is its ability to cause weight gain and its association with daytime sedation.[1] **Amitriptyline, nortriptyline, and doxepin** are tricyclic antidepressants and although they have sedative properties that make them useful to maintain sleep, they can also be associated with a large amount of side effects due to anticholinergic activity and adrenergic blockade. This side effect profile also makes them more dangerous in the elderly population.[1,12,13]

Doxepin is available as brand-name Silenor®, which is FDA approved for the treatment of insomnia in patients who have difficulty with maintaining sleep.[1,12] Silenor® is available in 3 mg and 6 mg tablets. This dose is lower than the available generic doxepin used for treatment of depression.[12,13] In clinical trials, low-dose doxepin showed efficacy in maintaining sleep and was generally well tolerated in the elderly population with limited daytime sedation.[14] Elderly patients over the age of 65 years old should be initiated at a dose of 3 mg within 30 minutes of bedtime and can be increased to a dose of 6 mg if needed. All other patients less than 65 years old should be initiated at 6 mg within 30 minutes of bedtime.[13, 15]

Although sedating antidepressants are utilized for the treatment of insomnia, according to a meta-analysis it appears that benzodiazepines and non-benzodiazepine receptor agonists are more effective.[16] There is little evidence about their effectiveness in patients who do not have depression.[7] When selecting a therapy for a patient's insomnia, one must also consider comorbid conditions, history of substance abuse, and characteristics of the sleep disorder.[1,16] All sedating antidepressants have been assigned the pregnancy category C.[12,13]

Table 6. Sedating Antidepressants[1,12,13]

Antidepressant	Usual Hypnotic Dose	Effect on Sleep	Main Side Effects
Trazodone (Oleptro®)	50-100 mg	Initiate sleep Maintain sleep	Falls Orthostatic hypotension Headache
Amitriptyline (Elavil®)	25-150 mg	Maintain sleep	Anticholinergic effects
Nortriptyline (Pamelor®)	50-150 mg	Maintain sleep	Anticholinergic effects
Doxepin (Silenor®)	3-6 mg	Maintain sleep	Anticholinergic effects
Mirtazepine (Remeron®)	15-30 mg	Maintain sleep	Weight gain Next-day sedation

Melatonin Receptor Agonist

Ramelteon (Rozerem®) is a FDA-approved melatonin receptor agonist for sleep-onset insomnia.[7] The role of ramelteon is to decrease sleep latency and increase total sleep time, by increasing stage 2 sleep and decreasing delta sleep.[1] Administration includes an 8 mg oral tablet taken once daily within 30 minutes of bedtime. Ramelteon works through agonist activity at MT_1 and MT_2 melatonin receptors located in the suprachiasmatic nuclei of the hypothalamus, and differs from other insomnia medications due to lack of direct effects on GABA neurotransmission.[8,17] Ramelteon exhibits an 8-fold agonism (compared to melatonin) at the MT_1 receptor and helps induce sleepiness, while agonism at MT_2 influences the regulation of circadian rhythms. After administration, absorption is rapid and metabolism includes extensive first-pass metabolism into the active metabolite that exhibits a 2 to 5-hour longer half-life than the parent drug.[17]

Liver dysfunction is a major concern for patients taking ramelteon, since metabolism is mainly through cytochrome P450 1A2 and 2C9 isoforms, and poses potential drug interactions with certain medications that metabolize through the same cytochrome isoforms. These drugs include ciprofloxacin, fluvoxamine, zileuton, and fluconazole. Rifampin, a CYP inducer, poses great concern for insomnia patients since it reduces plasma levels of ramelteon and its active metabolite. Concurrent use of any of these medications poses the risk of increased adverse drug reactions (ADR).[7] The common ADR's seen with ramelteon include dizziness, somnolence, fatigue, depression, decreased serum cortisol, nausea, and taste perversion. This medication should not be taken with a high-fat meal due to delays in maximum serum concentration and increased area-under-the-curve (AUC), possibly leading to ineffective use of the medication and higher probability of experiencing adverse effects.[17] It carries a pregnancy category of C.[7] Ramelteon is a non-controlled substance and is a good alternative for patients with a history of drug abuse. Other patient populations that can benefit from this medication are patients with chronic obstructive pulmonary disorder and sleep apnea.[1] Ramelteon is one of the safest medications for sleep due to its fewer side effects, decreased abuse potential, minor cognitive and motor impairment, as well as lack of withdrawal symptoms.[18]

Table 7. Melatonin Receptor Agonist[7]

Melatonin Receptor Agonist	Onset of Action	Duration	Usual Hypnotic Dose	Elderly Dose
Ramelteon (Rozerem®)	15-30 minutes	Short	8 mg	8 mg

Table 8. Orexin Receptor Antagonist[7]

Orexin Receptor Antagonist	Onset of Action	Duration	Usual Hypnotic Dose	Elderly Dose
Suvorexant (Belsomra®)	30 minutes	Intermediate	10-20 mg	10-20 mg

Orexin Receptor Antagonist

Suvorexant (Belsomra®) is a novel, new drug approved for the treatment of insomnia. Belsomra® is approved for the treatment of insomnia characterized by difficulty initiating sleep and maintaining sleep.[7,19-21] Suvorexant is an orexin receptor antagonist and is the first in its class. By blocking the binding of orexin to both orexin 1 and 2 receptor, it is thought to suppress an individual's wake drive because orexin is responsible for sustaining wakefulness.[7,19, 21] When compared to placebo in clinical trials, patients taking suvorexant fell asleep 5-10 minutes sooner and stayed asleep 15-25 minutes longer.[7] Suvorexant is given once daily within 30 minutes of bedtime in a dose of 10 - 20 mg. The lowest effective dose should always be utilized.[19, 20] The most commonly reported adverse effect is somnolence due to its long half-life. Serious adverse effects include sleep paralysis and suicide ideation.[19-21] Sleep paralysis is characterized by the inability to move or speak during the transition from sleep to awakening.[21] Suvorexant is metabolized by cytochrome 3A4, therefore many drug interactions with inhibitors and inducers of cytochrome 3A4 may require dosage decreases or increases, respectively.[7,19,20] Suvorexant is a schedule IV controlled substance (C-IV) and was well tolerated in clinical trials, however long term safety and efficacy data are not available.[22]

Sedating Atypical Antipsychotics

Use of sedating antipsychotics such as quetiapine (Seroquel®) and olanzapine (Xyprexa®) for the treatment of insomnia is controversial. According to the American Academy of Sleep Medicine's 2008 insomnia guidelines, it is recommended that these medications be utilized last line only in patients who have comorbid insomnia to a psychiatric condition that would benefit from treatment by these atypical antipsychotics.[3] However, a review of the available literature on the use of quetiapine for the treatment of insomnia found that due to its limited data on safety and efficacy and its adverse-effect profile, the benefit for using quetiapine for insomnia, even in patients with comorbid psychiatric conditions that could benefit from its use, does not outweigh the risks.[23] These agents are not addressed in the newer guidelines.[31]

Quetiapine and olanzapine both work primarily by dopamine antagonism in the central nervous system. Their primary uses are schizophrenia, bipolar disorder, and treatment-resistant major depressive disorder.[24] They also produce blockade at histamine (H1) receptors and serotonin type 2A ($5\text{-}HT_{2A}$) receptors, which is responsible for sedation.[23,24] The most common adverse effects from quetiapine and olanzapine include weight gain, diabetes, and sedation. Due to metabolism by the cytochrome P450 system, both quetiapine and olanzapine have drug interactions with both inhibitors and inducers of different cytochrome enzymes (Table 9).[24] Recommended dosing for these medications is not available due to it off-label use and lack of data, however the lowest dose should be utilized to avoid significant side effects.

Table 9. Sedating Antipsychotics[24]

Antipsychotics	Usual Dosage Range	Metabolism	Side effects
Quetiapine (Seroquel®)	25-100 mg	Cytochrome 3A4	Weight gain Diabetes Sedation
Olanzapine (Xyprexa®)	5-20 mg	Cytochrome 1A2 and 2D6	

Table 10. Over-the-Counter Sleep Products[7,25,26]			
OTC	**Onset of Action**	**Duration**	**Usual Hypnotic Dose**
Diphenhydramine	30 minutes	4-6 hours	50 mg
Doxylamine	30 minutes	4-6 hours	25 mg
Melatonin	1-5 hours	Unknown	1-10 mg

Over-the-Counter (OTC) Sleep Products

Antihistamines are available over-the-counter (OTC) for the treatment of insomnia. Diphenhydramine and doxylamine are the most commonly used and are generally effective at treating mild insomnia. Diphenhydramine is dosed at 50 mg at bedtime when needed and doxylamine should be given at 25 to 50 mg before bedtime.[25, 26] However, one of the disadvantages to the use of these medications is the development of tolerance to the sedative effects. Another problem with the use of antihistamines is the anticholinergic side effects that occur, making them problematic in the elderly population.[1]

Melatonin is a neurohormone produced in the pineal gland that appears to affect circadian rhythm by resetting the sleep-wake cycle. Evidence suggests that melatonin is effective for reducing sleep onset latency, but there is limited data on its ability to improve duration and quality of sleep. The suggested dose for melatonin is 1 to 10 mg in the evening, but the hypnotic dose is not well established.[25, 26] Over-the-counter melatonin is considered a dietary supplement, therefore it is not regulated by government standards for efficacy, purity, and safety as stringently as prescription products and variability among concentrations may exist. If patients are using melatonin for insomnia, recommended products are marked with a USP verified seal, which verifies quality, purity, strength, and ingredient identity for dietary supplements. These supplements meet USP standards after voluntarily undergoing a Good Manufacturing Practices audit, product and ingredient testing, and manufacturing documentation review.[27]

Non-pharmacological Treatment

Non-pharmacological therapy of insomnia typically involves psychotherapy towards helping a patient make beneficial cognitive or behavioral changes emphasized around sleeping. Cognitive Behavioral Therapy for insomnia (CBT-I) describes a process by which sleep is attained through control of those cognitive and behavioral components of sleep. CBT-I received the only strong recommendation from the American College of Physicians based on moderate-quality evidence.[31] It is recommended for all patients with chronic insomnia and in conjunction with other pharmacologic therapies. Cognitive control mainly revolves around eliminating disturbing or distracting thoughts and worries that may be preventing sleep. Behavioral control involves discovering and limiting stimuli or other factors natural to the patient that promote insomnia. These are described in a principle known as Sleep Hygiene.[1,28-30] Sleep Hygiene's main focus is the removal of behaviors or environmental factors that may impede a patient's ability to sleep.[1,28,29] It has been shown to be effective when used in combination with medication or CBT-I but is not recommended for use alone. Table 11 lists the recommendations made in the practice of Sleep Hygiene that may be given to patients by pharmacists.[28,29]

Table 11. Sleep Hygiene Recommendations[1,29]

• Designate a regular sleep and wake time that is followed every day of the week
  ○ These times should allow at least 7-8 hours of sleep
  ○ These times should not allow for oversleeping
• Avoid daytime napping
• The bed should only be used for intimacy and sleep
  ○ Watching television, eating, reading, etc. should not be done in the bed

Table 11. Sleep Hygiene Recommendations[1,29] (Cont)

• Sleep should not be forced. If one finds themselves unable to sleep after around 30 minutes they should
  ○ Leave the bed
  ○ Do something relaxing until they find themselves drowsy
  ○ Return to bed and try to sleep
  ○ Repeat as necessary
• A regular exercise schedule should be made
  ○ Exercise should not occur near bedtime
• Avoid large meals or large quantities of liquids near bedtime
• The bedroom should be kept as quiet, dark, and temperate as possible or to what extent is most comfortable
• Caffeine, alcohol, nicotine, or any other stimulants should be limited

Conclusion

Insomnia is a psychiatric condition characterized by dysfunction in the sleep-wake cycle, which results in the inability to initiate, maintain, and/or experience quality sleep. It may be diagnosed when sleep difficulty occurs at least 3 nights per week for at least 3 months and is not better explained by other sleep-wake disorders, effects of substances, or coexisting mental and medical disorders. The consequences from untreated insomnia include lost productivity, daytime fatigue, difficulty concentrating, anxiety, and depression, all of which impact an individual's ability to perform daily tasks successfully. All patients who suffer from insomnia should be educated and instructed about good sleep hygiene. New recommendations for chronic insomnia patients recommend CBT-I for all patients. Treatments such as benzodiazepines, non-benzodiazepine receptor agonists, sedating antidepressants, melatonin receptor agonist, and orexin receptor agonist may be utilized for short durations for the treatment of insomnia that does not improve with sleep hygiene or CBT-I alone.[3]

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