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“Sleep Disorders (Insomnia)”

August 2015

It has been estimated that there are 40 million adult Americans who complain of chronic sleep disorders and about 20 million suffer from occasional difficulties. In this lesson we review the dynamics and treatments associated with insomnia.

Pharmacists will be able to:

1. Define sleep & discuss its physiology.
2. List circumstances that indicate presence of sleep disorders.
3. Classify sleep disorders.
4. State causes & diagnosis of insomnia.
5. Describe treatment of insomnia.



Technicians will be able to:

1. Define sleep.
2. Classify sleep disorders.
3. Differentiate between pharmacological & non-pharmacological treatments for insomnia.

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Introduction

Sleep disorders are conditions that occur as a result of interference in sleep pattern, and excludes environmental stimuli such as noise, excessive heat or cold, or movements caused by riding in a car, train, boat or airplane. These disorders are common occurrences and are considered one of the most encountered health complaints. It has been estimated that there are 40 million adult Americans who complain of chronic sleep disorders and about 20 million suffer from occasional difficulties.

SLEEP

Sleep is defined as a periodic behavioral state of rest for the body and mind. It is accompanied by varying degrees of unconsciousness, relative inhibition of sensory and voluntary muscles and decreased but reversible response to external stimuli. Normal sleep is accompanied by a reduction in body temperature, metabolic rate, glucose consumption, and release of catabolic hormones. However, there is no complete shutdown of major organs or regulatory body systems. While sleep is essential, the precise function of sleep and how it provides a daily rejuvenation and revitalization of body functions and renewal of feeling refreshed, healthy and more alert is not completely known.

PHYSIOLOGY OF SLEEP

The sleep-wake cycle is controlled by neurophysiologic processes. Any disruption can result in sleep or circadian rhythm disorders. Circadian rhythm is a biological event controlled by an internal clock capable of generating oscillation that occurs in an interval of a 24 hour period. The hypothalamus is believed to control the time of the sleep cycle. Sleep occurs in humans, animals, and plants. Flowering of plants occur at about the same time each year. In humans the biological clock can be upset by the difference between the time at current locations and the time to which a person is accustomed. This phenomenon is termed "jet lag" and occurs when one travels from one time zone to another within a short period of time.

Sleep can be divided into two stages based on the characteristics of the following patterns: electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), which is a pattern of body surface such as muscles, and a pattern of eye movement. The two stages alternate during the night, and each cycle consumes 90 to 100 minutes during sleep. **The first stage is termed rapid-eye-movement (REM) sleep or dreaming sleep**, and consists of 25% of the cycle. It is characterized by rapid movement of the eyes in different directions, low muscular tone, and low, rapid voltage EEG. REM begins 90 – 120 minutes after falling asleep. The last stage of REM occurs around the early morning hours. Individuals experience about 4 to 5 periods of REM during the night. They are short after falling asleep, but become longer as morning approaches.

The second stage, known as non-rapid-eye-movement (NREM) sleep, is characterized by little or no eye movements. Dreaming is usually absent and muscles are more active than in REM. After onset of sleep, NREM, which composes approximately 75% of the sleep cycle, progresses through three phases that may last for 5 – 15 minutes each. During the first stages, the eyes are closed, but it is easy for one to wake up. The muscles are active, the eyes roll, open and close at moderate speed. The patient may experience sudden twitches and jerks. In the second phase sleep is light, heart rate is slower and body temperature is lower. Deep sleep is about to begin.

The third phase is marked by deep sleep. If awakened, the individual feels tired and confused for a few minutes. The NREM is the time when the body builds tissue, bones and muscles, and strengthens the immune system.

Human needs for sleep varies from one person to the next depending on age, gender, life-style, general health, amount of strength, mood, and demands of the day. Infants require 14 -15 hours of sleep; teenagers 8.5 – 9 hours; and most adults 7 – 9 hours. Women over 35 years of age tend to sleep more than men of the same age. Not having enough sleep can affect vitality, creativity, mental sharpness, emotional balance and ability to respond quickly to questions. The biological clock can be reset by one or two hours (or more) per day. This occurs when traveling to different time zone or when working night shifts. It usually takes about a week to go back to a normal day/night schedule.

EPIDEMIOLOGY

Self-reported data of U.S patients indicate:

1. Sleep around 6.8 hours per night during workdays, but an average of 7.4 hours per weekend night.
2. Women appear to sleep longer than men by approximately 45 minutes.
3. A number of studies have shown that there is a very small difference in sleep duration between African Americans and Caucasians.
4. Total sleep times among the elderly decrease linearly with age.
5. Sleep disorders that prevent people from falling asleep or having interrupted sleep affects about 35% to 40% of the population. In spite of the risk in morbidity and complication caused by such disorders, they are either ignored, mistreated or undertreated.
6. Incidence of sleep disorders are increasing due to the aging population.

SLEEP DISORDERS

Sleep disorders are those conditions that contribute to interruption of sleep cycle (REM & NREM) or to downgrading the quality of sleep. Included are problems with falling asleep, staying asleep during sleep hours, sleepiness during wake hours, or excessive sleep or abnormal behavior while the person is asleep. Individuals who have enough restful and good quality sleep are generally healthier than those who suffer from sleep disorders. Everyone experiences occasional sleeping difficulties, but repetitive problems may indicate the presence of a sleep disorder or an underlying health problem. A sleep disorder should be suspected if the patient:

1. Feels drowsy during the day.
2. Has tendency to fall asleep while sitting still, reading, watching TV, or sitting in gatherings.
3. Has difficulty staying alert and paying attention in classroom or work place.
4. Appears tired or pale.
5. Has difficulty controlling his/her temper and emotions.

6. Has tendency to rely on caffeine containing beverages.
7. Takes frequent midday naps.
8. Has difficulty staying awake while driving.

There are over eighty sleep disorders that mostly occur as a result of a variety of causes. They are broadly classified into the following categories: **1.dyssomnia, 2.parasomnia, 3.hypersomnia, and 4.Circadian Rhythm Sleep–wake disorders.**

Dyssomnia is a broad category which includes insomnia and sleep apnea. It is characterized by difficulty falling asleep, remaining asleep, or experiencing uncontrollable sleepiness any time during waking hours.

Parasomnia is a disruptive sleep disorder which involves abnormal behavior, movements, emotions and dreams during the sleeping hours or upon waking up. Often there is no memory of the occurrence of such events. Parasomnia includes sleep walking, sleep terror, sleep nightmares, sleep talking, confusional arousals (being unaware of where he/she is or of what's going on), and bed-wetting.

Hypersomnia is characterized by recurrent episodes of excessive, prolonged uncontrollable sleepiness during daytime and often at inconvenient times such as at work or while driving. (Narcolepsy is defined as excessive daytime drowsiness and uncontrollable, intermittent episodes of falling asleep during waking hours. It is due to inability of the CNS to control sleep and wakefulness).

Circadian rhythm sleep-wake disorders: These occur when the biological clock or circadian rhythm are disrupted due to change in sleep times. This may occur as a result of work shift or jet lag. In the scope of this lesson emphasis will be placed on insomnia.

INSOMNIA

Insomnia is a common, persistent sleep disorder characterized by inability of the person to fall asleep, stay asleep, and/or waking up very early in the morning. These occurrences result in inability of the patient to obtain a restful period of sleep and the quantity of hours needed for feeling refreshed upon awakening. The result may be in one or more of the following: fatigue, drowsiness during the day, low energy, difficulty to concentrate, mood swings, and diminished performance at work, school or during driving. The insomniac may feel the need to take daytime naps to compensate for lost sleep. However, such action may be counterproductive.

Prevalence

Insomnia is 40% more common in women than in men. It has been estimated that 10% - 14% of the population suffers from chronic insomnia, and 20% - 40% experience occasional insomnia. In a 2005 poll it was indicated that over 50% of adult Americans experienced one symptom of insomnia at least a few nights every week within the previous year. About 10% of the general population experience symptoms of day time functional difficulties. Insomnia has been associated with decreased work productivity and increased motor vehicle accidents.

Types of Insomnia

Insomnia may be classified as **transient, acute or chronic** based on duration of symptoms. **Transient** insomnia usually lasts for a few nights a week, and occurs as a result of situational stress, change in sleep schedule or sleep environment (i.e., noise, anxiety over a meeting or exam, sleeping in a hotel bed, jet lag). **Acute** insomnia may last from one night to a few weeks and may occur during short illness, recovery from surgery, or loss of a loved one. **Chronic** insomnia may last from a month to years, and it reflects factors associated with primary sleep dysfunction as in medical disorders such as angina pectoris, diabetes, migraine, depression, gastroesophageal reflux, peptic ulcer, asthma, hypertension, chronic bronchitis, emphysema, psychological disorders (such as bipolar disease or depression), substance abuse, or medications (such as alcohol, certain antidepressants, antihypertensives, and sympathomimetics). Night shift workers, especially those who rotate their schedule, may experience chronic insomnia. Certain individuals are adversely affected by caffeine, alcohol and nicotine. Even though alcohol can assist in falling asleep, it may result in frequent awakening. Eating prior to bedtime and performing vigorous exercise may delay falling asleep.

Causes

About 50% of insomnia is related to stress, anxiety, and depression. Other factors are lifestyle during the awake hours, sleep schedule and habits, general health of the individual and medications taken to treat medical problems. Environmental factors such as noise, temperatures, jet lag and switching from a day to night shift play a role in triggering insomnia. Pain and discomfort may also lead to problems.

Symptoms

As indicated earlier, a typical situation is characterized by difficulty falling asleep, waking up in the middle of the night and staying awake for hours struggling to sleep to no avail, or waking up very early in the morning. The amount of sleep needed for appropriate rest varies from one individual to the next. Quality is more important than quantity. Short sleepers are individuals who can function normally with no fatigue or drowsiness even with 4 hours or less sleep. The quality of sleep of these short sleepers is good, and the sleep is usually uninterrupted. Long sleepers are those who sleep 10-12 hours a night. The quality of their sleep is good and normal. This pattern begins in childhood and continues throughout life.

TREATMENT

Treatment of insomnia should be individualized based on the type, nature (difficulty falling asleep, maintaining sleep or waking up early in the morning), and severity of symptoms. **Treatment may be non-pharmacological and/or pharmacological.**

Non-Pharmacological Treatment

It is essential that non-pharmacological treatment be initiated either alone or concurrently with pharmacological treatment. Non-pharmacological treatment can reestablish normal sleep cycles. It is inexpensive and free of adverse effects. Evaluation of the patient is an important step. Family history is useful in identifying the underlying problems. About 30% of insomniacs have a family history. Sleep-awake patterns should be established. A review of current medication intake (including OTCs) is helpful in determining the role of these drugs

in causing insomnia. Non-pharmacological treatment includes education, sleep hygiene, stimulus control, sleep restrictions, relaxation training, and cognitive therapy.

The pharmacist plays an important role in disseminating information to patients.

Proper sleep hygiene may improve transient and short-term insomnia. This includes following a constant sleep-wake schedule, engaging in relaxing exercises 3-4 hours before bedtime, going to bed only when drowsy, refraining from napping especially close to bedtime, avoiding intake of caffeine, nicotine or alcohol 4-6 hours before retiring, avoiding poor sleep environment (i.e., noise, bright light), and avoiding the intake of excessive liquids or heavy meals. Stimulus control therapy is useful for sleep-onset insomnia. The patient should go to bed when sleepy. If sleep does not occur within 20 minutes, the insomniac should leave the bedroom and return only when drowsy. This cycle should be repeated as necessary. Sleep restriction therapy deals with association of the bed with sleep. Some insomniacs tend to spend more time in bed with the hope that this will lead to more sleep. This may lead to disappointment and aggravation of the problem. The patient should try to spend the same amount of time in bed as they actually sleep.

Pharmacological Treatment

Although it does not exist, the ideal sleep aid agent should have a quick onset of action; long duration to assist in maintaining sleep; with normal waking hours in the morning; minimal side effects such as daytime sedation, motor coordination, and cognitive impairment. It should not cause tolerance or dependence when used for several consecutive nights, and abrupt discontinuation should not result in withdrawal or rebound insomnia. Hypnotics may relieve symptoms of acute insomnia. However, the usefulness of these agents in the management of chronic insomnia is questionable. Taking them for longer than 4-6 weeks may lead to physical or behavioral dependence, withdrawal and rebound insomnia. Thus the use of hypnotics has its limitations. When using them in the elderly, the initial dose should be one at the low end of the dosage range. The following groups of medications are often used.

Benzodiazepines

These drugs tend to induce sleep by depressing the cortical areas and the sleep-wakefulness clock. They potentiate the activity of hypnotic gamma-aminobutyric acid, an inhibiting neurotransmitter located in the CNS. Examples include:

1. Flurazepam: When compared to barbiturates and non-benzodiazepine hypnotics, it is safer and has less potential for dependence and abuse. At normal doses, it does not have detrimental effects on REM sleep. It has long-acting metabolites with the potential for accumulation, causing impaired daytime functioning especially in the elderly. The sedative-hypnotic dose is 15-30 mg.
2. Temazepam: It gained popularity due to its short to intermediate half-life of 9 to 15 hours, which could reach 20 to 30 hours in the elderly. Thus, repeated use could cause accumulation and resultant daytime hangover. A 15 to 30 mg dose can cause an increase in total sleep time and reduction in the nocturnal awakening time.
3. Triazolam: is an ultra-short-acting benzodiazepine that is rapidly eliminated following absorption. It has an elimination half-life of 2 to 3 hours. It suppresses REM sleep early in the sleeping hours. Like temazepam, it improves the total sleep time and unnecessary awakening during the night.

4. Quazepam: has a half-life of 8 to 28 hours. It decreases latency; nocturnal awakening and total sleep time. However, it has more residual effect during the daytime than most of the other benzodiazepines.
5. Estazolam: is indicated for short-term treatment of insomnia. It is absorbed well from the GI tract and is capable of crossing the brain-barrier.

Non-Benzodiazepines

These medications have a similar therapeutic action as the benzodiazepines but have a distinct structure. Examples are zolpidem, zaleplon, eszopiclone, zopiclone, and zolpimist. These drugs are helpful in inducing initial sleep, but their effectiveness in maintaining sleep is questionable. In 2014 the FDA recommended that the dose of zolpidem and zolpimist for females be cut in half due to morning drowsiness. Additionally, zolpidem may cause tolerance after nightly use for 5 weeks.

Antihistamines

Diphenhydramine hydrochloride and doxylamine are widely used in non-prescription sleep aids. Their use is due to the drowsiness that they cause. Their action is exerted through the blockage of both the histamine and muscarine receptors. Both are used to manage transient and short-term insomnia. Their effectiveness in the management of chronic insomnia is questionable, as tolerance may develop following repeated use. The adverse effects of antihistamines as sleep aids include next morning hangover, production of anticholinergic effects such as dry mouth, blurred vision, constipation, urinary retention and in elderly patients, cognitive impairment. They are contraindicated in patients with prostate hypertrophy and difficult urination.

Melatonin

Melatonin is a peptide hormone that is secreted by the pineal glands, and is believed to have an effect on the sleep-wake cycles. This hormone is secreted at night, but its precise mechanism of action is not understood. It can influence the shifting of the circadian rhythms, produce sedation, and, as such, is used for sleep disturbances and jet lag. When taken in the morning, it delays the circadian cycle. If taken in the evening, it tends to advance it. It may be needed to assist patients to fall asleep in a shorter time, but has no influence on natural awakening, or total sleep time. It does not cause morning hangover. Patients should exercise caution when using melatonin, as its adverse effects are not fully understood. The optimal dose has not been determined, but it is recommended that a dose of 0.1-1 mg may be taken one to two hours before bedtime.

Tryptophan

Tryptophan is an essential amino acid and precursor of serotonin, a neurotransmitter, and is formed in relatively high concentrations in animal and fish protein. Its efficacy in treating insomnia has not been determined. Results of studies conducted for evaluation of its sedation hypnotic activity are inconclusive. In large doses, it may cause nausea and vomiting. The drug should not be used with serotonin reuptake inhibitors.

DIAGNOSIS

Unlike many disorders, there is no definitive test for diagnosing insomnia. Physical examination, medical and sleep history, and habits can assist in finding the reason of such sleep complaints. Insomnia often is accompanied by psychiatric, sleep or neurological disorders, intake of certain

medications, and pain caused by underlying diseases. However, insomnia can exist without the presence of other disorders due to bad sleep habits, or inappropriate sleep environment. The physician will try to find answers to the aforementioned situations. Ruling out the presence of medical problems may be achieved by conducting a thorough exam.

SUMMARY

Insomnia is a sleep disorder that is characterized by difficulty of falling asleep, maintaining sleep or waking up early in the morning. It is one of the most commonly encountered medical complaints. It has been estimated that 40 million American adults suffer from this disorder and 20 million experience occasional insomnia. Most people encounter trouble sleeping at one time or another. However, if such episodes become frequent, then the causes need to be investigated and proper treatment must be initiated. Sleep deprivation can disrupt a person's daily life; negatively affect energy, emotional stability and general health. Symptoms of insomnia include sleepiness during the day, irritability, tiredness and sleepiness while driving, reading, or watching TV, and difficulty concentrating. Insomnia can be treated non-pharmacologically and pharmacologically. Medications such as the benzodiazepines, non-benzodiazepines, antihistamines, melatonin, and tryptophan together with change in life-style and sleep habits are helpful. There are no definitive tests to diagnose insomnia. However, physical examination, medical and sleep histories may give clues to the causes.

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 - List circumstances that indicate presence of sleep disorders. YES NO
 - Classify sleep disorders. YES NO
 - State causes & diagnosis of insomnia. YES NO
 - Describe treatment of insomnia. YES NO

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3. Relevance of topic 1 2 3 4 5 6 7
4. What did you like most about this lesson? _____
5. What did you like least about this lesson? _____

Please Mark the Correct Answer(s)

1. Which of these is false regarding physiological processes accompanying normal sleep?
 - A. Elevation of body temperature
 - B. Reduction in metabolic rate
 - C. Reduction in glucose consumption membranes with blood & body fluids
 - D. Reduced release of catabolic hormones
2. Timing of sleep clock is believed to be controlled by the:
 - A. Adrenal gland
 - B. Thyroid gland
 - C. Hypothalamus
 - D. Prostaglandins
3. Which of the following is not a sleep disorder?
 - A. Drowsiness during day
 - B. Appearance of being tired
 - C. Lack of concentration
 - D. Tendency to drive fast
4. Which category of sleep disorder results from disruption of the biological clock?
 - A. Circadian rhythm sleep-awake disorder
 - B. Hypersomnia
 - C. Dyssomnia
 - D. Parasomnia
5. Which of the following is not a non-pharmacological therapy in the treatment of insomnia?
 - A. Cognitive-behavioral treatment
 - B. Control therapy
 - C. Diet rich in protein
 - D. Sleep restriction therapy
6. Which of the following is NOT considered sleep hygiene?
 - A. Follow a constant sleep-awake schedule
 - B. Relaxing exercises 3 – 4 hours before bedtime
 - C. Going to bed only when drowsy
 - D. Taking a nap close to bed time
7. Which of these is a non-benzodiazepine?
 - A. Zolpidem
 - B. Temazepam
 - C. Quazepam
 - D. Flurazepam
8. The FDA recommended that the dose of the following drug, used by women, be cut in half.
 - A. Diphenhydramine HCl
 - B. Zolpimist
 - C. Melatonin
 - D. Estazolam
9. Which of these is NOT a side effect of using antihistamines as a sleep aid?
 - A. Next morning hangover
 - B. Constipation
 - C. Euphoria
 - D. Dry mouth
10. Which statement is false about methods to use for diagnosis of insomnia?
 - A. MRI
 - B. Medical history
 - C. Sleep habits
 - D. Family history

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