**Summary: Normal Sleep Patterns and Sleep Disorders**

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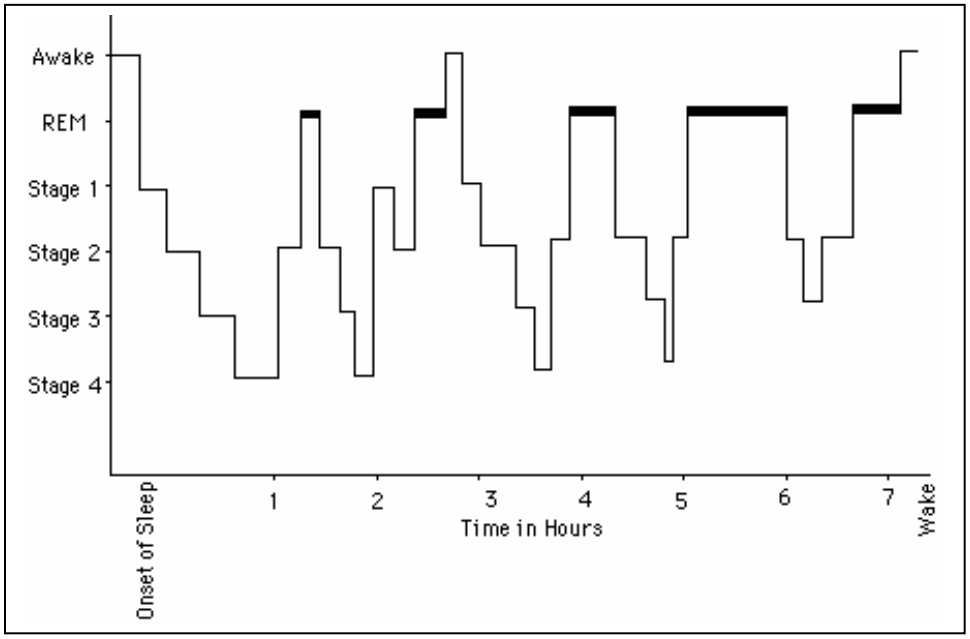
Objectives:
1. Understand characteristics of the normal sleep cycle, including sleep stages, and changes with aging.
2. For sleep disorders, categorize as hypersomnia, insomnia, parasomnia; for each disorder describe major clinical and physiological characteristics, and mechanisms if known.

# NORMAL SLEEP PATTERNS

**Introduction**: In the normal adult there are two main stages of sleep that alternate at about 90-minute intervals. **Rapid eye movement (REM) sleep** can be roughly described as a period when the brain is active and the body is paralyzed (except for eye movements, middle ear ossicles, and respiration). In **non-rapid eye movement (nonREM or NREM) sleep**, the brain is less active but the body can move. Non-REM sleep is composed of four stages that are differentiated on the basis of EEG characteristics. When normal individuals first fall asleep, they enter Stage 1 (sleep drowsiness) and then progress through Stages 2, 3, and 4 of NREM sleep. Stages 3 and 4 (deep sleep) are often called slow wave sleep or delta sleep because they are characterized by high amplitude, slow waves (also called delta waves) on EEG. Slow wave sleep may last from a few minutes to an hour, depending on the person's age, before reversion back to Stage 2 sleep. Shortly after this, the first REM sleep period begins, lasting about 15-20 minutes and is followed by another non-REM cycle. This alternating pattern continues throughout the night, but as the night progresses Stages 3 and 4 are less apparent and the periods of REM sleep grow longer. See graph below for an illustration of the time course. By the criterion of external arousability, REM is the deepest stage of sleep, but by the criterion of internal arousability, REM is the lightest stage of sleep, since a person is more likely to awaken spontaneously from REM sleep than from any other stage.

**COMPARISON OF WAKEFULNESS, NON-REM AND REM SLEEP**

| Category | EEG characteristics | Eye movements | Muscle tone (EMG) |
|---|---|---|---|
| Waking | Low voltage, fast | Normal tracking | Present |
| Non-REM sleep | High voltage, slow (EEG synchronization) | Absent | Variable; generally reduced |
| REM sleep | Low voltage, fast | Specific pattern of rapid eye movements | Absent (except ocular muscles) |




The chart shows a typical night's pattern of sleep in a normal young adult. The time spent in REM sleep is indicated by a **black bar**. The first REM period is usually short. The amount of stage 2 slow wave sleep increases during the night.

**Development patterns and changes with aging**: One of the most significant determinants of a person's normal sleep pattern is age. REM sleep occupies about 20-25% of the sleep time in normal young adults. In humans the daily total sleep requirement declines steadily throughout childhood and adolescence, levels off during the middle years, and then often declines further with old age. The need for REM sleep begins *in utero*. REM sleep fills approximately 80% of the total sleep time of infants born 10 weeks prematurely. In full-term neonates, REM sleep fills 50% of the sleep time. REM sleep declines sharply to about 30-35% of sleep time by age 2 and stabilizes at about 25% by 10 years of age. After that it shows little change until about age 65, when it further declines. The amount of stage 4 slow-wave sleep declines with age and in many people is nearly absent by age 70. As a consequence, older people spend proportionately more time in the lighter stages of slow-wave sleep, from which they awaken more often. Most adults in our culture learn to sleep in one extended period at night. However, the circadian rhythm of sleepiness is actually biphasic and normal afternoon drowsiness is more pronounced in the elderly.


**The human sleep pattern changes with age.**

**Function of REM sleep**: Most dreams occur during REM sleep. Deprivation of REM does not lead to serious psychological disturbance, as was once thought. The most important effect of REM deprivation is a dramatic shift in subsequent sleep patterns when the subject is allowed to sleep without interruption. The longer the deprivation, the larger and longer the REM rebound, suggesting that REM sleep is physiologically necessary. However, the purpose of REM sleep or dreaming remains largely unexplained.

There is activation of sensory systems during REM sleep. The visual system, particularly the superior colliculus circuit, is intensely activated, and all dreams have visual experiences. Neuroimaging studies of humans have also indicated activation of the limbic system, suggesting a biologic basis of activation of memories and emotions in REM sleep. Thus, the visual cortices and limbic areas to which they project may be operating as a closed system, functionally disconnected from frontal regions in which the highest order integration of visual information takes place. Such "cortical dysynchony" could explain many of the experiential features of dreams, including heightened emotionality, uncritical acceptance of bizarre dream content, a dearth of parallel thoughts or images, temporal disorientation, and the absence of reflective awareness. Studies in animals indicated that those neurons that had been active during the day in encoding spatial position fired at a significantly higher rate in REM sleep than inactive neurons, suggesting that a general function of REM sleep is "off-line" processing of information acquired during the day. The atonia noted in REM sleep is under the control of the magnocellular nucleus of the medulla; this phenomenon is maintained via the reticulospinal tract which mediates inhibition of motor neurons.

**Neural mechanisms involved in the sleep-wake cycle**: The body's sleep-wake cycle is usually under the control of circadian rhythms. These rhythms are regulated by the

suprachiasmatic nucleus (SCN) of the hypothalamus. Incoming light which is transduced by retinal ganglion cells (melanopsin) is believed to be the primary factor synchronizing circadian rhythms. Several studies have found this process to occur via NMDA. Serotonin acts as a modulatory neurotransmitter; serotonergic input from the dorsal raphe nucleus in the midbrain periaqueductal gray area will act to inhibit the effects of light on the system and is associated with different aspects of the sleep wake cycle. There is minimal serotonergic input during REM sleep, and maximal input directly following REM. Thus these neurons may normally inhibit phasic REM events and their silence during REM sleep indicates a termination of this inhibition. In contrast, many potential sleep-promoting factors have been identified, including muramyl peptides (found in bacterial cell walls), lipopolysaccharides, prostaglandins, interleukin-1, interferon-alpha2, tumor necrosis factor, delta sleep-inducing peptide, and vasoactive intestinal peptide.. Besides enhancing sleep, all also exert effects on body temperature and on the immune response. One ancillary function of the sleep state may be to optimize the processes that counter infections.

In the past few years it has been established that the cholinergic activating system, through projections to the thalamus, is important in EEG desynchronization characteristic of waking and REM sleep. REM-on neurons (selective activity during REM sleep) in the brainstem use ACh as a neurotransmitter. Activity in this group of neurons recruits activity in effector neurons for REM sleep phenomena. Most of the physiologic events of REM sleep have effector neurons location in the brainstem reticular formation, e.g. the pontine reticular formation (PRF). These neurons are important for the rapid eye movements (i.e. generator for saccades is in PRF), and the muscle atonia of REM sleep. Many peptides (e.g. substance P) are co-localized with ACh in brainstem neurons; they may modify responsiveness to ACh and may have independent actions. In addition, histamine-containing neurons are located in the posterior hypothalamus and are REM-off. The histamine system has been conceptualized as one of the wakefulness-promoting systems, in agreement with drowsiness as a common side effect of antihistamines. Orexin, a hypocretin that has been previously associated with feeding behaviors, has also been found to have a role is sleep behavior. Many areas of the brain associated with the sleep-wake cycle, specifically the lateral and dorsal hypothalamus, have orexin neurons and receptors. Orexin A has been found to activate NE neurons in the locus coeruleus, which are believed to play a role in promoting wakefulness.

## SLEEP DISORDERS

**General concepts**. About 15% of people living in industrialized countries have serious or chronic sleep problems. Basically there are three kinds of complaints regarding sleep:

- trouble staying awake (**hypersomnia**),
- trouble sleeping (**insomnia**), and
- abnormal sensations or behavior during sleep (**parasomnias**).

These complaints often go together, e.g. people who have trouble sleeping may fail to get an adequate amount of normal sleep and have difficulty staying awake the following day. Trouble staying awake and trouble sleeping may be referred to together as **dyssomnias.** Insomnia and hypersomnia may be symptoms in mood disorders, particularly depression. The most common disorders are (1) obstructive sleep apnea, (2) insomnia, (3) restless legs syndrome, (4) narcolepsy and idiopathic hypersomnia.

**Diagnostic testing**: Two types of sleep studies are used to supplement the clinical diagnosis of sleep disorders. A polysomnogram is an all-night recording of eye movements, EEG, EKG, EMG, ear oximetry, airflow at the nose and mouth, and thoracic and abdominal wall

motion. A multiple sleep latency test (MSLT) is a measure of daytime sleepiness. The time needed to fall asleep for brief naps during the day is measured.

## I. HYPERSOMNIAS (Trouble staying awake – excessive daytime sleepiness)

The most common causes of hypersomnia are insufficient sleep, medications, sleep apnea (central or obstructive), and narcolepsy. Patients may not complain of sleepiness so much as its consequences, including fatigue, headaches, decreased energy, difficulty concentrating, irritability, or an auto accident ("falling asleep at the wheel").

**A. Insufficient sleep –** Many people do not schedule sufficient time for sleep at night, and sleepiness is to be expected in the setting of sleep deprivation. This is managed by education the patient about healthy sleep habits.

**B. Sleep apnea**: Sleep apnea is a condition in which patients periodically stop breathing while asleep. There are two types of sleep apnea- central and obstructive. The most common cause of sleep apnea is due to temporary obstruction of the upper airway. The extreme changes in the concentrations of oxygen and carbon dioxide in the blood that develop after 1 minute or more without air rouse the sleeper, and a few noisy, choking gasps refill the lungs. Obstructive sleep apnea is the most common medical cause of excessive daytime somnolence. Of major importance to the diagnosis is a history of apneic episodes during sleep. Usually the patients are not aware of the episodes because they are brief and arousal is only partial, so the history must be obtained indirectly, typically from a spouse or roommate. Symptoms/signs that are common include loud snoring and pauses in breathing. Additional symptoms include gasping for breath during sleep, dull headaches, and automatic behaviors. Polysomnography is used to confirm the diagnosis and to quantify the severity. The most effective treatment of obstructive sleep apnea (beneficial in over 90% of cases) is nasal continuous positive airway pressure (nasal CPAP), which raises the pressure in the oropharynx, and thus in the upper airway, reversing the pressure gradient across the wall of the airway and propping it open.

**C. Narcolepsy**: Narcolepsy is a syndrome consisting of excessive daytime sleepiness and disordered regulation of REM sleep, resulting in intrusion of components of REM sleep into NREM sleep and the waking state.

1. For the **narcolepsy-cataplexy subtype**, the two most significant and consistent symptoms are **excessive daytime somnolence** and **cataplexy** (sudden loss of postural tone that occurs while the patient is awake but is otherwise identical to the atonia that occurs during REM sleep). The principal symptom is irresistible sleep attacks lasting 5-30 minutes during the day. These attacks may occur without warning and at inappropriate times, typically precipitated by strong emotion, especially laughter. The sleepiness that occurs in narcolepsy cannot be relieved by any amount of normal sleep. The atonia may involve only a single muscle group, or it may be generalized and lead to collapse; consciousness is preserved. Narcolepsy-cataplexy typically starts around adolescence; daytime sleepiness is most often the first symptom to appear, followed by cataplexy. **Sleep study results:** A period of REM sleep that occurs in the first 15 minutes of sleep is referred to as a **sleep-onset REM** period, and these are diagnostic for narcolepsy. **Pathogenesis**: Both genetic predisposition and environmental triggers are involved. There is an association between major histocompatibility complex (MHC) genes and narcolepsy-cataplexy, which is hypothesized to be an autoimmune disorder.

Hypocretin deficiency (demonstrated by low CSF hypocretin-1 levels) is the cause of most narcolepsy-cataplexy cases in animals and humans. Autopsy studies have shown a selective loss of posterior hypothalamic neurons that produce the neuropeptide hypocretin (orexin). (Hypocretins (orexins) are synthesized in the hypothalamus with widespread projections, especially to brainstem nuclei containing norepinephrine, histamine, serotonin and dopamine neurons. Hypocretin neurons integrate metabolic and sleep- and wake-related inputs. ) Additional models hypothesize hyperactivity in the cholinergic system with hypoactivity in the catecholaminergic system.

2. **Narcolepsy without cataplexy** is defined as excessive daytime sleepiness and multiple sleep-onset REM periods (SOREMPs) on the MLST.

D. **Idiopathic hypersomnia** disorders are poorly defined conditions characterized by excessive daytime sleepiness and not diagnosed as narcolepsy (no REM abnormalities during the MSLT).

**II. INSOMNIA (Trouble sleeping)**: Many different physiological and psychological factors can interfere with sleep. The objective in patient evaluation is to identify the contributing factors and treat those for which therapy is available. Patients with primary insomnia have been shown to have less diurnal sleepiness, higher heart rates, higher core body temperature, and greater metabolic activity than age and gender matched controls. The most severe case of primary insomnia has an insidious onset during childhood and follows a chronic course. It is useful to identify three main patterns of insomnia: sleep-onset delay (trouble falling asleep), early morning arousal (trouble staying asleep), and sleep fragmentation (repeated awakenings). Only one type of sleep-onset delay is described below.

**A. Sleep-Onset Delay** due to psychophysiologic insomnia: This may be due to anxiety related to life stressors or to depression. Any conditions associated with physical discomfort can also contribute.

**B. Restless legs syndrome**: Restless legs syndrome (RLS) is a sensorimotor disorder often severely affecting sleep, characterized by a **strong urge to move the legs** accompanied by a strange feeling in the leg; episodes are precipitated by rest with inactivity and the episodes and **worse in the evening or night** than in the morning. The **periodic leg movements** (PLM) may occur during sleep (PLMS) and/or while lying or sitting up awake (PLMW). RLS involves a disorder of the transition states between wake and sleep. Although RLS produces chronic loss of sleep, there is no profound frank sleepiness in the daytime. RLS patients report fatigue and trouble concentrating during the day, but do not fall asleep and appear to be overstimulated in the daytime.

Early-onset RLS (starting before age 45) appears to result mostly from a pervasive iron metabolism abnormality producing brain iron insufficiency. The **impaired iron status** produces a hyperdopaminergic state with an exaggerated circadian pattern of DA release. The iron deficiency probably also disrupts other neurotransmitter systems, such as hypocretin (orexin) and histamine. Late-onset RLS (starting after age 45) has more diverse causes, but patients appear to have DA abnormalities similar to those in early-onset RLS cases. RLS etiology appears to have both a genetic and a strong environmental component, with the genetic component more import for early- than for late-onset RLS.

The pathogenesis probably involves **abnormalities in subcortical CNS dopaminergic systems,** with DA receptor dysfunction and increased DA production. Dopaminergic agonists and levodopa provide effective treatment for RLS. The pathophysiology may involve iron

deficiency leading to brain DA abnormalities. Also there is evidence for involvement of hypocretin-1 (orexin-A) and histamine.

**III. PARASOMNIAS – Abnormal Behavior during Sleep –** Most undesirable movements or behaviors that occur during sleep are associated with NREM sleep, probably because the atonia of REM sleep prevents most movements of any kind.

**A. NREM Sleep Parasomnias -** Common examples of NREM sleep parasomnias include **night terrors** and **sleepwalking (somnambulism).** These are relatively common in children, but they rarely lead to medical attention unless they are frequent and intense. In most cases, they resolve by late adolescence. The examples may represent a disorder of arousal from slow wave sleep resulting in episodes of only partial awakening.

1. **Night terrors (Sleep Terror Disorder):** Night terrors are a sudden, partial arousal from delta sleep associated with screaming and frantic motor activity. These episodes occur during the first third of the major sleep episode and begin with a terrifying scream followed by intense anxiety and signs of autonomic hyperarousal. Persons with night terrors may not fully awaken after an episode and usually have no detailed recall of the event the following morning. There is believed to be a genetic component to this phenomenon.

2. **Sleepwalking (Somnambulism):** Sleepwalking is considered a disorder of impaired arousal. Sleepwalking is defined as repeated episodes of arising from sleep and walking about. It usually occurs during the first third of the sleep episode. Upon awakening, the person has amnesia for the episode. Episodes typically last less than 10 minutes.

**B. REM Sleep Parasomnias**

**1. REM sleep behavior disorder (RBD)**: In this condition, the atonia that normally accompanies REM sleep breaks down and patients "act out" parts of dreams. This is a motor, behavioral and experiential disorder typically affecting middle-aged or older males. The vigorous and violent behaviors of RBD commonly result in injury. The core EMG abnormalities of RBD include intermittent loss of the usual skeletal muscle atonia of REM sleep, with increased muscle tone and/or excessive phasic muscle twitching. RBD can be an acute or chronic disorder. Acute RBD found in drug withdrawal or intoxication states is generally a reversible condition. Chronic RBD requires ongoing pharmacotherapy, and is commonly associated with many other conditions, especially synucleinopathies (Parkinson disease, dementia with Lewy bodies, and multiple system atrophy). The only published autopsy case involved an 84-year-old man with Lewy body disease, and marked decrease of pigmented neurons in the locus coeruleus and substantia nigra. A close association of RBD with narcolepsy-cataplexy has also been described, and there are patients with overlapping parasomnias, demonstrating motor-behavioral dyscontrol extending across NREM and REM sleep. The probable cause of RBD is pontine tegmental lesions, involving serotonergic, monoaminergic and cholinergic neurotransmission. It is thought that the emergence of RBD results from lesion localization related to any underlying neurological disorder, explaining how an array of etiologically different CNS disorders could trigger RBD.

**2. Nightmare disorder (Dream Anxiety):** This condition consists of repeated awakenings with detailed recall of extended and very frightening dreams. The awakenings are more frequent in the second half of the sleep period. On awakening, the person rapidly becomes alert and oriented.

**Comorbidity with Psychiatric Disorders:**
Sleep and psychiatric disorders are highly comorbid with the highest rates being with anxiety and depression. Studies suggest that the presence of a sleep disturbance may delay recovery from depression. Many antidepressant medications, particularly SSRI's have been found to improve sleep disturbances in addition to relieving depressive symptoms.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**Practice questions**

1. Which of the following changes in sleep patterns occurs between the ages of 20 and 90?

A. The number of afternoon naps decreases
B. The amount of stage 4 slow-wave sleep increases
C. The total sleep time per day increases markedly
D. The percentage of REM sleep decreases

2. Mary Smith, a 5-year-old girl, is seen by her pediatrician. The night before, her parents were awakened at 2:00 am by her screams. Mary was agitated, sweating profusely, and breathing rapidly, and her pulse was racing. She returned to normal over the next 20 minutes, and went back to sleep. This episode would be classified as:

A. REM sleep parasomnia
B. NREM sleep parasomnia
C. hypersomnia
D. insomnia

3. A 34-year-old male presents with a history of being very sleepy several times during the day and having "sleep attacks" (usually five to ten minutes long with loss of muscle tone), and occasional short episodes of bilateral loss of muscle tone. Which of the following would be most likely on sleep testing?

A. the patient has a sleep-onset REM cycle
B. muscle atonia does not occur during REM sleep
C. the patient shows only stage 4 sleep
D. the patient has frequent apneic episodes during sleep

4. A 58-year-old woman started having strong urges to move her legs when she was watching TV or reading in the evenings. This continued for several years. She also noted strange feelings in her legs during these evening periods. She did not have the same urges in the mornings. She reported not sleeping well, and her husband said she moved her legs a lot during the night. She did not fall asleep during the day. Abnormalities in which of the following are most likely involved in this condition?

A. brainstem cholinergic systems
B. cortical noradrenergic systems
C. subcortical dopamine systems
D. cortical GABA systems

5. A 62-year-old man had vigorous behaviors during sleep and he hit his wife during one of the episodes. The following year he was diagnosed with Parkinson's disease. A lesion in which of the following would be most likely as the cause of his sleep disorder?

A. globus pallidus
B. pontine tegmentum
C. putamen
D. inferior olive

6. Which of the following is characteristic of normal REM sleep?

A. high voltage, slow EEG pattern
B. paralysis of ocular muscles
C. muscle atonia in limbs
D. occurs immediately after the first episode of Stage 1 sleep

ANSWERS
1. D
2. B
3. A
4. C
5. B
6. C