InetCE

Volume 7	2003	Number 6

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Sleep Disorders: Etiology and Treatment

***InetCE* 221-146-04-068-H01**

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LEARNING OBJECTIVES

1. State the prevalence and consequences of chronic, adult sleep disorders.
2. Describe signs and symptoms of sleep disorders, as gathered through a patient interview and assessment for triage and medication monitoring.
3. Provide information to patients regarding nonpharmacologic interventions for sleep disorders.
4. Identify over-the-counter (OTC), herbal products, and nutraceuticals used for insomnia.
5. Review prescription medications used in the treatment of sleep disorders.

ABSTRACT: Human beings require sleep as a natural process of restoration, and disorders of sleep have been shown to increase morbidity and mortality. Pharmacists may elicit information to assist the patient in identifying appropriate self-care or physician referral through careful interview and assessment skills. Common causes of insomnia may be alleviated through lifestyle behavior modification (e.g., exercise, diet, tobacco, alcohol, and caffeine) and by encouraging patients to adhere to good sleep hygiene principles (e.g., regular wake and sleep times, sleep in bed). OTC sleep aids containing antihistamines, multivitamin supplements, and herbal products (e.g., valerian and melatonin) may be useful for treatment of temporary, mild sleep disorders. Patients should be cautioned regarding the potential side effects of self-care sleep aids, including residual drowsiness and psychomotor impairment. Patients with sleep apnea should avoid medications with central nervous system (CNS) depression. Short-acting benzodiazepines have replaced barbiturates and barbiturate-like drugs as the first-line treatment for transient and short-term insomnia. Ultra short-acting nonbenzodiazepine, sedative hypnotics such as zaleplon and zolpidem may offer an alternative treatment. Patients using sedative hypnotics should be cautioned regarding the potential for daytime psychomotor impairment, tolerance, dependence, and potential for withdrawal. Pharmacists may assist the patient and his or her physician in monitoring the safety and efficacy of self-care and prescription medications for short-term treatment of insomnia.

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SLEEP DISORDERS: ETIOLOGY AND TREATMENT

Narrative

Sleep provides vital emotional and physical restoration, but a significant number of adults experience sleep difficulties. Sleep disorders may be acute or chronic, focused on quality or quantity of sleep, and may respond to behavior and/or pharmacologic therapy. This paper provides a brief overview of chronic, adult sleep disorders, assessment techniques, and treatment approaches.

Introduction

Sleep is the natural process for physical, mental, and emotional restoration. In most countries, adults tend to have a single sleep period during the nighttime hours. The hypothalamus, thalamus, brainstem, and midbrain use a variety of endocrine and neurologic chemical transmitters to regulate the sleep/wake cycle. The circadian rhythm refers to the many physiologic changes (endocrine, thermoregulatory, cardiac, pulmonary, renal, gastrointestinal, cognitive) that occur daily during the 24-hour sleep/wake cycle. Intrinsic factors (e.g., aberrations in endocrine transmitters) and extrinsic factors (e.g., light/dark alterations or changes in posture) may invoke transient changes in the circadian rhythm and subsequently lead to changes in sleep patterns.

Individual requirements for sleep vary widely (3 to 10 hours per night), but studies suggest that individuals who sleep fewer than 4 hours or more than 9 hours have a potential increase in mortality when compared with those who sleep 7 to 8 hours per night.[1] According to the National Sleep Foundation 2002 "Sleep in America" Poll of 1,000 adults, the average duration of sleep was 6.9 hours during the weekdays and 7.5 hours on the weekends.[2] The duration of sleep, as well as the timing of sleep (bedtimes and wake-up times), have remained consistent over the past 4 years, and the majority (73%) of respondents rated the quality of their sleep as being good or better. Factors associated with high-quality sleep were age (65 years of age or over, 53%; 30 to 64 years of age, 38%; 18 to 29 years of age; 37%), overall health (excellent, 51% vs. good health, 31% vs. poor health, 18%), and whether households had children (without children, 43% vs. with children, 35%).

In a 1995 National Institute of Aging survey, however, more than 80% of persons over the age of 65 reported having a sleep disorder ranging from trouble falling asleep to not feeling rested after sleep.[3] Sleep patterns are distorted in the elderly and they are more prone to lighter and fragmented sleep.[4]

Sleep disorders have been identified as an independent risk factor for falls in the elderly.[5] A telephone survey of nearly 1,000 elderly individuals indicated that approximately 19% had fallen during the past 12 months, and there was an increased odds ratio of falling associated with difficulty falling asleep (OR 2.06, CI_{95} 1.45-2.94), waking up during the night (OR 2.05, CI_{95} 1.57-2.67), waking up in the morning (OR 2.55, CI_{95} 1.58-4.12), waking up too early in the morning and not being able to fall asleep again (OR 2.14, CI_{95} 1.49-3.07), daytime sleepiness (OR 2.40, CI_{95} 1.31-4.39), and napping during the day (OR 1.83, CI_{95} 1.22-2.75).[6] Falls in the elderly impose a significant financial burden on society, are the leading cause of death from injury, and have a negative psychologic impact leading to increased morbidity.[6]

Another survey of elderly people found that a little over 13% were poor sleepers, and the

primary causes were worry (43%) and physical discomfort (23%).[7] Worry may be a symptom of anxiety or depression associated with the many losses that occur with aging, such as loss of employment, loss of loved ones, and loss of independence. Physical discomfort may be associated with respiratory, endocrine, rheumatic, or neurologic medical conditions. The prevalence rates of sleep disturbances appear to increase with age and are frequently related to somatic diseases and medications with adverse effects affecting sleep.[8]

Sleep Disorder Definitions

There are over 80 pathophysiologically different sleep disorders that are classified into 3 main categories by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*: primary sleep disorders, sleep disorders related to another mental disorder, and other sleep disorders.[9] Primary sleep disorders are further divided into parasomnias (atypical behaviors associated with sleep) and dyssomnias (aberrations in amount, timing, or quality of sleep).

Parasomnias such as sleep walking (somnambulism) and sleep terrors disorders are deviations in arousal. Teeth grinding (sleep bruxism) affects 10% to 20% of the population and usually begins between the ages of 17 to 20 years with spontaneous remission around age 40.[1] Bedwetting (sleep enuresis) typically affects the young, resolves by adolescence, and returns in late adulthood as a symptom of underlying urologic abnormalities.

Dyssomnias appear to be more frequent and have a higher impact on morbidity and mortality. While amount, timing, and quality of sleep may be individualized, there are distinct primary and secondary sleep disorders. Many dyssomnias are associated with medical or psychiatric disorders including, but not limited to, schizophrenia, depression, bipolar disorders, chronic pain syndromes, dementia, neurologic abnormal movement disorders (Parkinson's, Huntington's chorea, Tourette's syndrome), closed head and spinal cord injuries, cardiac ischemia, heart failure, asthma, chronic obstructive pulmonary disease, and gastroesophageal reflux. In order to treat the underlying disease state, health care providers must conduct a thorough interview and assessment to identify the specific sleep disorder.

Insomnia may be described as the inability to fall asleep (sleep onset or sleep latency), stay asleep during the period when sleep should normally occur (sleep maintenance), or wake feeling unrefreshed (nonrestorative sleep).[10] The nature of the sleep disturbance and the duration of the complaint provide important clues to the possible etiology of insomnia. Transient causes of insomnia that require behavior modification include extrinsic situational insomnia (e.g., unfamiliar bed, significant life change) and high-altitude insomnia. Persistent psychophysiologic insomnia is a behavioral disorder, often triggered by a stressful event, in which the patient is preoccupied with a perceived inability to sleep adequately at night.[1]

The 2 most common transient shifts in the circadian rhythm causing sleep-timing disorders are travel and shift work. Rapid time zone change, also known as jet lag syndrome, is characterized by excessive daytime sleepiness, delayed sleep onset, frequent arousal from sleep, and gastrointestinal discomfort in people who experience transmeridian air travel. [1] It may last 2 to 14 days depending on the direction of travel, the age of the patient, the patient's

ability to adapt, and the number of time zones crossed. Shift work changes may be attributable to scheduled employment during the nighttime hours or an elective choice to remain awake at night to meet work or recreational commitments. Research has suggested that the risk of such nocturnal activities include a marked increase in non-alcohol–related, fatal-to-the-driver road accidents between midnight and 6:00 a.m., cardiac disorders, gastrointestinal disorders, and reproductive disorders. [1]

Sleep apnea is the temporary halt in breathing that lasts for 10 to 150 seconds and occurs from 30 to several hundred times per night in 2 to 5 million Americans. [1] Obstructive sleep apnea (OSA) is attributable to the upper airway collapsing. Risk factors for OSA include increasing age, male sex, and obesity. Chronic loud snoring, excessive daytime sleepiness or fatigue, memory impairment, headache, personality changes, and cognitive changes are signs and symptoms of OSA. Central sleep apnea (CNA) is owing to the respiratory control center in the brainstem failing to initiate breathing. It is important to recognize sleep apnea and refer the patient to a physician for treatment of the underlying cause (e.g., surgical restructuring of the upper airway, continuous positive airway pressure therapy), as untreated patients are at high risk for mortality. All medications that cause CNS depression should be avoided, as they may weaken the brain's ability to regulate the interactive, physiologic changes with breathing.[11]

Restless leg syndrome and nocturnal myoclonus (limb movement) are 2 distinct idiopathic dyssomnias that only require treatment for moderate-to-severe cases. Restless leg syndrome discomfort may be described as inability to keep lower extremities still during times of inactive wakefulness. A patient may report cramping, creeping/crawling sensations in calves or thighs, which are relieved by movement. Iron- or folic acid–deficiency anemia and renal failure are potential causes for the symptoms.[1] Nocturnal myoclonus is composed of rhythmic, brief (fewer than 5 seconds) episodes of muscle contraction in the foot that recur every 20 to 40 seconds.[1] These muscle contractions may or may not lead to sleep disorders, but tend to increase in incidence with age reaching a peak of 44% in healthy adults over 65 years of age.[1] Treatment of nocturnal myoclonus begins with a laboratory screening for uremia and anemia, and may include a trial of clonazepam or levodopa in severe cases.

Narcolepsy is a chronic disease, usually beginning in the second decade of life, characterized by disturbed nocturnal sleep leading to excessive daytime sleepiness and sleep attacks.[12] It appears to have a strong genetic influence, as the risk for narcolepsy increases in first-degree relatives of patients with narcolepsy. Cataplexy (generalized muscular weakness), hallucinations, and sleep paralysis (episodic loss of voluntary muscle tone) are symptoms of narcolepsy. Therapy includes behavior modification, antidepressants, and stimulants. Patients with narcolepsy should be referred to their health care provider for sleep laboratory evaluation to confirm the diagnosis.

While transient sleep disorders (single episodes) are fairly common, chronic sleep disorders (persisting for at least 1 month) affect less than 20% of adults.[13] Chronic sleep disorders can have a significant impact on individual lives as well as society. Not only do poor sleepers have daytime drowsiness, but they have been found to receive fewer promotions, have increased rates of absenteeism, have demonstrated poor productivity, and have an increased

risk in motor vehicle accidents.[14-16] Some of the potential physiologic consequences of sleep deprivation include increased cortisol levels, decreased glucose tolerance, increased sympathetic nervous system activity, increased blood pressure, and increased risk of coronary events and death.[18]

Patient Interview and Assessment for Sleep Disorders

Oftentimes, pharmacists are the first contact for patients who are seeking self-care advice for OTC and herbal supplements. Additionally, pharmacists are charged with ensuring the safe and effective use of prescription medications. Thus, the pharmacist-patient interaction may be focused on triage and referral or monitoring of medications with new prescriptions and refills. Regardless of the direction, and even if the end result is referring the patient to his or her primary care provider, taking time to interview the patient develops a personal pharmacist-patient relationship. This may be therapeutic for the patient, and improve job satisfaction for the pharmacist.

The assessment of sleep disorders primarily relies upon a thorough and detailed patient interview. Good interviewing requires both the knowledge of what information is needed from the patient and the skill in eliciting the information. As health care providers, pharmacists encounter a variety of individuals, and must be consistently respectful of human differences. Pharmacists have a professional duty to demonstrate a nonverbal and verbal positive regard for the patient. While the pharmacist assesses the patient's posture, gestures, eye contact, and voice qualities for information to assist in triaging the patient's complaint, the patient will be monitoring the pharmacist's same behaviors for signs of interest and understanding. Using facilitative responses, such as nodding of head and "Go on," and reflective statements that summarize or repeat the patient's words encourage the patient to provide more details.

Every attempt should be made to conduct the interview in a comfortable and private setting. While the reality exists that patients may approach pharmacists in a public area, such as the aisle of the pharmacy, the pharmacist has the responsibility to move the conversation to a more private area, such as the corner of the store.

Beginning with open-ended questions (free-response questions) and then clarifying with closed-ended questions (yes/no questions) will assist in directing the interview. Just as with other patient complaints, sleep related symptoms should be investigated within the context of the 7 qualities of symptoms, including:

1. Location of the symptoms. Where do you have difficulty sleeping/falling asleep (e.g., couch, chair, bed, hotel room, hospital)? What is your normal sleep routine?
2. Quality of the symptoms. Describe the drowsiness—eyes, muscles, and mental status? How would you rate the quality of your sleep?
3. Quantity or severity of the symptoms. How bad is the problem? How much does it interfere with your daily activities at home, at work, and in relationships (mildly upsetting, moderately severe, severely incapacitating)?
4. Setting in which the symptoms occur. When do you have difficulty sleeping? When are you drowsy? Describe the environment. Describe your emotional state.

5. Onset, duration, and frequency of the symptoms. When did you start having difficulty sleeping? How long does the insomnia last? How often does it occur? Do you fall asleep easily? How long do you sleep?
6. Factors that worsen or improve symptoms. What have you tried, and did it make it better or worse?
7. Associated complaints/symptoms. What other changes have you noticed? Do you wake up with a bad taste in your mouth? Do you experience leg jerking? Nocturnal sweating? Morning headaches?

Determining contributing factors is an important part of the interview process. Patients should be questioned about the presence of other medical conditions, including arthritis, angina, peptic ulcer disease, gastroesophageal reflux disease, respiratory disease, heart failure, diabetes, or epilepsy. Major life changes or stresses, such as job changes and family dynamic changes, may contribute to temporary alterations in sleep patterns.

Direct questioning may determine if the patient awakens feeling refreshed with a high energy level or feeling fatigued from multiple disruptions in the sleep cycle. Patients should be interviewed regarding snoring (e.g., determine how loud, and if changing positions attenuates the snoring) and difficulty breathing at night (e.g., awaken short of breath or with a feeling of being choked). Movement during sleep should also be assessed.

If patients are unable to answer the questions for themselves, it is helpful to ask if they have ever been told that they snore or are restless. Having the patient keep a sleep diary for 2 weeks assists in collecting information and organizing it for his or her primary care physician. The diary should include patient's bedtime, sleep latency, awakening, quality of sleep, daytime sleepiness and naps, amount and type of food, and medication administration. Taking the time to thoroughly interview the patient will assist with obtaining a detailed sleep diary and will encourage the patient to become an active participant in his or her health care.

There are many drugs that can cause insomnia, hypersomnia, or interfere with normal sleep cycles, including dream sleep. Pharmacists should ask about changes in prescription medications, OTC medications, and nutraceuticals. The more lipophilic a medication is, the more likely it is to rapidly enter the CNS, affect sleep/wakefulness, and rapidly redistribute out of the CNS expressing a short duration of action with a single dose or a long duration of action with accumulation. Likewise, total body fat increases during aging and may decrease the clearance of fat-soluble medications. Alterations in metabolism (e.g., aging) and clearance (e.g., hepatic and renal impairment) may lead to increased levels of medications and subsequent side effects associated with sleep. Adjusting the administration time of medications, such as dosing diuretics in the morning to avoid nocturnal diuresis, may assist with managing symptoms of sleep disorders.

Sleep onset and maintenance may be impaired by cimetidine, phenytoin, levodopa, hormones/steroids (oral contraceptives, thyroid hormones, corticosteroids, testosterone), monoamine oxidase inhibitors, and sympathomimetics (albuterol and similar products, pseudoephedrine, theophylline).[1, 13, 18] Cardiovascular medications and anorexiants may lead to disruptive sleep and nightmares.

Other prescription medications that may affect sleep and wakefulness include antidepressants, antipsychotics, anxiolytics, anticonvulsants, analgesics, antihistamines, antiemetics, chemotherapy agents, and smooth muscle relaxants.

A detailed patient interview should also include obtaining information regarding patients' use of substances known to lead to sleep disturbances, such as nicotine, caffeine, alcohol, and illicit drugs. Nicotine is a stimulant similar to caffeine. Caffeine is the most common pharmacologic cause of sleep disorders. Caffeine produces sleep latency, more frequent arousals, and a reduction in total sleep time for up to 8 to 14 hours after ingestion.[1] Alcohol is a CNS depressant that initially promotes sleep, but ultimately it disrupts and fragments sleep leaving the patient with nonrestorative sleep and resultant daytime drowsiness.[19] The sleep of chronic alcoholics remains disturbed for years after discontinuing alcohol use.[1] The use of amphetamines or cocaine decreases total sleep time initially, which returns to normal with chronic use and then causes rebound insomnia on withdrawal.[1]

Nonpharmacologic Treatment of Sleep Disorders

Management of chronic sleep disorders begins with an attempt to identify the underlying cause. While medications may provide short-term benefits, behavior modification may lead to sustained improvements. One study of 78 outpatient adults found that behavioral therapy was more effective in maintaining results than pharmacologic treatment alone.[20] Good sleep hygiene techniques include a variety of simple interventions centered on maintaining healthy schedules of diet, exercise, and sleep. The following list includes good practices for sound sleep:[13]

- Attempt sleep in bed only when drowsy/tired and sleep only until refreshed to improve sleep efficiency.
- Minimize noise, light, and excessive temperature during the sleep period.
- Maintain a regular schedule for going to bed and arising every day and avoid daytime napping—especially for more than 1 hour or after 3:00 p.m.
- Use bedroom for sleep and sexual activity only.
- Try a light snack before bedtime and avoid a large meal within 2 hours of bedtime.
- Participate in regular exercise, especially time spent outdoors.
- Avoid caffeine, nicotine, alcohol, or strenuous exercise within 4 hours of bedtime.
- Increase exposure to light during waking hours and to dark during sleep hours.
- Consider relaxation techniques, such as visualization and progressive muscle contraction/relaxation.

The effects of physical exercise on sleep in patients over the age of 60 was the subject of a recent Cochrane Review.[21] The study concluded that exercise improved sleep onset latency and total sleep duration.

Teaching patients about relaxation techniques, establishing sleep patterns, and controlling the external environment empowers patients to improve their health. Supplying personalized education on proper sleep hygiene establishes a pharmacist-patient relationship that provides benefit to both parties.

Over-the Counter (OTC), Herbal Products, and Nutraceuticals

Nearly 14% of adults buy and/or use OTC sleep aids and 4.3% use OTC medication to stay awake during the day.[2] It is important to counsel patients to follow the

manufacturer's administration directions, use the lowest effective dosage, and self-treat only on a short-term basis. Elderly patients are particularly sensitive to adverse effects, and should use lower starting doses. Patients should be advised that the Food and Drug Administration (FDA) does not ensure consistency of content or purity for herbal and nutritional supplements. Patients should report use of OTC, herbal, and nutraceutical sleep aids to their health care providers and pharmacists. Patients should be advised that using sleep aids may interact with other prescription and nonprescription medications.

The sedating antihistamines diphenydramine and doxylamine (central histamine-$_1$ antagonists) are the common ingredients in OTC sleep aids. Even though these agents may induce drowsiness, a majority of persons state that they have "hangover" effects the next day.[22] Higher doses beyond diphenhydramine 50 mg do not appear to increase sedation, but may increase the adverse effects, including paradoxical excitation.[22] They may be useful in younger patients, but should be avoided in the elderly owing to daytime sedation, anticholinergic effects (e.g., constipation and urinary retention), and potential for cognitive impairment. In a prospective, cohort study of hospitalized patients 70 years of age or older, 42% of the 114 patients who received diphenhydramine during their hospital stay experienced cognitive decline.[22]

Valerian has been used in Europe since the seventeenth century, and the FDA is considering approving it as an OTC sleep aid. It is thought to act similar to benzodiazepines with effects on γ-aminobutyric acid (GABA) receptors and possibly by modulating the catabolism of GABA.[23] The increase in GABA within the synaptic cleft decreases CNS activity and leads to relaxation or sedation. While there is a paucity of safety and efficacy data, valerian may be more effective than placebo in reducing the time to sleep onset.[23] Other small human studies indicate that valerian enhances sleep maintenance, improves quality of sleep in elderly and nonelderly patients with chronic insomnia, and improves mood.[24] The usual dose is 150 to 300 mg valerian extract containing 0.8% valerenic acid and 1% to 1.5% valtrates taken 30 to 45 minutes prior to attempting sleep. It may take 2 to 4 weeks to see improvement in mood and sleep.[25] Valerian appears to be a safe, mild sedative with limited side effects (e.g., mild gastrointestinal distress, idiosyncratic stimulatory reaction) when used appropriately for short-term treatment of insomnia.[24-27] Caution should be used with long-term use because of the potential for benzodiazepine-like withdrawal syndrome or rebound insomnia. Valerian may increase the sedative effects of other OTC medications, herbal products, nutraceuticals, and prescription medications that are known to cause dizziness or drowsiness.

Kava is a South Pacific herbal product, which has been used by natives since the late 1700s and more recently marketed in mainland United States for anxiety, but the research results regarding its effectiveness for sleep has been inconsistent and not all patients benefit.[23] Side effects include gastrointestinal discomfort, headache, dizziness, skin rash, impaired psychomotor activity, yellowing of the skin and nails, hepatotoxicity, neurotoxicity, and questionable addiction.[24-27] The usual dose is 2 to 4 grams as decoction (or standardized formulas containing 70% kavalactones) as needed, and not to exceed more than a few weeks of chronic use.[24] Kava may amplify the sedative effects of other OTC medications, herbal products, nutraceuticals,

and prescription medications that are known to cause dizziness or drowsiness. There has been an increase in concern regarding the significant adverse effects in relation to the inconsistent benefits, and caution should be advised when considering any product containing kava. The FDA issued a Consumer Advisory alert in 2002 to alert consumers on the potential risk of severe liver toxicity. Other countries are reportedly considering possible removal of products containing kava from the market. Given the availability of alternative sleep aids, it would be prudent to advise against the use of kava-containing products.

Melatonin is a dietary supplement that is a naturally occurring neurohormone manufactured by serotonin and secreted from the pineal gland in the late evening to induce sleep and regulate the circadian rhythm.[28] The standard rhythmic pattern of nocturnal melatonin increase is absent until 3 months of age, peaks in the first few years, stabilizes throughout adulthood, and then falls off until it is barely detectable in old age.[24] Melatonin is also an antioxidant, an antiestrogenic, and has oncostatic properties.[25] Some antidepressants, vitamin B_6, and vitamin B_{12} promote increased melatonin levels, while nonsteroidal anti-inflammatory drugs (NSAIDs), β-blockers, calcium-channel blockers, diuretics, benzodiazepines, alcohol, and caffeine may impair melatonin production.[24-27] Manufactured melatonin improves sleep onset, but owing to the short half-life sleep maintenance may not be enhanced. [28-30] Pharmaceutical companies are attempting to develop extended-release formulations to address this issue. Supplemental melatonin may be beneficial for individuals with decreased melatonin levels (e.g., the elderly), some children with sleep disorders (e.g., Down syndrome, epilepsy, autism, cerebral palsy), and insomniac patients with blindness, schizophrenia, manic-type bipolar disorder, fibromyalgia, or cancer.[23-30] The usual dose is 0.1 mg to 5 mg taken 30 to 90 minutes before bedtime, and it may take 1 to 4 weeks of continuous dosing to appreciate the full effects of melatonin in chronic insomnia.[25] Approximately 1 out of 2 people could benefit from the use of melatonin 3 to 5 mg for short-term relief of jet lag, a sleep disorder caused by travel between time zones.[31] Supplemental melatonin may cause headaches, dizziness, and abdominal cramps.[23] The supplement may be contraindicated in autoimmune and immune system disorders, individuals taking medications that might cause immune suppression, and patients receiving concomittant therapy with antidepressants or calcium-channel blockers.[24-27]

Patient Counseling for Sedatives/Hypnotics

When considering the use of sedative/hypnotic therapy for short-term relief (7 to 10 days) of insomnia, patients should be fully informed of the goals of treatment, the risks attributable to sedation, dependence, abuse, and withdrawal. Patients should be advised regarding the presence of impaired psychomotor skills (even if they do not feel drowsy) when using sedatives/hypnotics, especially when operating machinery or equipment. Patients should be advised about the possible combined effects when taking sedatives/hypnotics with other drugs that have CNS depressant activity or with other medical conditions that impair respiratory function. Chronic administration for more than 10 days may lead to physical dependence secondary to neuroadaptation, which requires continued administration in order to avoid withdrawal. Abuse is the self-administration of a substance in a socially unacceptable manner or not as the substance was intended or directed for use.

Sedatives/hypnotics should be used with caution in patients with concurrent or history of substance abuse, as they have a higher risk of hypnotic abuse and dependence.[32] Management of withdrawal includes slow tapering and discontinuation of the medication. Patients should be advised to take the medication only as prescribed and only when able to get 6 or more hours of sleep.

Barbiturates and Barbiturate-Like Sedatives/Hypnotics

Barbiturates (secobarbital, phenobarbital) and barbiturate-like drugs (chloral hydrate) were the first compounds developed as sedatives/hypnotics and for short-term treatment of insomnia in the 1960s. It is believed that they enhance the activity of GABA to induce CNS depression ranging from mild sedation to deep coma and even death. While they improve sleep induction and maintenance, this effect is limited to intermittent use (less than 2 weeks) with 1- to 2-week, medication-free periods. The lowest effective dose should be used and adjustments should be made for the elderly; significantly, chronically ill; hepatically impaired; and renally impared. Barbiturates have been shown to produce lethargy, vertigo, headaches, depression, cognitive and psychomotor impairment, myalgic or arthralgic pain, mood or personality distortion, restlessness, hypersensitivity reactions, severe dermatologic skin eruptions, adverse gastrointestinal effects, and fetal harm in pregnant women.[32] Periodic, complete blood counts (CBCs) should be monitored, as barbiturates have been shown to cause megaloblastic anemia, agranulocytosis, and thrombocytopenia.[32] Barbiturates may intensify the adverse effects (e.g., sedation, respiratory depression) of other CNS depressant medications, including benzodiazepines, antihistamines, tranquilizers, alcohol, antidepressants, and narcotic pain relievers. Barbiturates are potent inducers of several hepatic cytochrome P450 enzymes, and may decrease the effectiveness of a variety of medications, including oral contraceptives (use a back-up method), oral anticoagulants (monitor closely), doxycycline (select a different antibiotic), and corticosteroids (monitor patients with respiratory disorders controlled on steroids).[32] Additionally, barbiturates have been shown to enhance the hepatotoxicity potential of acetaminophen at OTC dosing ranges.[32] To prevent rebound insomnia, the medication should be tapered over several days to weeks.

The use of barbiturates and barbiturate-like drugs has significantly declined over the past few decades owing to their excessive CNS depression, rapid development of tolerance, drug-drug interactions, and potential for lethal overdose. Benzodiazepines have become the first-line treatment for transient and short-term insomnia.

Benzodiazepine Sedatives/Hypnotics

Benzodiazepines are the most common prescription medications used to treat insomnia because of their established efficacy since the 1970s, relative safety when used appropriately, and low cost. The medications appear to bind the benzodiazepine receptors (BZ-1 and BZ-2, nonselectively), which modulate the activity of the inhibitory neurotransmitter GABA to produce sedation, muscle relaxation, increased seizure threshold, and anxiolysis. The BZ-1 receptor appears to be associated with sedation and the BZ-2 receptor is associated with cognition, memory, and psychomotor function. All benzodiazepines may be used for insomnia, but because of hangover effects and daytime sleepiness, the short-acting benzodiazepines (onset 15 to 30 minutes and duration 6 to 8 hours) are

recommended. Estazolam, flurazepam, quazepam, temazepam, and triazolam have been studied specifically for the treatment of sleep disorders. Flurazepam may be more effective with continued use for sleep maintenance disorders owing to the accumulation of an active metabolite with a longer half-life (74 to 160 hours).[32] This prolonged effect may result in residual daytime impairment and, therefore, should be limited to those patients with a primary anxiety disorder who are to be treated for daytime anxiolytic effects. For patients with sleep latency aberrations and concern about daytime sleepiness, triazolam has a short half-life for the parent drug (2.5 hours) and lacks an active metabolite.[32] Patients using triazolam, however, may be more likely to develop tolerance and resultant diminished effect with continuous use. Additionally, concomitant oral administration of triazolam with grapefruit juice has been reported to increase bioavailability of the drug significantly, and may result in oversedation.[32]

The potential for dependence, tolerance, daytime sedation, rebound insomnia, and anterograde amnesia limit the usefulness of benzodiazepines.[28] While respiratory depression is not as common with oral administration as the intravenous benzodiazepines, patients with compromised systems (e.g., pneumonia, asthma, chronic pulmonary conditions, sleep apnea) may be susceptible to benzodiazepine-induced adverse effects and should be monitored closely. Patients should be cautioned against the consumption of alcohol with benzodiazepines.

Geriatric patients are especially susceptible to the CNS side effects of benzodiazepines, such as confusion, weakness, vertigo, syncope, and ataxia.[8] Similar to other psychotropic medications, using benzodiazepines in the elderly has been shown to lead to a small, but significant increased risk of falls and subsequent hip fractures.[34-36]

The effect of benzodiazepines on vigilance and psychomotor activity has lead to research in motor vehicle accidents related to benzodiazepine use. In a retrospective review of nearly 20,000 drivers, the odds ratio of having a crash while on benzodiazepine compared with the odds while not taking the medication was risk ratio 1.62, CI 95%, 1.24-2.12.[36] Extrapolating this data, it is predicted that over 100 lives could be saved annually if individuals taking benzodiazepines did not drive. Another study demonstrated elderly motor vehicle drivers on long-acting benzodiazepines are at an increased risk of accidents within the first week of use (risk ratio 1.45, CI 95%, 1.04-2.03), and this risk is continued with long-term use up to 1 year (risk ratio 1.26, CI 95%, 1.09-1.45).[37] Patients must be counseled to use extreme caution when operating machinery while using ~~a~~ benzodiazepine, as benzodiazepines not only cause symptomatic sedation but also asymptomatically impair psychomotor activity both in short-term and long-term use.

Intermittent, short-term dosing, use of short-acting benzodiazepines, appropriate dosing for decreased hepatic and renal clearance, and careful tapering may assist in managing benzodiazepine adverse effects. If a patient has been using benzodiazepines for more than 10 days, s/he should be monitored for withdrawal symptoms, including irritability and anxiety, rebound insomnia, seizures, and palpitations.[38] In a small study of 34 patients on chronic benzodiazepine therapy, the addition of controlled-release melatonin lead to a higher successful benzodiazepine discontinuation rate (11 out of 18 vs. 4 out

of 16 on placebo) while preserving sleep quality over 12 weeks.[30]

Benzodiazepines still remain first-line therapy for transient or short-term insomnia. Concern regarding the potential adverse effects of chronic use of benzodiazepines has lead researchers to study the use of other medications with sedative effects and develop sedatives that are structurally different from benzodiazepines for the treatment of chronic insomnia.

Nonbenzodiazepine Sedatives/Hypnotics

Zaleplon (Sonata®) is a nonbenzodiazepine hypnotic agent that selectively binds the benzodiazepine-1 $GABA_A$ receptor complex and produces a decrease in sleep latency and an increase in subjective ratings of sleep quality similar to the effect of benzodiazepines.[39, 40] Unlike benzodiazepines, which act nonselectively at both benzodiazepine receptors, zaleplon does not appear to produce residual daytime sleepiness; persistent, decreased memory and cognitive functions; appreciable myorelaxant effects; increased seizure threshold; anxiolytic activity; or rebound insomnia upon withdrawal.[39-41] The usual dose of zaleplon is 5 to 10 mg given immediately before going to bed or when actually in bed, as the onset of action is rapid. Because of a short elimination half-life (1 hour), it does not appear to produce daytime sleepiness and is mostly effective for patients with impaired sleep onset rather than patients with sleep maintenance disorders. Elderly or patients with hepatic impairment should use the lower dose. Zaleplon may produce a variety of psychiatric adverse effects, photosensitivity, and constipation.[32] It has an abuse potential similar to benzodiazepines, and despite its pharmacokinetic properties, there have been a few case reports of physical dependence and withdrawal symptoms.[32] It is a substrate of the cytochrome P450 3A4 (minor pathway of metabolism) and, therefore, may have increased sedation or decreased effectiveness with 3A4 enzyme inhibitors or inducers, respectively. Zaleplon should not be used concomitantly with other CNS depressants, including OTC pain and cough/cold preparations.

Zolpidem (Ambien®), an imidazopyridine, selectively binds the BZ-1 receptor inducing sedation similar to zaleplon. It has a rapid onset of action and a short half-life (1.4 to 4.5 hours), but elimination may be delayed by up to 50% in the elderly or in hepatic impairment.[42] The usual dose is 5 to 10 mg at bedtime. Zolpidem is as effective as benzodiazepines in reducing sleep latency and it improves sleep maintenance even after discontinuation.[43, 44] It appears to induce a sleep pattern that resembles the natural physiologic pattern, thereby protecting sleep architecture, and may be of benefit where other hypnosedatives have not been effective (e.g., dementia, night-time wandering).[8] It is generally well tolerated at recommended doses, and the most common adverse effects include xerostomia, constipation, sinusitis/pharyngitis, drowsiness, dizziness, headache, diarrhea, and nausea.[32] The major pathway of metabolism is through cytochrome P450 3A4. The sedative effects may be enhanced when zolpidem is administered concomitantly with cytochrome P450 3A4 inhibitors (e.g., amiodarone, cimetidine, diltiazem, verapamil, grapefruit juice, selective serotonin reuptake inhibitors, ketoconazole, erythromycin, clarithromycin), and the efficacy may be slightly diminished with enzyme inducers (e.g., glucocorticoids, St. John's wort, carbamazepine, phenobarbital, phenytoin, rofecoxib).[8, 32] There have been case reports of abuse potential, but the risk of abuse with

zolpidem appears to be much lower than with benzodiazepines.[8]

Antidepressants

Despite the lack of well-controlled studies, antidepressants with sedative activity are frequently used to treat insomnia, based upon the association between depression and sleep disorders. Unlike benzodiazepines, they have a low propensity for physical dependence, tolerance, and withdrawal symptoms. While they have the significant benefit of treating comorbid conditions, it is important to be aware of the potential adverse effects.

Low-dose, bedtime tricyclic antidepressants (TCAs) (e.g., amitriptyline, nortriptyline, doxepin) are commonly used to treat insomnia in patients with a variety of depression and anxiety disorders, migraines, eating disorders, nicotine dependence/smoking cessation, and neuropathy. In general, the doses used for insomnia do not appear to produce significant adverse effects. The elderly, however, may be more susceptible to anticholinergic effects (e.g., vision disturbance, urinary retention, constipation, dry mouth), orthostatic hypotension, and cardiovascular conduction abnormalities. Intentional or unintentional overdose of TCAs may be lethal.

Trazodone is a serotonergic antidepressant that is not well tolerated at antidepressant doses because of sedation. Trazodone has minimal anticholinergic effects unlike TCAs and OTC sleep aids. Nevertheless, trazodone has a significant, potential adverse effect of producing orthostatic hypotension (attributable to α-$_1$ blockade) and, therefore, the patient's blood pressure should be monitored. Additionally, trazodone may cause priapism.[32] There has been little research comparing trazodone with benzodiazepines, and what studies are available do not clearly differentiate trazodone as demonstrating superior efficacy and safety.[45-47]

Conclusion

While transient or short-term sleep disorders are fairly common (10%-30% of Americans), those lasting for greater than 3 weeks should be referred to a physician for treatment of the underlying disorder. Pharmacists may elicit information to assist the patient in identifying appropriate self-care through careful interview and assessment skills. Common causes of insomnia may be alleviated through lifestyle behavior modification (e.g., exercise, diet, tobacco, caffeine, alcohol) and encouragement of patients to adhere to good sleep hygiene principles (e.g., regular wake and sleep times, sleep in bed). OTC sleep aids containing antihistamines, multivitamin supplements, and herbal products (e.g., valerian and melatonin) may be useful for treatment of temporary, mild sleep disorders. Patients with sleep apnea should avoid medications with CNS depression. Barbiturates and barbiturate-type drugs are no longer recommended for the treatment of insomnia owing to excessive CNS depression, rapid development of tolerance, drug-drug interactions, and potential for lethal overdose. Short-acting benzodiazepines have become the first-line treatment for transient and short-term insomnia. Patients should be cautioned regarding daytime sleepiness, tolerance, anterograde amnesia, and psychomotor impairment. Short-acting nonbenzodiazepine sedatives that are selective benzodiazepine-1 receptor modulators, such as zaleplon and zolpidem, may offer an alternative treatment. For patients with comorbid conditions, such as depression, migraines, or neuropathic pain, an antidepressant might be the treatment of

choice for complaints regarding sleep disorders. Pharmacists should take time to assist patients in monitoring the safety and efficacy of prescription medications (e.g., h as benzodiazepines, zolpidem, and zaleplon for short-term treatment of insomnia.

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