SLEEP DISORDERS

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Sleep cycle

- Circadian rhythms are endogenous; can persist without environmental clues.
- Circadian and arousal neurons (OFF midget ganglion cells) react to blue light, regulate slow biochemical processes
- May also induce rapid phototransduction.
- Cryptochromes enable animals and humans to synchronize their circadian clocks by absorbing blue light and transferring the light signal through the optic nerve to a different part of the brain from the center for vision.
- They are linked to Vitamin B2 and are found in a different part of the retina than is rhodopsin.

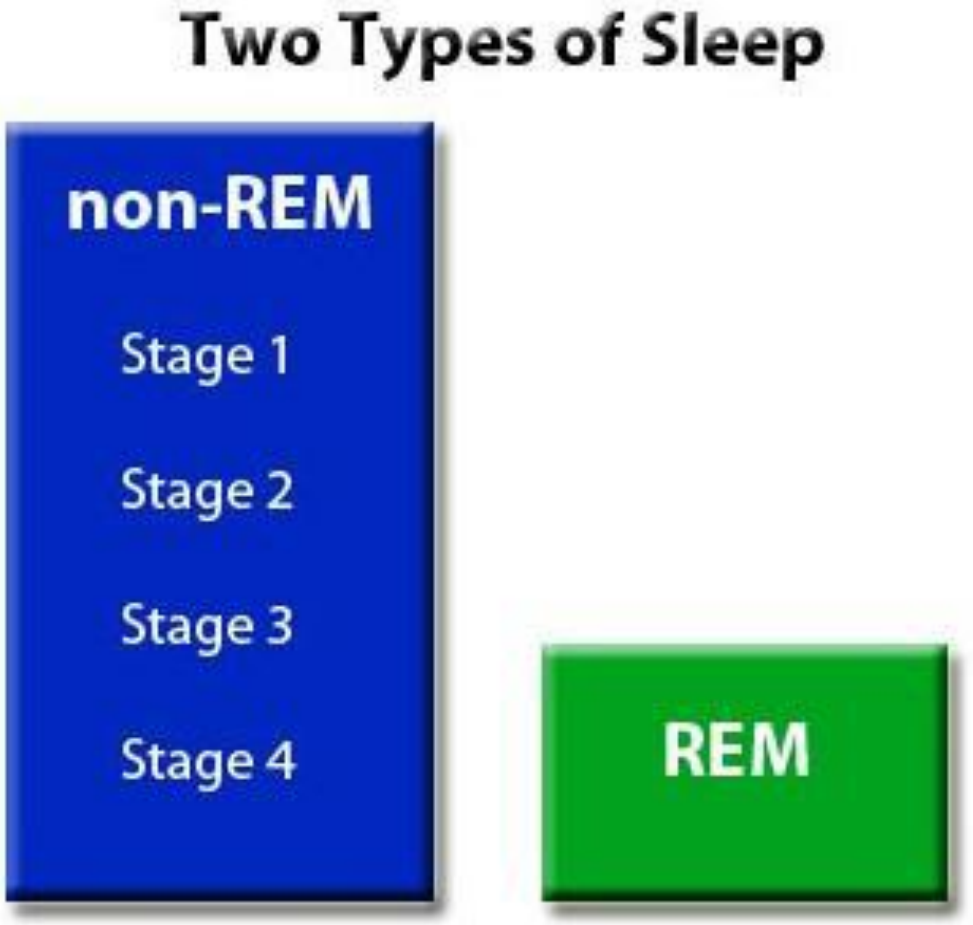
Sleep cycle

- Cryptochromes dimerize, activate CLOCK (4q12) transcription.
- One of the domains of the CLOCK protein is also shared with PER protein.
- PER and TIM gene products shuttle between cytoplasm and nucleus, regulating target gene expression.
- PER and TIM are transcribed in the morning; their mRNAs accumulate.
- TIM protein degraded by light.
- PER cannot accumulate until sufficient TIM is present to bind PER.

Sleep cycle

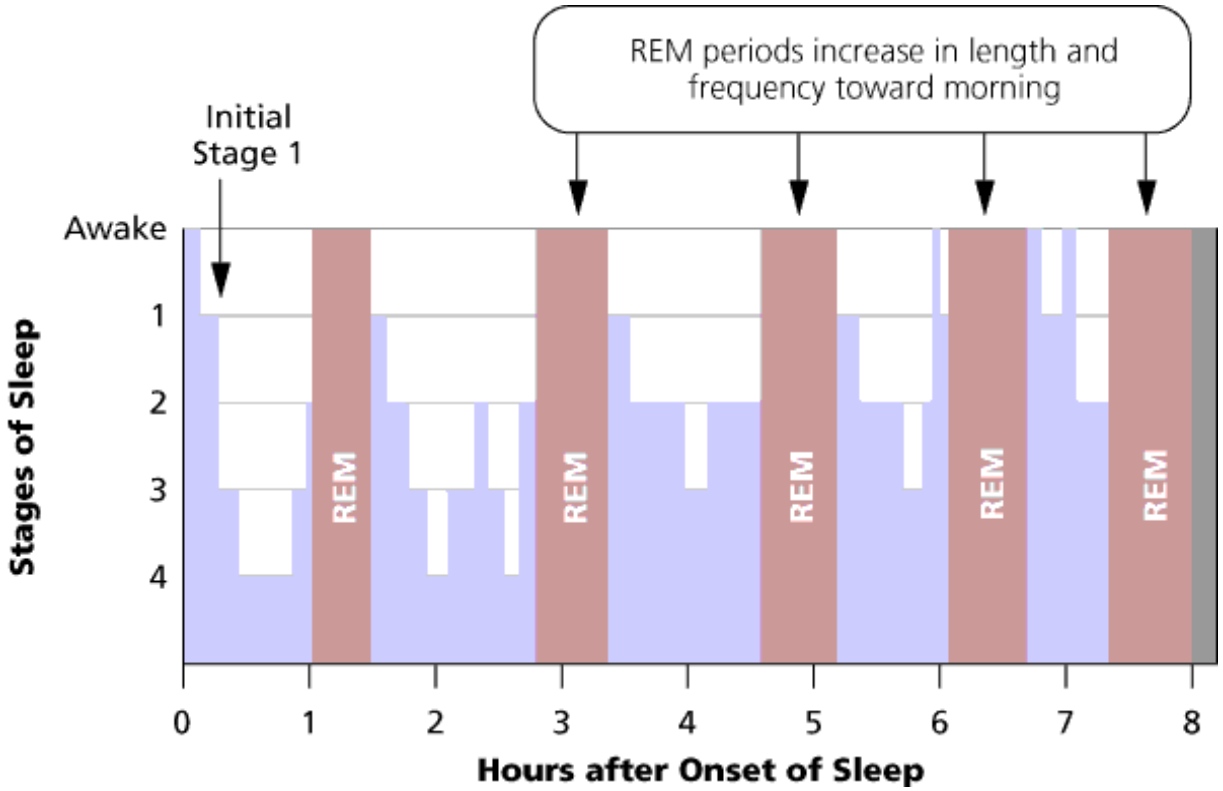
- With dusk, TIM degradation decreases and TIM-PER complexes form, become functional, and enter the nucleus to repress gene transcription.

Stage 1 (now N1):
Highly relaxed (hypnagogic)
Stage 2 (now N2):
Rapid busts of activity
Stage 3 (with Stage 4 are now N3):
Slow wave sleep + bursts of fast activity
Stage 4:
Delta waves



Types of sleep

- NREM sleep
- Maintain muscle tone
- Absence of eye movements
- Absence of thoughts
- Slow EEG cycles
- REM sleep
- Loss of muscle tone
- Eye movements and dreaming
- Sexual arousal
- Rapid EEG cycles (sawtooth pattern)


REM periods increase in length and frequency toward morning
Initial Stage 1
Awake
1
2
3
4
Stages of Sleep
REM
REM
REM
REM
REM
0
1
2
3
4
5
6
7
8
Hours after Onset of Sleep

NREM EEG patterns

- α-waves
- Relaxation with eyes closed
- β-waves
- Active mental concentration
- θ-waves
- Lightest stage of sleep (N1)
- Sleep spindle and K-complex
- Largest amount of time spent in sleep (N2)
- Bruxism common
- δ-waves
- Deepest stage of sleep (N3)
- Slow waves
- Sleep disorders such as somnambulism and enuresis

Sleep cycle

- Posterior hypothalamus
- Arousal
- Histaminergic neuron mediation
- Orexin

Sleep cycle

- Anterior hypothalamus
- Suprachiasmatic nucleus of the anterior hypothalamus receives input via the retino-hypothalamic tract
- Light entrains rhythm, affects timing.
- GABAminergic neurons are the non-REM-on cells
- Inhibit histaminergic neurons in posterior hypothalamus as well as nucleus reticularis pontis oralis in the midbrain
- Many activated by heat
- Off during waking and REM-sleep.

Sleep cycle

- EEG changes of synchronized postsynaptic potentials generated to rhythmic firing of thalamic relay neurons is a result of GABAminergic inhibitory neurons in the nucleus reticularis that serves as a shell around the thalamus hyperpolarizing thalamocortical neurons
- Results in a rebound low-threshold Ca^{2+} spike in the thalamocortical cells.
- Rhythmic firing occludes transmission of sensory information through the thalamus and cortex.

Sleep cycle

- Nucleus reticularis pontis oralis extends from rostral pons to midbrain
- REM-waking-on cells project to spinal cord and extra-ocular muscles
- Waking and REM-sleep associated with cholinergic cell activity
- Depolarize GABAminergic inhibitory neurons in the nucleus reticularis
- Asynchronous firing.

Sleep cycle

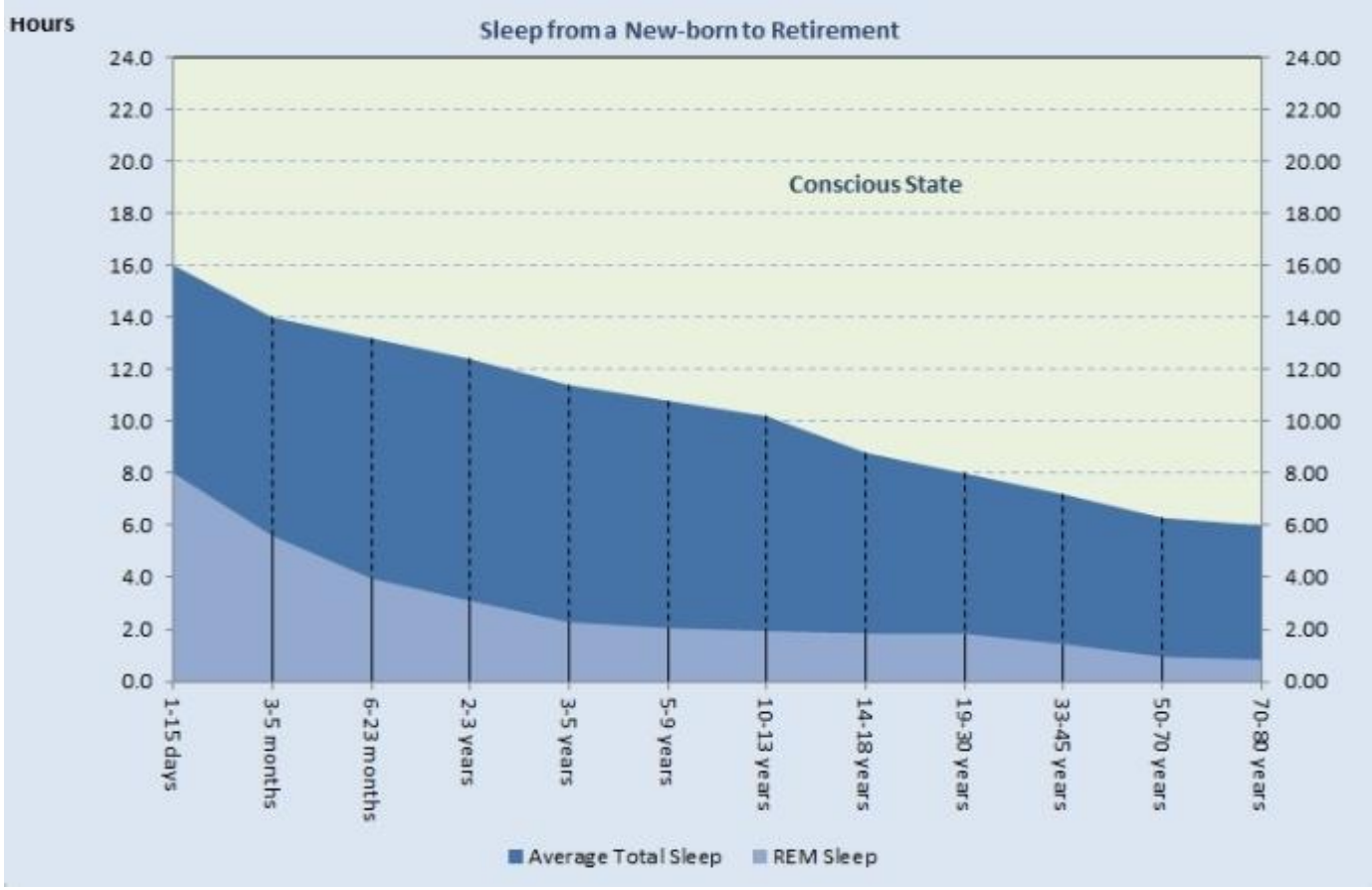
- REM-on cells are GABAminergic
- Inhibit serotonergic and adrenergic activity during sleep
- REM-on cells may be glutaminergic
- Responsible for loss of muscle tone.
- Both are found in the nucleus reticularis pontis oralis.

Sleep cycle

- PGO-on cells fire in bursts to initiate spikes in cells of lateral geniculate nucleus (cholinergic) and are related to rapid eye movements but are not necessary for REM sleep.
- PGO-off cells are serotonergic, in dorsal raphe nucleus.

Sleep Measure	Normal Young Adult	Normal Elderly Adult	Depressed Young Adult
Sleep latency	About 10 min	>10 min	>10 min
REM latency	About 90 min	About 90 min	About 45 min
Sleep efficiency	About 100%	<100%	<100%
Percentage delta	About 25%	<25%	<25%
Percentage REM	About 25%	<25%	>25%

Age	Number of Sleep Periods /24 Hours
Neonate	6–9
1–2 y	2–3
5–10 y	1



Effects on sleep

- Sympathetic activity:
- Broadly decreases as NREM deepens
- But rises compared to wakefulness during REM sleep
- Renal flow reduced but filtering enhanced
- Growth hormone secreted after sleep onset
- Maximal thyroid secretion about midnight
- Melatonin increases in late evening

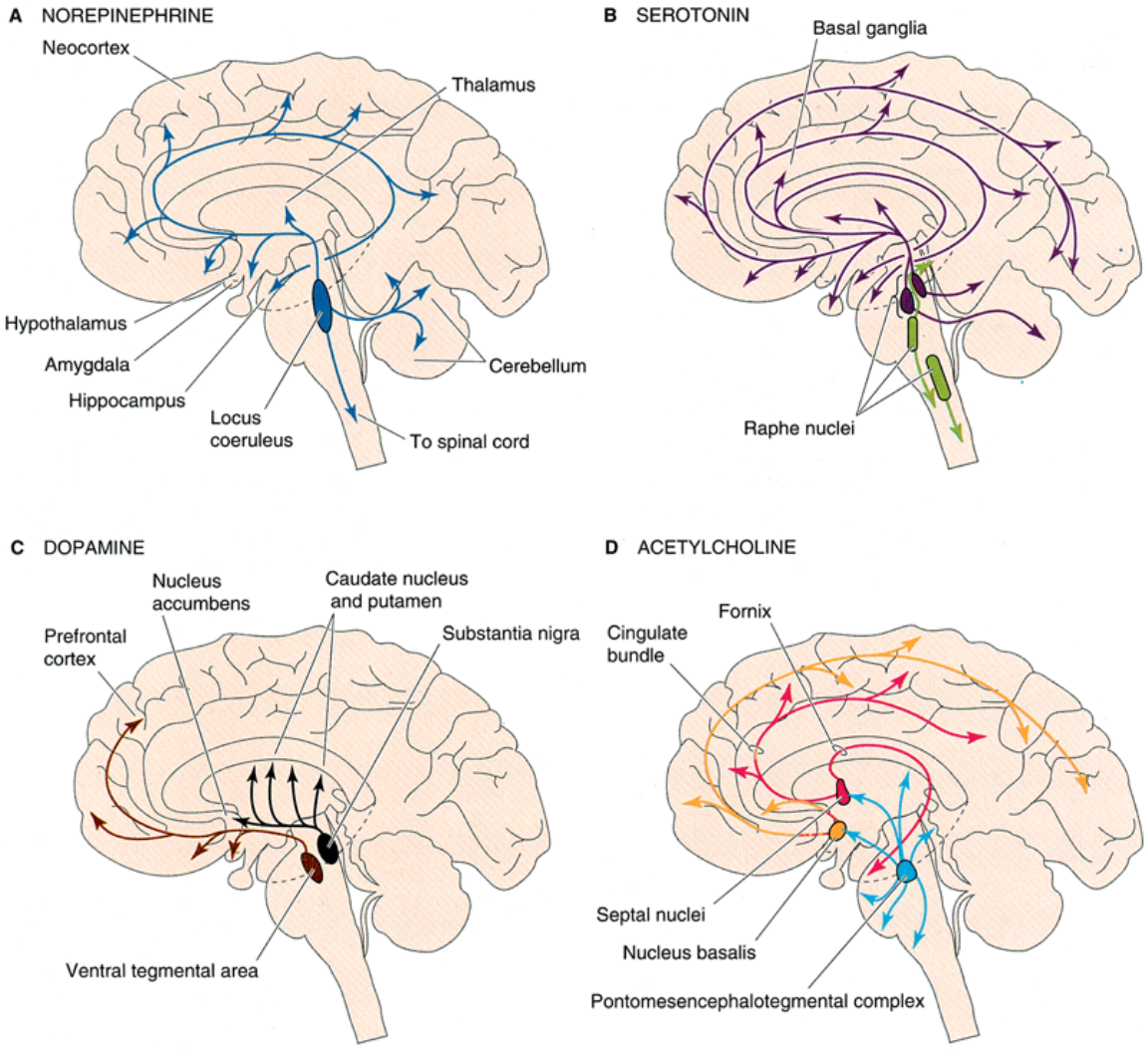
Effects on sleep

- Respiratory flow is less adaptive during sleep
- Response to hypoxia lower in NREM sleep (further still in REM)
- Arousal to respiratory resistance is lowest in N3
- Cough reflex suppressed during REM and NREM sleep
- Reduced cerebral blood flow and metabolism in NREM
- REM sleep:
- Comparable to wakefulness
- Increased activity in limbic system, visual association areas, hippocampus, and anterior cingulate gyrus

Effects on sleep

- Depression:
- Increases REM but decreases REM latency by 50%
- Decreases N3
- Sleep deprivation can remit symptoms in 60% of patients
- Amount of REM sleep predicts onset of depression
- Alcohol:
- Moderate amounts evoke short sleep latency, but waking later
- Intoxication eliminates REM, but increases REM rebound
- Benzodiazepines:
- Mild decrease in REM and N2 sleep
- Over time tends to increase sleep latency

Neurotransmitters and pathways



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

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Acetylcholine

- Acetylcholine projections originate principally in the ventral tegmentum
- Project to the hypothalamus, thalamus, amygdala, hippocampus, basal forebrain, and the pre-frontal cortex.
- Regulate arousal, cognition, and memory, among other functions.
- REM promoting cholinergic pedunculopontine and lateral dorsal tegmental nuclei are counterbalance to the waking serotonergic dorsal raphé and the noradrenergic loci ceruleus nuclei (whose firing is related to state of attention).

Cholinergic cell groups

- Cholinergic cell groups in the basal forebrain include the medial septum, diagonal band, and the nucleus basalis of Meynert.
- These topographicaly innervate the entire cerebral cortex and hippocampus and amygdala.
- Pontine cholnergic cell groups innervate the brain stem reticular formation as well as the thalamus.
- The pedunculopointine nucleus is located ventrolaterally near the superior cerebellar peduncle
- Controls firing of glycinergic neurons in the lateral reticulospinal pathway.

Cholinergic cell groups

- The laterodorsal tegmental nucleus is a component of the periaqueductal gray matter just rostral to the locus ceruleus.
- VIP, substance P are neurotransmitters also found in cholinergic ganglia.

Sensory phenomena

- REM sleep is associated with pontogeniculate orbital activity (visual effects) and cortical activation coupled with atonia.
- Serotonin inhibits REM activity.
- Autoscopy (out of body activity) is related to dorsal prefrontal and temporal lobes.
- The ventrolateral periaqueductal gray is the switch between REM and awake states.

Sensory phenomena

- Hypoxia and hypotension turn off locus ceruleus activity (serotonin)
- Lead to a cholinergic response.
- Recall that 85% of vagal efferents are in the neck
- May be a protective response of inactivity (healing).
- Norepinephrine stimulates melatonin secretion.

Fatigue

- Up to 75% of patients with fatigue have psychiatric symptoms.
- Sleep disorders are very common in patients with fatigue.
- Daytime sleepiness is a common finding.
- Anemia, diabetes mellitus, and hypothyroidism may underly the symptomatology.

Sleep deprivation

- Cerebrum most affected by sleep deprivation
- Biggest effect on complex cognition, learning, memory
- Decreases attention
- Children have sleep talking (mumbling or even conversations while asleep)
- Loss of REM sleep only:
- REM sleep increases
- REM rebound up to 50%
- REM latency decreases

Sleep deprivation

- Long term sleep deprivation:
- Lymphocyte levels decline
- Blood pressure rises
- Hormone receptor upregulation
- Cortisol levels rise
- Glucose tolerance is reduced
- Greater amygdala activation
- Increased negative mood
- Lower prefrontal cortical activity
- Sleep recovery after loss of all sleep:
- Delta wave sleep increases as much as 80%
- May be at the expense of REM sleep as well

Insomnia

- Primary insomnia represents a state of hyper-arousal.
- Persistent if arises in childhood
- Psychophysiologic if maladaptive response
- May be precipitated by stressful event leading (secondary) insomnia
- Persists after the precipitating event resolves
- Paradoxical if patient perception of sleep does not match objective findings on polysomnography.

Insomnia

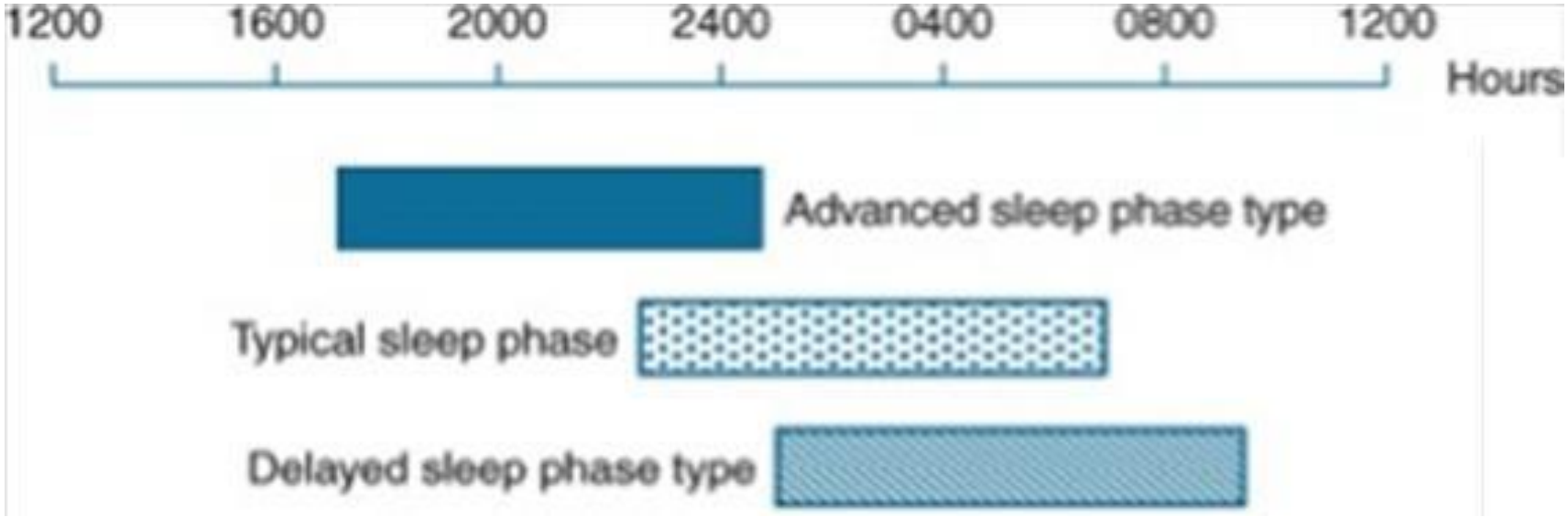
- Sleep onset insomnia
- Initial, early insomnia
- Sleep maintenance insomnia
- Middle insomnia
- Problem staying asleep
- Late insomnia
- Early awakening
- Difficulty returning to sleep

Insomnia

- Secondary insomnia may be associated with active stressors, inadequate sleep hygiene, drug use, a chronic medical condition, or active psychiatric illness
- Shift work disorder (seen in those whose work shift varies) may present as insomnia.

Insomnia

- Delayed sleep phase syndrome is a delay in sleep period of >2 hours compared to usual findings should also be considered in patients with insomnia.
- Excessive daytime sleepiness (hypersomnia)
- Increased N3 sleep pattern
- May drift between wake state and N1 up to 4 hours after waking


1200
1600
2000
2400
0400
0800
1200
Hours
Advanced sleep phase type
Typical sleep phase
Delayed sleep phase type

Insomnia

- Cataplexy
- Muscular weakness triggered by strong emotions
- Weakening of facial muscles to total collapse
- Fully conscious
- Low levels of orexin

Insomnia

- Narcolepsy
- Sudden sleep attacks (REM)
- Associated with ESD
- Sleep more poorly than normal
- Enter REM sleep rapidly
- Low levels of orexin
- 60% may have sleep paralysis
- Conscious but atonic
- May be associated with hallucinations
- Frequently after arousal from REM sleep

Other sleep disorders

- REM sleep disorder
- Lack of paralysis during REM sleep
- Acting out dreams
- >60 years of age
- Nightmare disorders
- Function of REM sleep

Other sleep disorders

- Somnambulism
- Usually in children
- “Glazed look”
- N3
- May be associated with night terrors
- Not related to dreaming

Therapies

- Insomnia as a conditioned response to temporal and environmental clues
- Behavioral therapy effective for sleep onset and maintenance
- Relaxation techniques
- Sleep restriction
- Make waking time constant with progressive lengthening of sleep time as sleep improves
- Cognitive therapy
- Maintains improvement longer than other therapies

Pharmacologic therapy

- Modafinil as wake stimulating agent in EDS and narcolepsy
- Dopamine reuptake inhibitor
- Orexin inhibitor
- Sodium oxybate
- Mechanism not understood
- Methylphenidate is a catecholamine reuptake inhibitor
- SNRI controlling cataplexy

Pharmacologic therapy

- Trazodone antidepressant improves sleep latency and total sleep time.
- Permits return to sleep following awakening at night
- Daytime sedation (at high doses) and potential for anticholinergic side effects (even at low doses).
- Antihistamines commonly cause delerium in elderly patients.
- Daytime drowsiness.
- Drugs less effective than cognitive therapy for long-term (>12 months) success.

Pharmacologic therapy

- Zolpidem is a benzodiazepine receptor agonist.
- Best in initiating and maintaining sleep
- No rebound insomnia
- Common side effect of benzodiazepines
- Little daytime drowsiness.
- Mild cognitive impairment.
- May be used intermittently.
- Dependency is a problem with long-term use
- Melatonin receptor agonists not well studied.

Obstructive sleep apnea

- Present in up to 24% of men (women, 9%)
- Most patients are obese.
- Smaller upper airways
- Daytime sleepiness or fatigue.
- Snoring common.
- Nighttime nasal congestion.
- Complain of lack of energy.
- Decreased N3 and REM sleep
- Multiple awakenings
- Obstructive apnea is at least 10 seconds of cessation of ventilation.

Obstructive sleep apnea

- Hypopnea is at least a 30% reduction in air flow for at least 10 seconds with at least a 4% reduction in SaO_2.
- If the number of apneic and hypopneic episodes (Apnea-Hypopnea Index) is >15 (or >5 if daytime somnolence), obstructive sleep apnea is diagnosed.
- May see bradycardia followed by tachycardia
- Nocturnal arrhythmias
- Pulmonary and systemic hypertension
- Thrashing about

Obstructive sleep apnea

- Polysymnography for diagnosis.
- Two consecutive night polysymnography highly sensitive for diagnosis of obstructive sleep apnea.
- 10% weight loss leads to a 25% reduction in apneic or hypopneic episodes.
- Nasal dilators generally insufficient therapy
- Oral appliances designed to advance the mandible and pull the tongue forward to open the airway are not consistently effective

Obstructive sleep apnea

- Continuous positive airway pressure (CPAP) pneumatically splints the upper airway throughout the respiratory cycle.
- Diminishes disabling symptoms.

Apnea

- Central sleep apnea
- Breathing repeatedly stops and starts
- Without obstructive symptoms
- May be aggravated by CPAP although metrics improve
- Treatment offers no survival advantage in patients with heart failure with or without preserved ejection fraction
- Obesity hypoventilation syndrome
- Pickwickian syndrome
- Failing to breathe sufficiently rapidly or deeply
- Leads to EDS

Periodic limb movement disorder

- Daytime sleepiness or fatigue; restless in bed
- Nocturnal myoclonus
- Periodic episodes of repetitive and stereotyped limb movements during non-REM sleep.
- Usually there is extension of the big toe in combination with partial flexion of the ankle, knee, and hip.
- Movements occur at regular 20-40 second intervals and are associated with arousal.

Periodic limb movement disorder

- Primary cause of insomnia (17%).
- Found in 44% of those older than 65 years of age.
- Improves with treatment of obstructive sleep apnea.
- Dopamine agonists and clonazepam also useful.

Restless leg syndrome

- Accompanies 25% of those with periodic limb movement disorder.
- Found in up to 15% of the general population
- Up to 35% in those over 65 years of age.
- 85% also suffer from periodic limb movement disorder.
- Urge to move legs
- Accompanied by uncomfortable or unpleasant sensations
- Symptoms worse when inactive.
- Worse at night or symptoms only present at night

Restless leg syndrome

- Associated with higher risk of cardiovascular complications under anesthesia.
- Iron deficiency in substantia nigra
- Dopamine agonists and clonazepam have been useful therapies
- Pramipexole
- Gabapentin enacarbil
- Ropinirole
- Zolpidem

Rhythmic movement disorders

- Repetitive movements immediately prior to sleep or in N1
- Infancy and childhood
- Head banging or rolling
- Body rocking while on hands and knees