Sleep Disorders

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Overview of Sleep

What is sleep?

Overview of Sleep

In Greek and Roman mythology, Hypnos was the god of sleep and was believed to sprinkle drops of poppy milk into people’s eyes so that the opium would make them fall asleep. He then fanned them with his wings so that they could sleep in comfort.

Overview of Sleep

Lucretius, an Epicurean poet and philosopher in the Middle Ages went so far as to describe sleep as the “absence of wakefulness.”

Overview of Sleep

In 1917, von Economo published a paper on “Encephalitis Lethargica,” and in 1929, “Sleep as a Problem of Localization.”

Overview of Sleep

He stated that patients who had insomnia had lesions in the anterior portion of the hypothalamus and that patients who had hypersomnia had lesions in the posterior hypothalamus.

Overview of Sleep

He designated this area of the “interbrain,” or hypothalamus, as the “center for regulation of sleep.”

He put to rest the popular concept of his time that sleep cannot be localized.
Overview of Sleep

• In 1926, Papez published a more complete description of the reticular formation and its caudal projections down into the spinal cord in cats.

• In 1928, Hans Berger demonstrated that the brain produces clearly identifiable electrical activity that can be recorded using surface electrodes.

• He showed that a different pattern of electrical activity of the brain exists during consciousness compared with sleep.

Overview of Sleep

• In the 1930s, Frederic Bremer hypothesized that sleep was a passive process, and that wakefulness required a high level of continuous sensory input from the periphery to maintain activity within the cerebral hemispheres.

• In 1949, Moruzzi and Magoun defined the ascending reticular activating system “whose direct stimulation activates or desynchronizes the EEG, replacing high-voltage slow waves with low-voltage fast activity.” They postulated that sleep is an active process.

Overview of Sleep

• They went on to state, “the effect is exerted generally upon the cortex, and is mediated in part by the diffuse thalamic projection system.”

• Thus, they demonstrated that reticular formation stimulation triggers cortical arousal, and that damage to the reticular formation impairs arousal.

Overview of Sleep

• By the middle of the twentieth century, it was established that sleep and wakefulness are different states that are controlled by the brain and that sleep is not a passive period devoid of activity.

• With the discoveries of REM and non-REM sleep by Aserinsky and Kleitman, and REM/non-REM cycling by Dement and Kleitman in the 1950s, the door was wide open for researchers to gain more exact insights into the study of the science of sleep and wakefulness.
What is Sleep?
- Sleep is a complex physiologic state that occurs periodically in most vertebrate species, and is a reversible behavioral state of perceptual disengagement from and unresponsiveness to the environment.
- It is a very complex amalgam of physiological and behavioral processes. It is usually, but not necessarily, accompanied by postural recumbency, quiescence, and closed eyes.

Sleep:
- Allows the central nervous system to repair and restore itself
- Assists with overall energy conservation
- Facilitates the consolidation of memory

Stages of Sleep
- Sleep consists of two distinct states: non-rapid eye movement sleep (non-REM sleep) and rapid eye-movement sleep (REM sleep).
- Non-REM sleep is subdivided into four stages on the basis of relatively distinguishable EEG patterns.
- REM sleep is characterized on a psychological level by dreaming.

On a physiologic level, REM sleep is characterized by:
- Cortical activation
- Bursts of extraocular and middle ear muscle activity
- Variability of heart and respiratory rates
- Actively induced atonia of major muscle groups
- Increased cerebral blood flow.

In short, REM sleep is a very active brain in a paralyzed body.

Polysomnography is the diagnostic test used for sleep studies during which a number of physiologic variables are measured and recorded during sleep. Sensor leads are placed on the patient to record:
- Brain electrical activity
- Eye and jaw muscle movement
- Leg muscle movement
- Airflow
- Respiratory effort in chest and abdominal excursion
- EKG
- Oxygen saturation

EEG activity is recorded from central (C3 or C4) and occipital (O3 or O4) derivations.
- Electro-oculographic (EOG) activity is recorded from the right and left eyes from the outer canthi.
- Jaw muscle movement is measured from the submental lead.
Stages of Sleep
Each 30 seconds of recording is one epoch, and is categorized as wakefulness, stage 1, 2, 3, 4, or REM.

Stage W – or wakefulness
- EEG: predominant alpha activity for more than 50% of the epoch mixed with beta
- Eye movements: slow and rapid
- Muscle activity: High

Stage 1
- EEG: Alpha activity replaced by predominant low-voltage, mixed frequency background activity sometimes with vertex sharp waves
- Eye movements: Slow
- Muscle activity: decreased from awake

Stage 2
- EEG: Sleep spindles and K complexes in a background that has less than 20% delta activity
- Eye movements: none
- Muscle activity: decreased from awake

Stage 3
- EEG: Slow waves, delta activity comprising 20% - 50% of the epoch; sleep spindles are usually present
- Eye movements: none
- Muscle activity: decreased from awake

Stage 4
- EEG: More than 50% of the epoch has delta activity
- Eye movements: none
- Muscle activity: decreased from awake
Stages of Sleep
- REM
- EEG: Low-voltage, mixed-frequency activity and saw-tooth theta waves which may be present
- Eye movements: rapid
- Muscle activity: essentially absent

Sleep Disorders
Dyssomnias are associated with difficulty in initiating and maintaining sleep or excessive sleepiness. They are further classified as intrinsic, extrinsic, and circadian rhythm disorders.

Intrinsic Disorders (etiologic origin originates within the body)
- Obstructive sleep apnea
- Central sleep apnea
- Idiopathic insomnia
- Narcolepsy
- Periodic limb movement disorder
- Restless leg syndrome
- Central alveolar hypoventilation syndrome

Sleep Disorders
- Risk factors include obesity, increased neck circumference, retrognathia, macrognathia, acromegaly, hypothyroidism, neuromuscular disorders, and use of alcohol or sedative medications.

- Signs and symptoms include loud, irregular snoring, day time hypersomnia, awakening unrefreshed, falling asleep during quiet activities, morning headache, difficulty concentrating, irritability, and depression.

Sleep Disorders
Obstructive sleep apnea is a disorder characterized by intermittent nocturnal upper airway occlusion. This occlusion causes loud, irregular snoring, hemoglobin desaturation, and recurrent arousals from sleep.

- It affects 2% of women and 4% of men over the age of 50.
- Decrease in pharyngeal muscle tone seen in all sleeping persons is a major contributor to the symptomatic obstruction. Sedative drugs and alcohol can further decrease muscle tone and worsen the occlusion. Anatomic upper airway narrowing from increased soft tissue mass, retrognathia, macrognathia, and abnormally large tonsils, soft palate, or uvula can further facilitate obstruction.

Sleep Disorders
Overnight polysomnography is the key to a definitive evaluation of sleep and breathing.
Sleep Disorders

- Polysomnography consists of recording EEG, electrooculography, EMG, electrocardiography, pulse oximetry, nasal and oral airflow measurements, and measurement of chest and abdominal wall movement during a night of sleep.
- Polysomnography in a patient with obstructive sleep apnea typically demonstrates repeated apneas (a reduction of airflow of > 80% for at least 10 seconds) and hypopneas (a decrease in airflow for > 10 seconds by more than 50% or a decrease in airflow of < 50% but with an arousal or a 3% desaturation).
- Five or more hypopneas or apneas per hour with some associated symptom of hypersomnolence with polysomnography is diagnostic of obstructive sleep apnea.

Sleep Disorders

- Management of OSA consists of nonsurgical and surgical options. Nonsurgical treatment consists of use of non-invasive positive pressure ventilation and EMAs, or Elastic Mandibular Advancement dental devices. Surgical options include uvulopalatopharyngoplasty and tracheostomy.
- There are 2 main types of delivery of non-invasive positive pressure ventilation:
  - Continuous positive airway pressure (CPAP)
  - Bi-level positive airway pressure (BiPAP)

Sleep Disorders

- CPAP is a machine that has a mask which goes over the nose and possibly the mouth as well.
- It provides increased positive air pressure to help overcome obstructions associated with sleep disordered breathing.

Sleep Disorders

- BiPAP is an advanced version of CPAP
- It uses different air pressures for inhalation and exhalation.
- These machines are typically used when users of CPAP have difficulty breathing against the pressure from the machine.
- It can help reduce stomach bloating due to swallowed air that is sometimes a problem with CPAP.

Sleep Disorders

- Uvulopalatopharyngoplasty as a surgical option for management consists of removal of the uvula, posterior soft palate, and redundant periphergeal tissue. Long term cure rates with this procedure are less than 50%, and many patients ultimately require CPAP or BiPAP.
- Tracheostomy is curative for OSA, but is reserved for patients with very severe OSA who are noncompliant or unresponsive to maximal CPAP.

Sleep Disorders

- Central sleep apnea syndrome is a rare type of apnea that occurs not when the throat is blocked, but when the patient cannot make the effort necessary to pull air into the lungs. It is usually the result of problems in the neurological control of breathing, or with the muscles associated with breathing.
- Idiopathic insomnia is a lifelong inability to get adequate sleep that has no observable cause. It is assumed that this difficulty is due to an abnormality of sleep-wake control systems in the brain. It may also be due to a problem in the sleep-inducing and maintaining systems, or hyperactivity in the arousal systems.
Narcolepsy is a disorder characterized by excessive daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations primarily related to abnormal regulation of REM sleep.

Cataplexy is emotionally induced muscle weakness that is pathognomonic of narcolepsy. It is triggered by emotional expressions such as laughter, anger, or excitement. It is transient partial or complete muscle weakness of part of or the entire body, lasting several seconds to several minutes.

Sleep paralysis is a terrifying experience in which the patient becomes transiently unable to move just before sleep onset or just after awakening. These episodes typically last only a few seconds. It is related to the atonia of REM sleep.

Hypnagogic hallucinations are vivid dreams which are often distressing, that occur at the time of transition from wakefulness to sleep.

Polysomnography should be performed to rule out symptomatic sleep apnea or movement disorders as the cause of excessive daytime sleepiness.

In narcolepsy, it will typically be normal but may show excessive sleep fragmentation.

A Multiple Sleep Latency Test should be performed the next day after the polysomnogram. As with the polysomnogram, EEG, heart rate, muscle activity, and eye movements are monitored and recorded.

The test consists of five opportunities to take a nap each lasting between 10 and 30 minutes. There is a nap every two hours.

Evidence of narcolepsy consists of an abnormal tendency to rapidly fall asleep during the MSLT nap opportunity (within 5 minutes) plus occurrence of two or more episodes of REM sleep during the MSLT naps. Approximately 85% of patients with narcolepsy will have a positive MSLT.

Narcolepsy is a lifelong condition that requires treatment with stimulant medication plus self-management of sleep.

Medications include wakefulness promoting agents such as modafinil or stimulants such as methylphenidate.

Cataplexy can be suppressed by tricyclic antidepressants such as clomipramine, Selective Serotonin Reuptake Inhibitors (SSRIs) such as Paroxetine and Fluoxetine, and Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs) such as Venlafaxine or Duloxetine.

Gamma hydroxybutyrate, or Xyrem, is a controlled substance central nervous system depressant that additionally can be used with good success in cataplexy and excessive daytime sleepiness.

Gamma hydroxybutyrate has significant abuse potential. It is also known as the “Date Rape” drug, and therefore has a potentially high street value.

Before prescribing Xyrem physicians must be enrolled in the Xyrem Patient Success Program, which was initiated by a joint effort between the FDA and Orphan Medical, the manufacturer of Xyrem. This program ensures use of a designated centralized pharmacy, review of educational materials with the physician and patient, enrollment in a post marketing surveillance program, and office visits with the physician at least every 3 months. The first prescription is for a 1 month supply with prescription maximums of a 3 month supply.
Further management of narcolepsy includes regular periods of bed rest and prevention of sleep deprivation with planned naps of limited duration (20 – 30 minutes).

Periodic limb movement disorder occurs when the sleeper periodically moves a limb, usually a leg, in exactly the same way over the course of the night. A typical movement would be a kick or flex of the leg every 10 seconds. These movements disrupt sleep and lead to insomnia and daytime sleepiness. These movements often disturb the partner more than the sleeper.

Restless leg syndrome is characterized by uncomfortable feelings (tingling, itching, crawling, pulling, or achy) in the legs right before falling asleep. These feelings are relieved by moving the legs but return when movement stops. This interferes with falling asleep and can cause severe insomnia. These movements disturb the sleeper more than the partner.

Epidemiology of Restless Leg Disorder

- Age-adjusted prevalence: up to 10% of adults
- Incidence and prevalence increase with age
- Symptom severity increases with age
- Secondary restless leg syndrome occurs frequently in association with peripheral neuropathy, arthritis, vascular insufficiency
- Associated with Parkinson disease, multiple sclerosis

Subjective symptoms of Restless Leg Syndrome

- Creepy, crawly, tingly sensations
- Sensations described as like worms or bugs crawling under the skin
- Painful, burning, or aching
- Sometimes indescribable

Diagnosis of Restless Leg Syndrome

- Intense, irresistible desire to move limbs, usually with uncomfortable feeling in the limbs
- Motor restlessness
- Symptoms are worse or present only at rest; they are alleviated with movement
- Symptoms are worse in evening or at night
- Associated with jerking movements of all limbs

Role of iron in Restless Leg Syndrome

- Low ferritin levels may be associated with RLS and frequently respond to treatment with iron
- 25% - 30% of patients with iron deficiency anemia have RLS

Treatment:

Dopaminergic agonists: Clonazepam, Gabapentin, Pramipexole, Codeine, Levodopa, Opiates

Central alveolar hypoventilation syndrome – during sleep, everyone naturally takes less air into the lungs than when awake.

- If there are problems with gas exchange in the lungs, as in emphysema, there may be problems getting enough oxygen during the night, and sleep is disturbed.
- Because we naturally take in a larger volume of oxygen during the day, there may not be similar problems during the day.
Sleep Disorders
- Extrinsic Disorders (etiology develops from outside the body)
- Insufficient sleep syndrome
- Environmental sleep disorder
- Altitude insomnia
- Adjustment sleep disorder
- Nocturnal eating/drinking syndrome
- Stimulant dependent disorder

Sleep Disorders
- Circadian Rhythm Disorders
- Time zone change syndrome
- Delayed sleep phase syndrome
- Shift work sleep disorder

Sleep Disorders
Parasomnias are motor, behavioral, or autonomic events that occur in a particular relationship to the sleep process, but are not necessarily associated with excessive sleepiness or disrupted sleep. They are further classified as arousal disorders, sleep-wake transition disorders, REM associated disorders, and a miscellaneous group.

Arousal Disorders
- Confusional arousals
- Sleepwalking
- Sleep Terrors

Sleep-Wake Transition Disorders
- Rhythmic movement disorder
- Sleep starts
- Sleep talking
- Nocturnal leg cramps

REM-associated Parasomnias
- Nightmares
- Sleep Paralysis
- REM sleep Behavior Disorder

Other Parasomnias
- Bruxism
- Enuresis
- Infant sleep apnea
- Central hypoventilation
- Sudden infant death syndrome
- Benign neonatal myoclonus
- Sleep related abnormal swallowing syndrome
Sleep Disorders
MEDICAL AND PSYCHIATRIC SLEEP DISORDERS
Sleep Disorders Associated with Medical Conditions
- Alcoholism
- Sleeping Sickness
- Nocturnal cardiac ischemia
- Asthma
- Sleep related gastro-esophageal reflux disease
- Fibromyalgia

Sleep Disorders Associated with Neurological Disorders
- Degenerative brain disorders – Alzheimer’s disease, Pick’s Disease, Parkinson’s Disease, ALS, fatal familial insomnia.
- Sleep related epilepsy
- Sleep related headache

Sleep Disorders
Sleep Disorders Associated with Psychiatric Disorders
- Psychosis
- Mood Disorders
- Anxiety Disorders
- Panic Disorders

We are learning that many of the medical conditions we commonly treat in medicine appear to function on a 24 hour clock. Further research and investigation can have significant implications regarding treatment of these disorders.

A relatively new field of medicine related to sleep is Chronomedicine, or chronobiology. It is the scientific study of biological rhythms and timing mechanisms, sleep-wake cycles, heart rate, and body temperature. It examines time related phenomena in living organisms.

There are a variety of important biological, physiological, and psychological functions that show regular peaks and declines across a 24 hour cycle.

Evaluation
- An in-depth sleep history must be obtained, including a review of the patient’s activities over a 24 hour period.
- Obtain a detailed description of abnormal events that may or may not be disturbing to the patient such as night terrors, respiratory disturbances, seizures, cardiovascular abnormalities, gastrointestinal disturbances, enuresis, etc.
- Interview from other family members/significant others is essential, often providing information of which the patient may not be aware.
Evaluation
• In addition to understanding the primary complaint and the pattern of sleep and wakefulness, the clinician must have a clear knowledge of the patient’s general physical health and the use of medication, drugs, and/or alcohol.
• Psychological testing with the Minnesota Multiphasic Personality Inventory and other psychometric instruments that measure depression and anxiety may be indicated.
• A detailed 2-week sleep log that documents the time of going to bed and estimates the number of hours of sleep as well as the time of awakening should be obtained.

Treatment
Potential treatment options include:
• Comfortable bedding
• Good sleep hygiene
• Continuous positive airway pressure (CPAP or BiPAP)
• Supplemental oxygen
• Medication
• Psychiatric counseling

References

References
Stobo, John; Traill, Thomas; Hellman, David; Ladenson, Paul; Bret, Principles and Practice of Sleep Medicine. 2006.

References
Myegnign C, Poitier J, Degos JD. Amyotrophic Lateral Sclerosis with Respiratory Insufficiency as the Primary Complaint. Eur Neurology 1985; 24: 115 – 120.
References
Barthlen GM. “Nocturnal Respiratory Failure as an Indication of Noninvasive Ventilation in the Patient with Neuromuscular Disease.” Respiration 1997; 64 (supplement): 35 – 38.