The Science and Mysteries of Sleep

Mark T Gabr, MD, FAASM

What is Sleep?

- Sleep is a reversible behavioral state of perceptual disengagement from and unresponsiveness to the environment. Sleep deprivation is typically followed by compensatory increase.

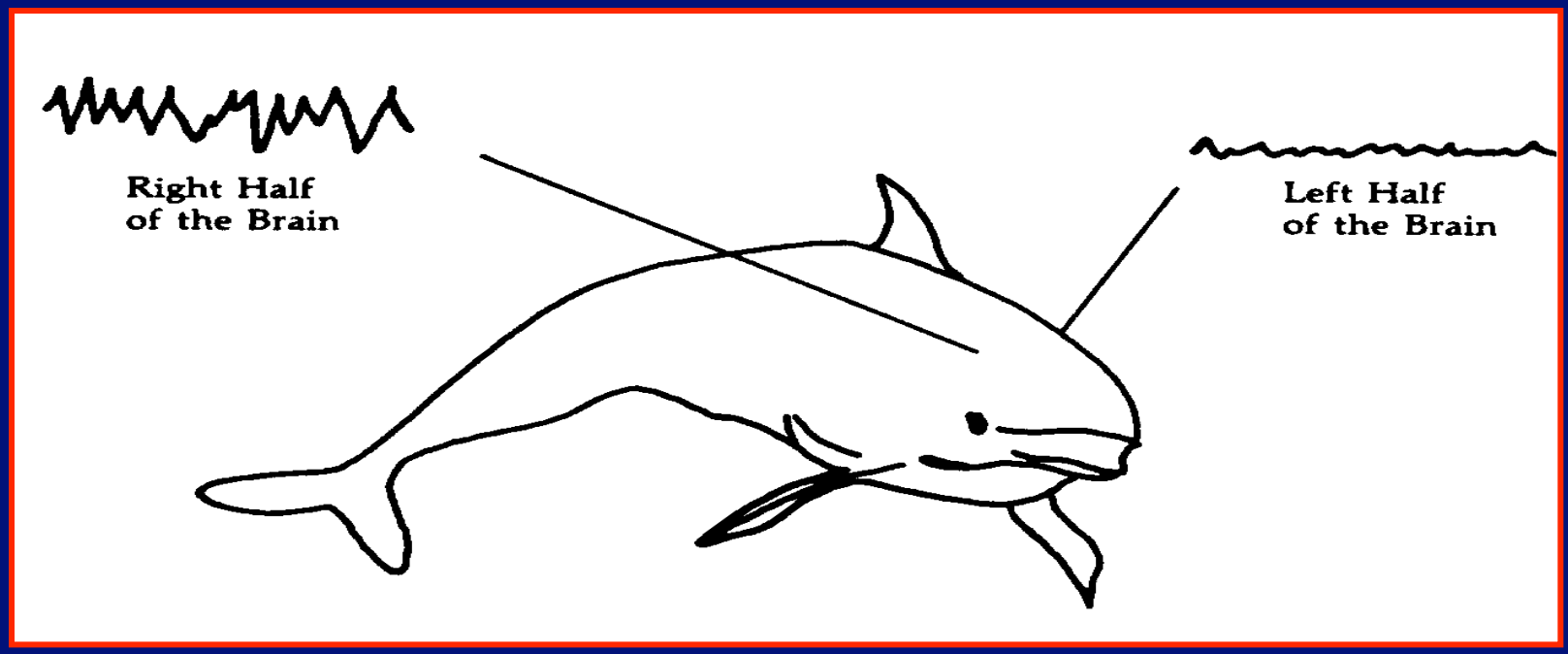
- Sleep is an active and highly organized brain state with very complex physiological and behavioral changes.

- Sleep is present in the entire animal kingdom, including insects. It has persisted throughout the evolution of mammals and birds, and is even present in lower forms.

Sleep Phylogeny

- Reptiles, amphibians, fish - sleep is usually determined by behavioral criteria.
- Birds – Sleep is very similar to that in mammals, but REM sleep is much shorter and alternates with NREM sleep in very short intervals (9 sec / 2.5 min).
- Mammals - all mammals sleep, and all except one species (Cetaceans) have the cyclical alternation between REM and NREM sleep.

Sleep Phylogeny

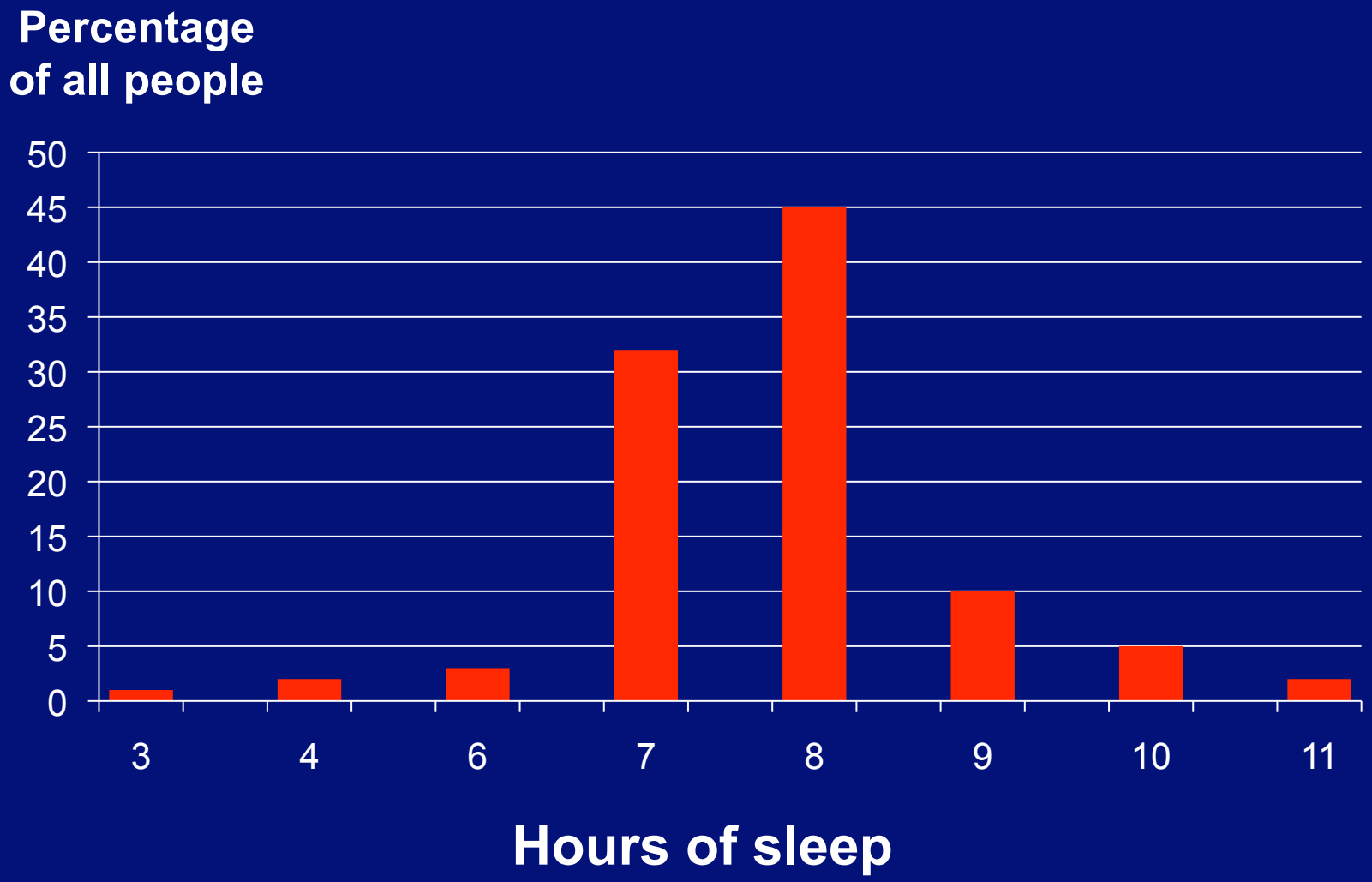


Unihemispheric sleep in the dolphin

Determinants of Sleep

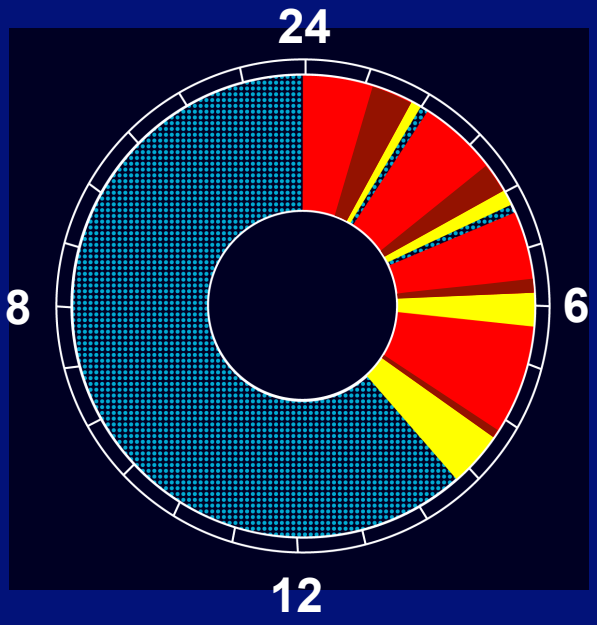
- Homeostasis: sleep loss increases daytime sleepiness and recovery sleep.
- Circadian Rhythms: sleep-wake periodicity over the 24 hours of the day; controlled by the SCN.
- Age: the ability to sleep decreases, not the need for sleep.
- Individual Sleep Differences: specific value varies from person to person and may be genetically determined.

Total Sleep Requirement



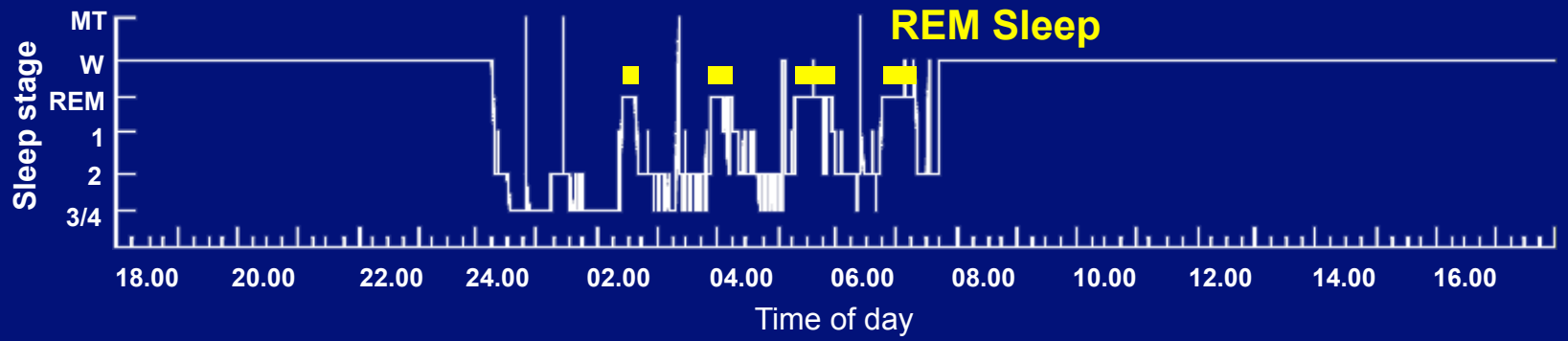
What Happens in Sleep?

NREM / REM Sleep Cycle



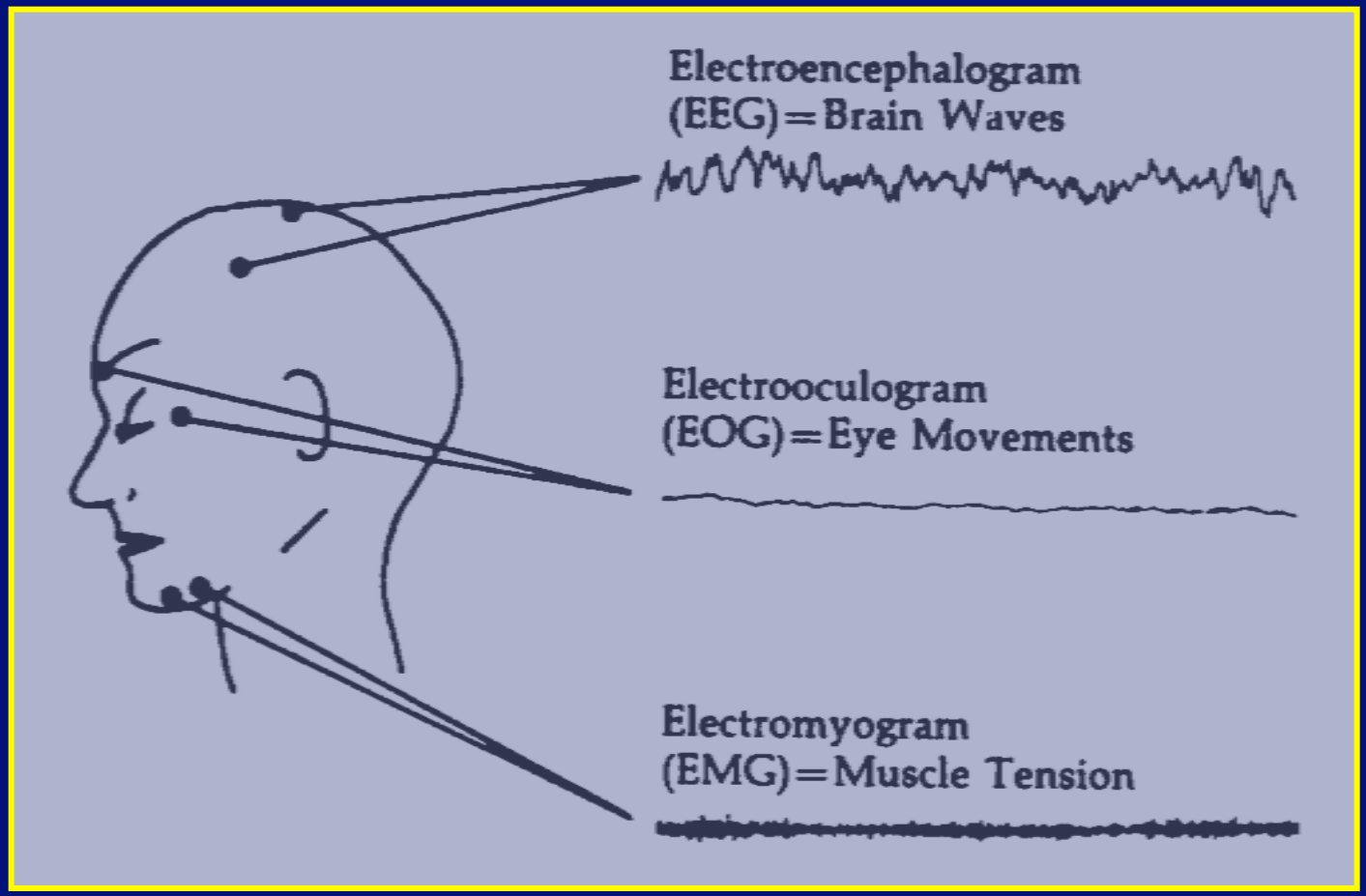
REM sleep
Stage 1-2 sleep
Stage 3-4 sleep
Wakefulness

Courtesy of R. Ristanovic, MD.

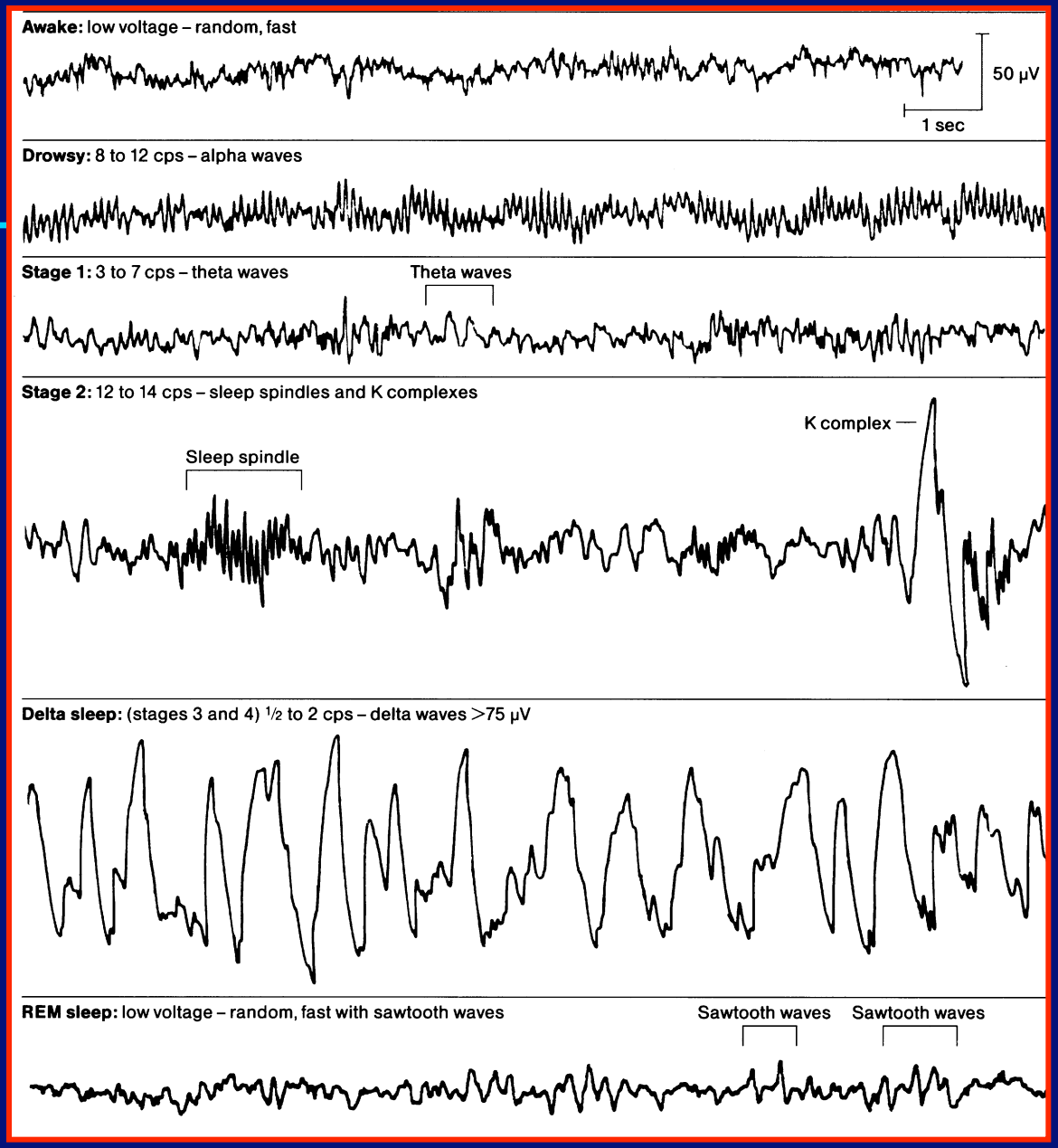


Adapted from Rogers et al. *Sleep*. 1994;17:590.

Electrographic State Determination



EEG in wakefulness, NREM and REM sleep



NREM vs. REM Sleep

Physiologic Variable	NREM	REM
Heart rate	Regular	Irregular
Respiratory rate	Regular	Irregular
Blood pressure	Regular	Variable
Skeletal muscle tone	Preserved	Absent
Brain O2 consumption	Reduced	Increased
Response to CO2	Same as W	Depressed
Response to O2	Same as W	Same as W
Temperature	Homothermic	Poikilothermic
Penile tumescence	Absent	Present

REM Sleep Physiology

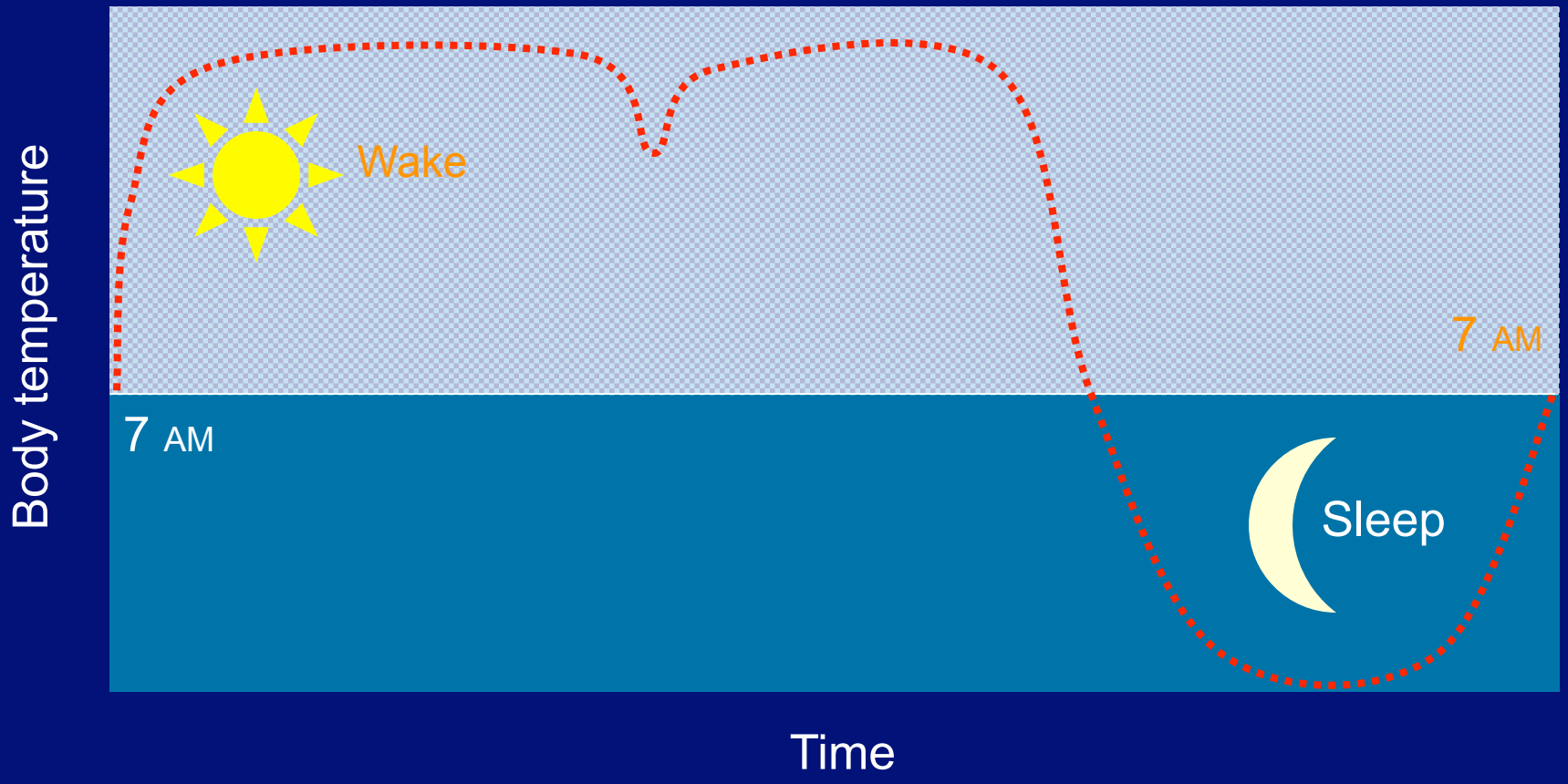
Tonic Components

1. EEG Desynchronization
3. EMG Atonia
4. Penile Tumesence

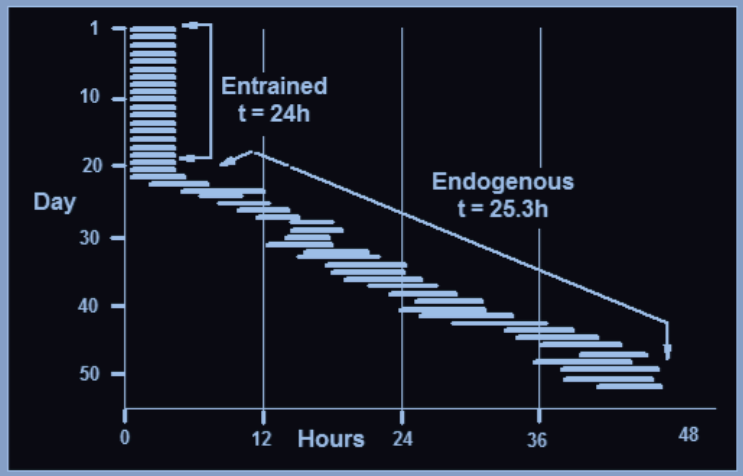
Phasic Components

1. Rapid Eye Movements (PGO-Spikes)
2. Muscle twitches
3. Irregular respirations
4. Cardiovascular instability

Circadian Rhythm of Sleep and Core Body Temperature



Free-running rhythm & Entrainment

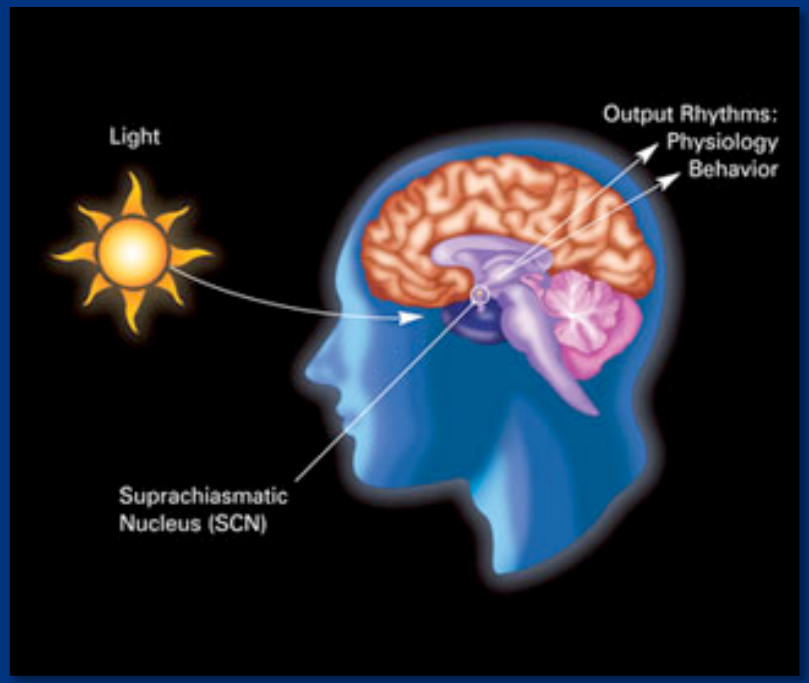


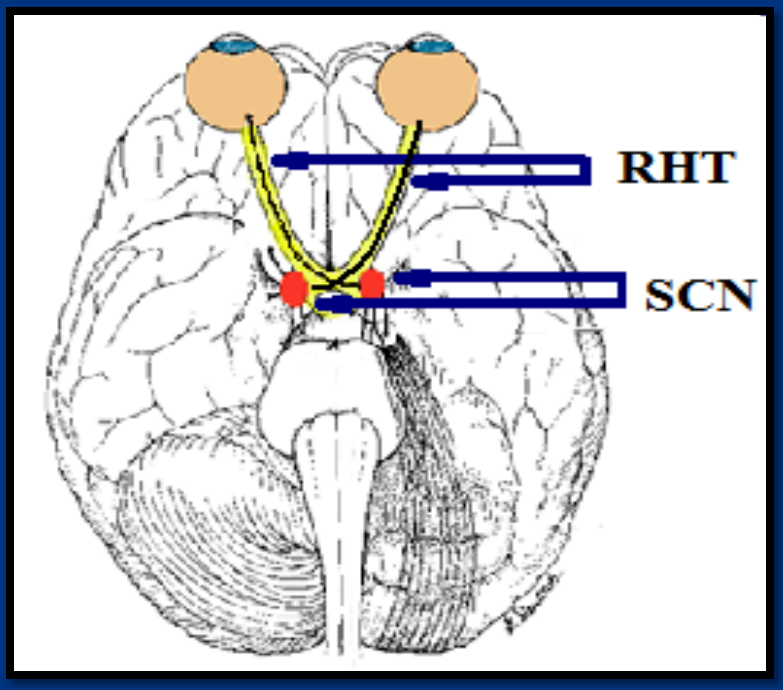
- The natural endogenous circadian period of humans is slightly more than 24 hours, generally about 24.2 hours. In a time-free environment (no time cues) days are longer than 24 hours, arising one hour later every day. This is called **free-running rhythm**.

- Keeping the basic 24-hour cycle involves daily synchronization of the internal clock with the shorter solar day, a process known as **entrainment**. It involves advancing the internal clock by a fixed time period (about 0.2 hour) every day. This adjustment is derived from exposure to environmental time cues (**Zietgebers**).

Czeisler et al, science, 1999

Suprachiasmatic Nucleus (SCN)

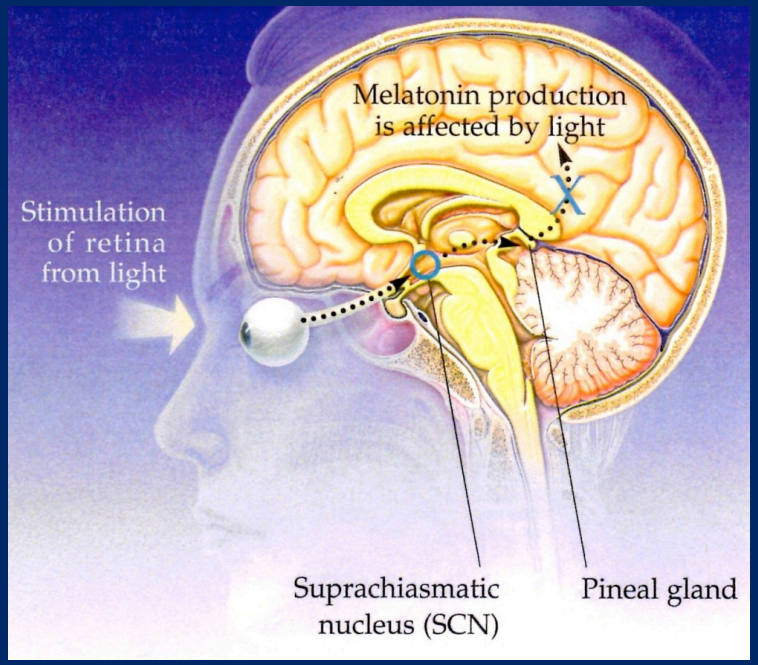


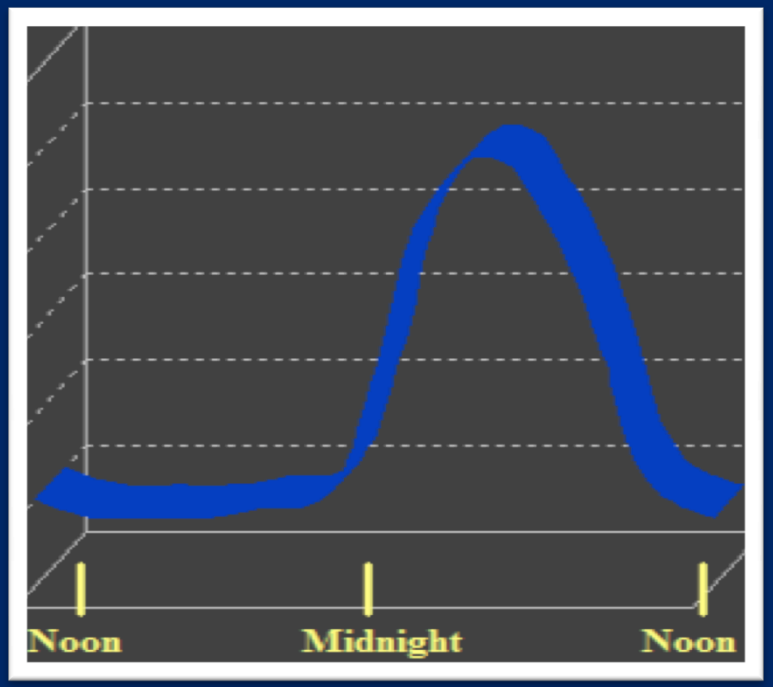


- The suprachiasmatic nucleus (SCN) is the central master pacemaker (Biological Clock) which regulates sleep-wake cycle and other circadian rhythms. It is a paired structure of 10K neurons each, located at the base of the anterior hypothalamus above the optic chiasm.

- Light is the strongest time cue that synchronizes circadian rhythms with the environment. Light reaches the SCN via the retinohypothalamic tract (RHT).

Melatonin & The Circadian System

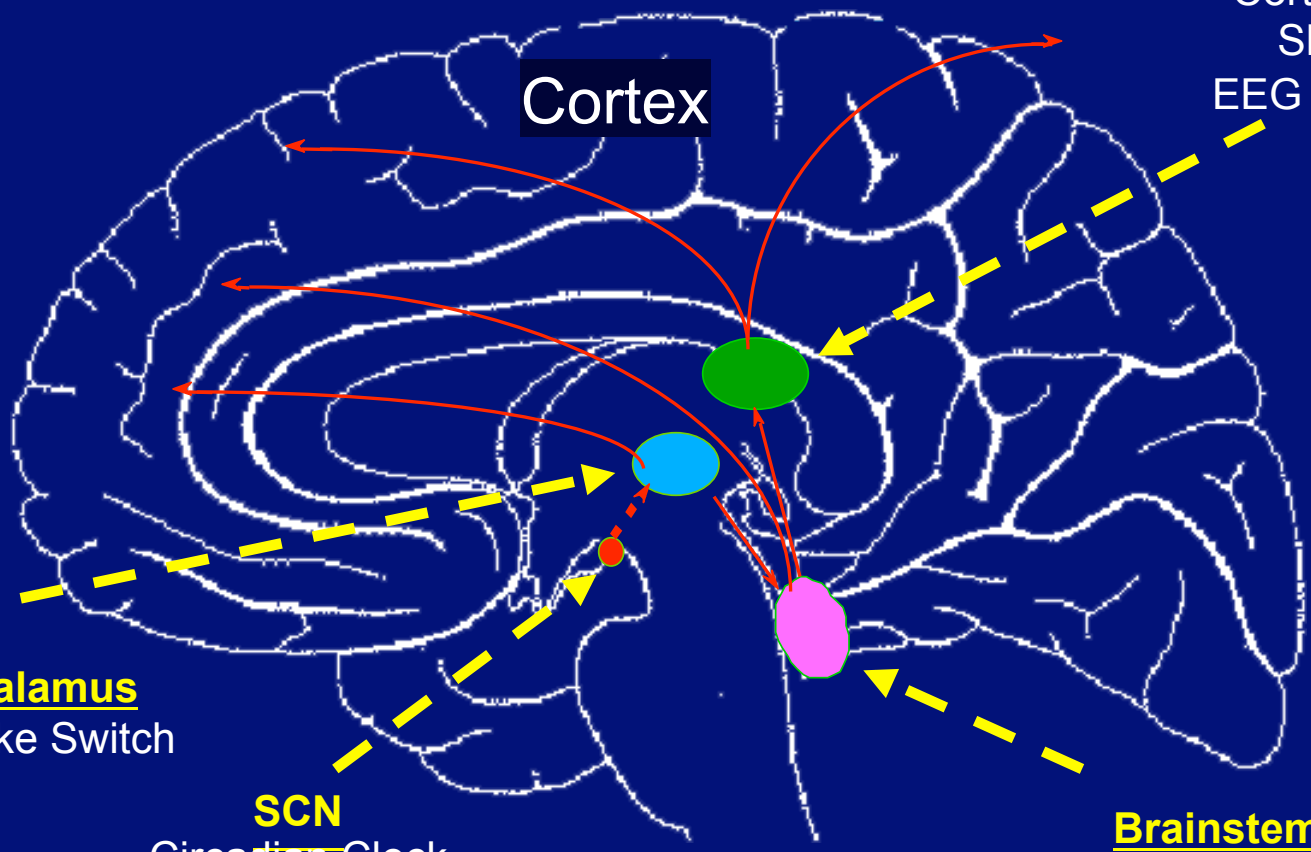




Melatonin is the endocrine secretion most closely linked to the circadian system. It is actively secreted by the pineal gland for 10-12 h at night in the dark. Melatonin secretion is activated by darkness and suppressed by light. The SCN regulates the secretion of melatonin by the pineal gland, and melatonin itself has a feedback effect on the SCN by decreasing its firing rate, thus promoting sleep.

Sleep Neurophysiology

"Sleep Centers"



Thalamus
Cortical Activation
Sleep Spindle
EEG Synchronization

Hypothalamus
Sleep/Wake Switch

SCN
Circadian Clock

Brainstem
Ascending Cortical Activation
REM/SWS Switch

Courtesy of E. Mignot, MD. Stanford University.

Sleep Neurochemistry

Neurotransmitters and Sleep/Wake Promoting Substances

Wakefulness	NREM Sleep	REM Sleep
Acetylcholine	GABA VLPO Neurons	Acetylcholine REM-on
Norepinephrine	Galanin	Glycine Atonia
Histamine		Monoamines (NE, HA, 5-HT) REM-off
Serotonin		
Hypocretin		
Dopamine		

Why do we sleep?

Many Proposed Theories – No Answers

We know a lot about what happens if we do not sleep, but very little on the reason for sleep.

- Restoration - Animals with high metabolic rates sleep longer.
- Memory Processing - Decision making, reasoning and episodic memory improve with sleep.
- Immune Theory - Sleep deprivation affects the immune system.
- Growth Theory - SWS increases growth hormone production.
- Energy Conservation - Rest allows the animal to be more prepared to activity when awake.
- Preservation - Keeping quite when it is dark may prevent the animal from being seen by predators.

Functions of Sleep

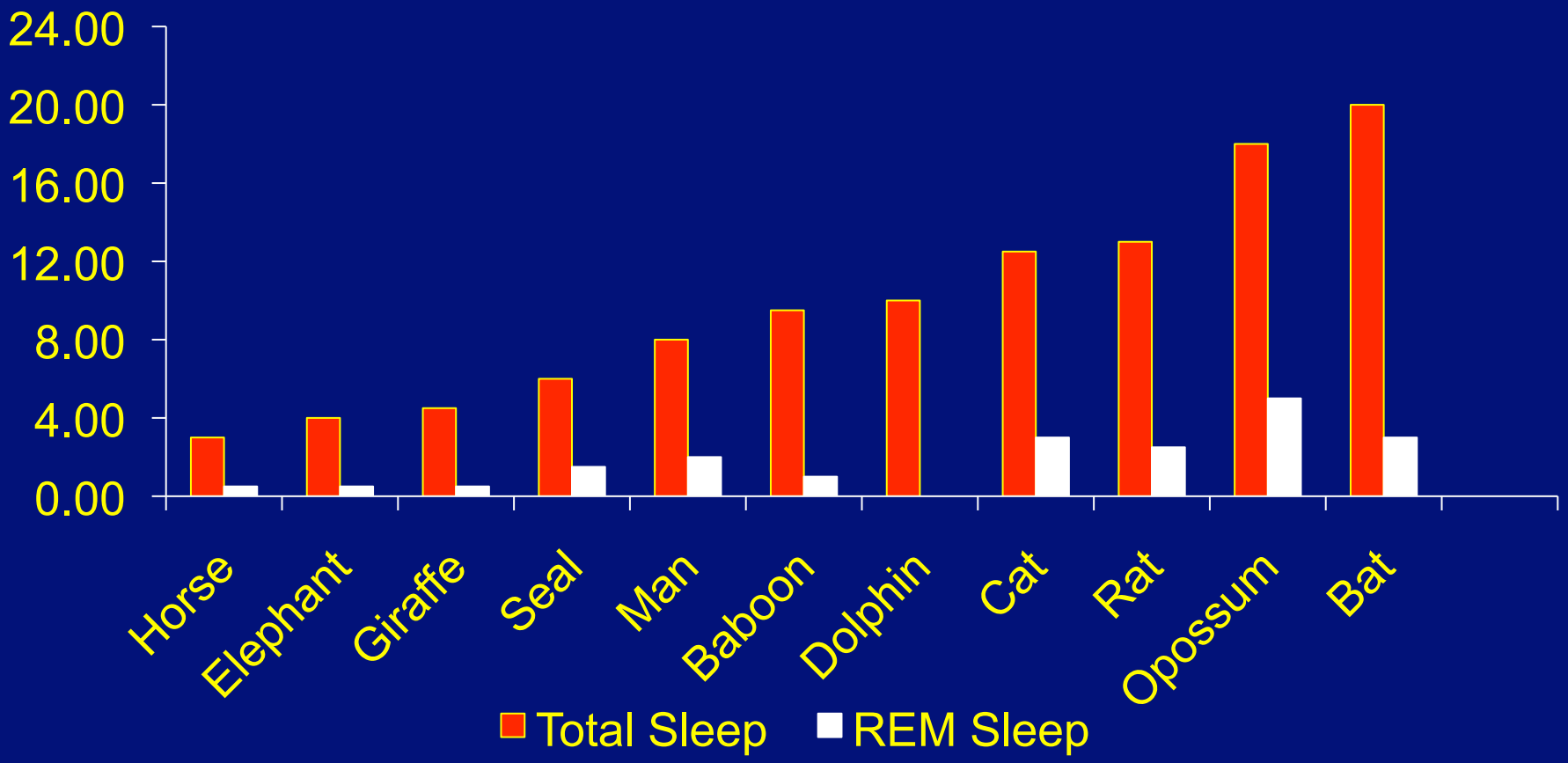
Sleep is essential for survival

- Total sleep deprivation in rats leads to death within 10 – 20 days, faster than if they were totally deprived of food but slept normally. Fatal Familial Insomnia leads to death after several months.

- Sleep drive in humans is so strong that sleepiness increases with small reductions in nightly sleep times and sleep loss can cause severe functional impairments.

- All studied land mammals show maximal sleep at birth, leading to the conclusion that sleep is required for brain development.

Mammals sleep per 24 Hours



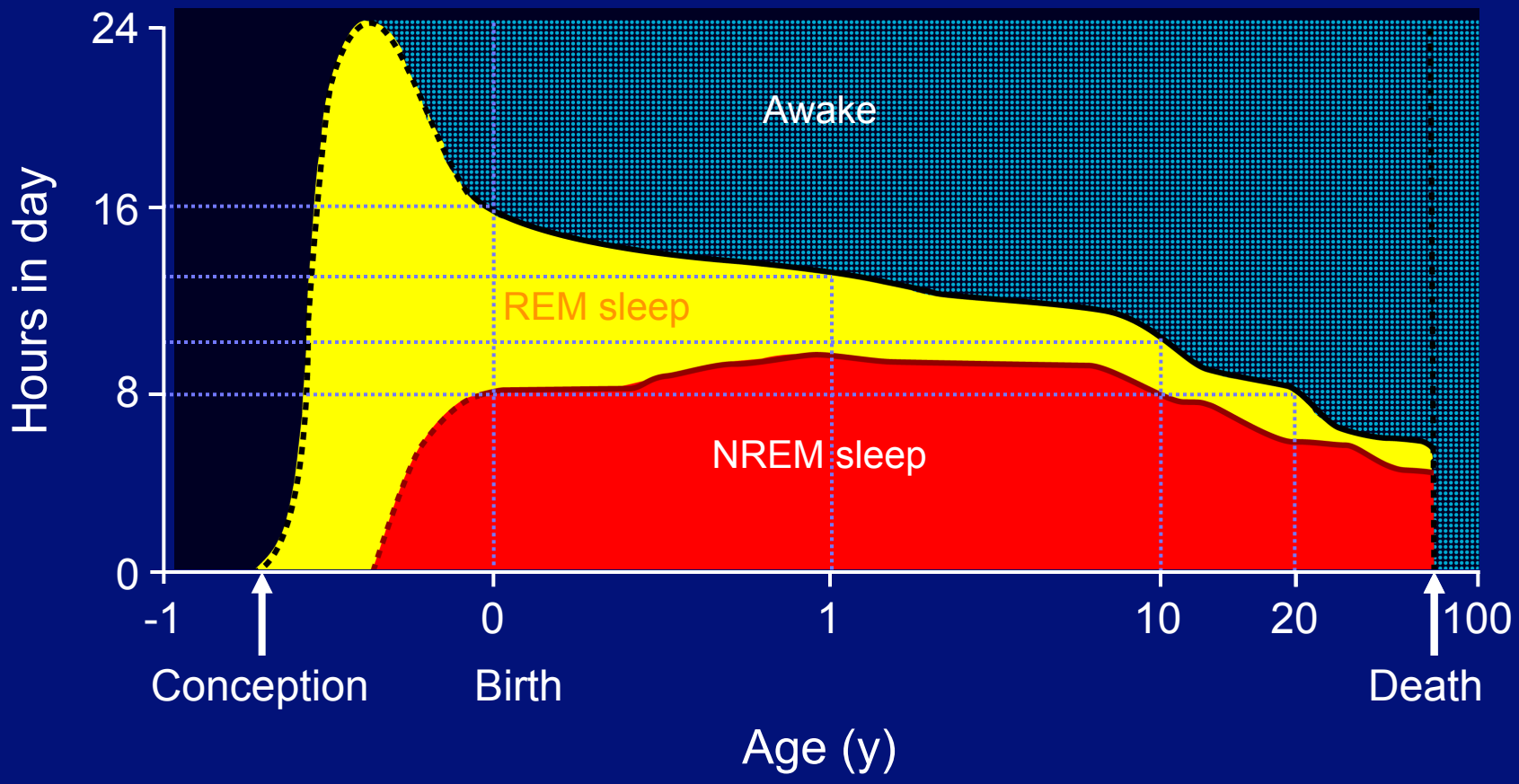
Functions of Sleep:
NREM Sleep: Neural Integrity

- There is huge variation in the amount of sleep that different species need, and that is not related to evolutionary classification. The opossum sleeps for 18 hours a day, whereas the elephant gets by with only 3 hours.

- Animal size is the major determinant of the amount of sleep! There is greater sleep requirement in species with low energy reserve. Small animals have higher metabolic rates and higher brain temperatures resulting in large amount of free radicals with increased cellular injury.

- NREM sleep may allow brain cells to repair membranes damaged by free radicals during waking (neuronal integrity).

Sleep Ontogeny



Hobson. Sleep and Dreaming. In: *Fundamental Neuroscience*. 1999.
Roffwarg et al. *Science*. 1996;152:604.

Functions of Sleep:
REM Sleep: Neural Maturation

- The amount of REM sleep is highest early in life and in immature animals. The champion REM sleeper is the Platypus with 8 hours a day in REM sleep, while the dolphin has no REM sleep! Michel Jouvet 's theory: Genetic programing of neuronal connections (neural maturation).

- REM sleep deprivation can alleviate clinical depression, thus mimicking the effect of SSRI antidepressants. REM sleep may allow monoamine receptors (Serotonin, norepinephrine and histamine) to rest and regain full sensitivity which is crucial during waking for mood regulation.

- Contrary to popular belief, REM sleep has not been proven to play a role in memory consolidation or learning ability. People who have brain damage preventing REM sleep, or who have drug-induced blockade of REM sleep, have normal –or even improved- memory.

Disorders of Sleep

Mark T Gabr, MD, FAASM

Sleep Disorders are common

- Estimated 70 million Americans have clinically significant sleep problems
- Prevalence of insomnia about one-third of adult population
- Obstructive Sleep Apnea prevalence in patients with essential hypertension is over 25%

Sleep Disorders are Serious

- Chronic insomniacs report decreased quality of life, memory and attention problems, decreased physical health
- Increased incidence of motor vehicle crashes in patients with OSAS
- Total direct costs of insomnia in U.S. $13.9 billion (1995)

Sleep Disorders are Treatable

Multiple successful treatment modalities exist, including pharmacotherapy, surgical intervention, behavioral therapy, continuous positive airway pressure

Sleep Disorders are Underdiagnosed

- Less than 14% of medical interns questioned patients about sleep (Haponik,1996)
- Survey of 222 V.A. patients; no sleep symptoms recorded despite 47% prevalence (Meissner,1998)
- Survey of 10 million ICD dx:100,000 cases OSAS expected; 73 diagnosed (1992)

Sleep Disorders - Socioeconomic Consequences

- 40 million Americans suffer from chronic disorders of sleep.
- 95% of these remain unidentified and undiagnosed.
- The annual direct cost of sleep-related problems is $16 billion, with an additional $50-$100 billion in indirect costs (accidents, litigation, property destruction, hospitalization, and death).

Sleep Disorders - Socioeconomic Consequences

- More than 100,000 motor vehicle accidents annually are sleep-related.
- Disasters such as Chernobyl, Three Mile Island, Challenger, and Exxon Valdez were officially attributed to errors in judgment induced by sleepiness or fatigue.

Disorders of Sleep

- **Hypersomnia**: Disorders of Excessive Sleepiness
- **Insomnia**: Difficulty initiating and maintaining sleep
- **Parasomnia**: Abnormal behavior during sleep; Disorders of Arousals from NREM and REM Sleep

Excessive Daytime Sleepiness

Challenges in the Diagnosis

- Need to differentiate EDS from fatigue or tiredness
  - Sleepy patients often present with “lack of energy,” “tiredness,” or “fatigue” complaint
- Need to distinguish between EDS and the lethargy of depression
- Denial of symptoms is common
- Patients may be unaware of symptoms if onset is insidious
- Multiple causes of EDS

EDS is often unrecognized

Meissner et al. *West J Med*. 1998;169:146; Chervin. *Chest*. 2000;118:372; Guilleminault and Brooks. *Brain.* 2001;124:1482; Kapur et al. *Sleep Breath*. 2002;6:49; Ruggles and Hausman. *WMJ.* 2003;102:21.

Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the *most appropriate number* for each situation.

0 = would *never* doze

1 = *slight* chance of dozing

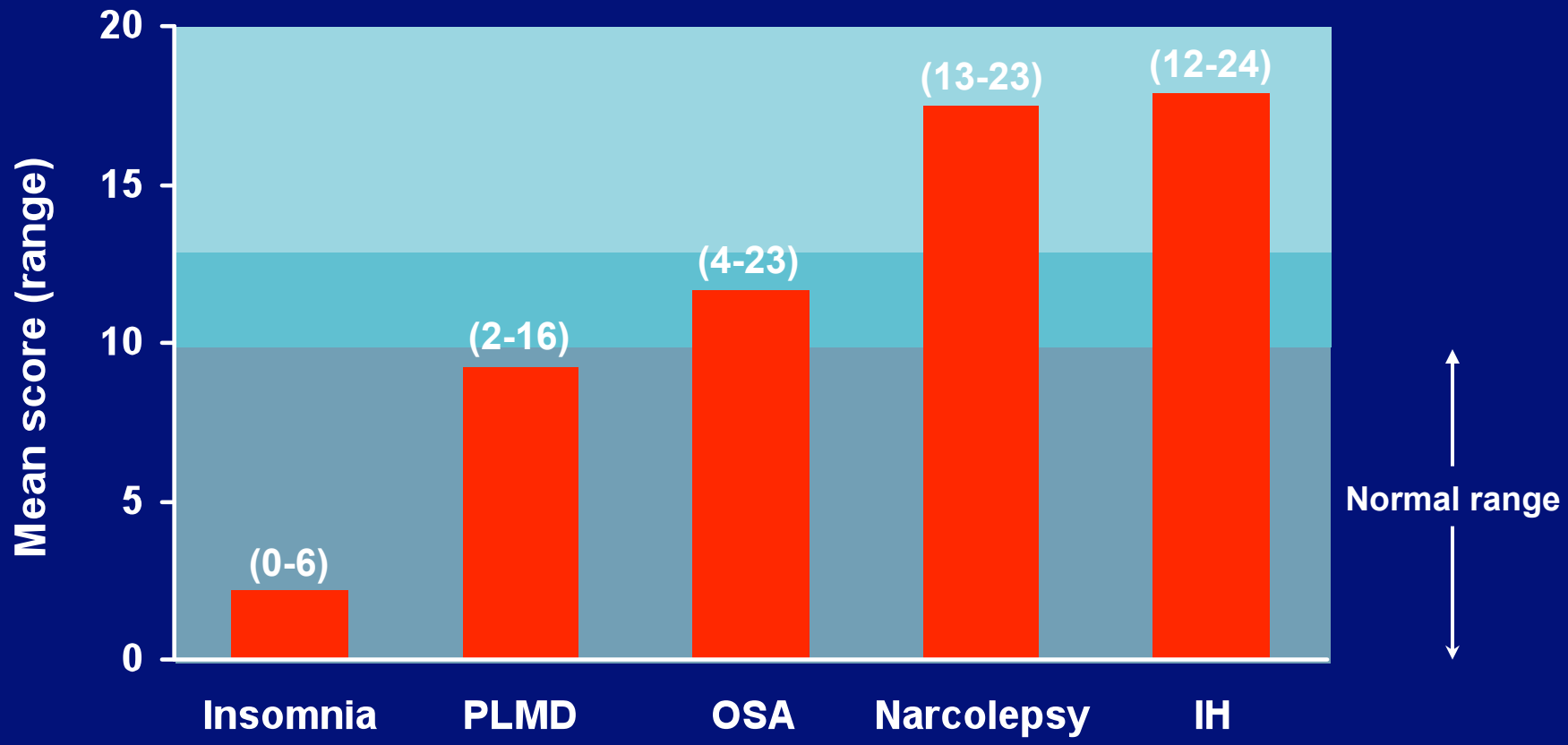
2 = *moderate* chance of dozing

3 = *high* chance of dozing

Situation	Chance of Dozing
Sitting and reading	_____
Watching TV	_____
Sitting inactive in a public place (eg, a theater or a meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car while stopped for a few minutes in traffic	_____

Johns. *Sleep*. 1991;14:540.

ESS Scores in Select Conditions



PLMD = periodic leg movement disorder; OSA = obstructive sleep apnea; IH = idiopathic hypersomnia.

Adapted from Johns. *Sleep*. 1991;14:540.

Obstructive Sleep Apnea

Types of Sleep Disordered Breathing

- Apnea

  Cessation of airflow ≥ 10 seconds

- Hypopnea

  Decreased airflow ≥ 10 seconds associated with:

  - Arousal
  - Oxyhemoglobin desaturation

Measures of Sleep Apnea Frequency

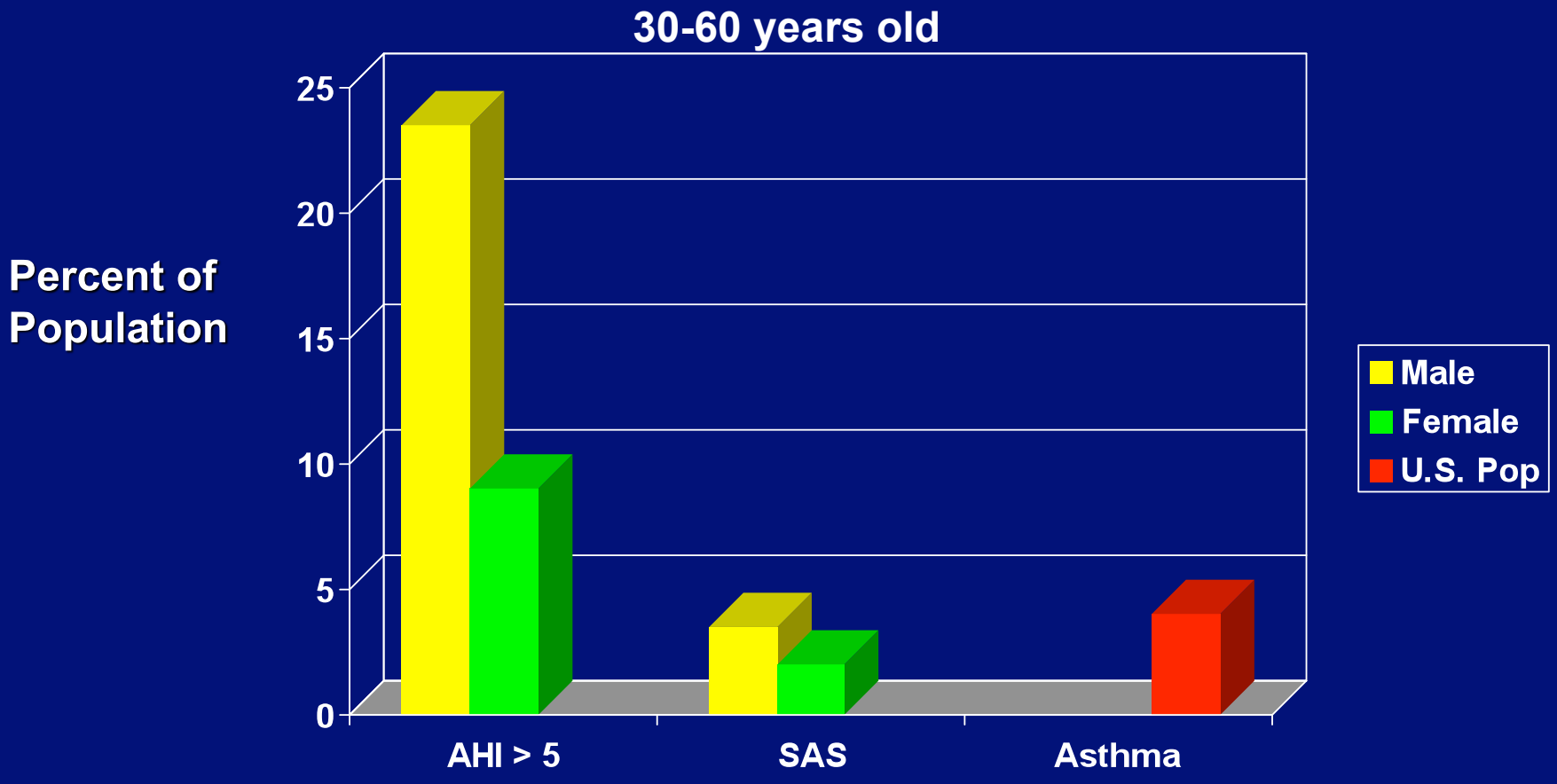
- **Apnea Index**

  # apneas per hour of sleep

- **Apnea / Hypopnea Index (AHI)**

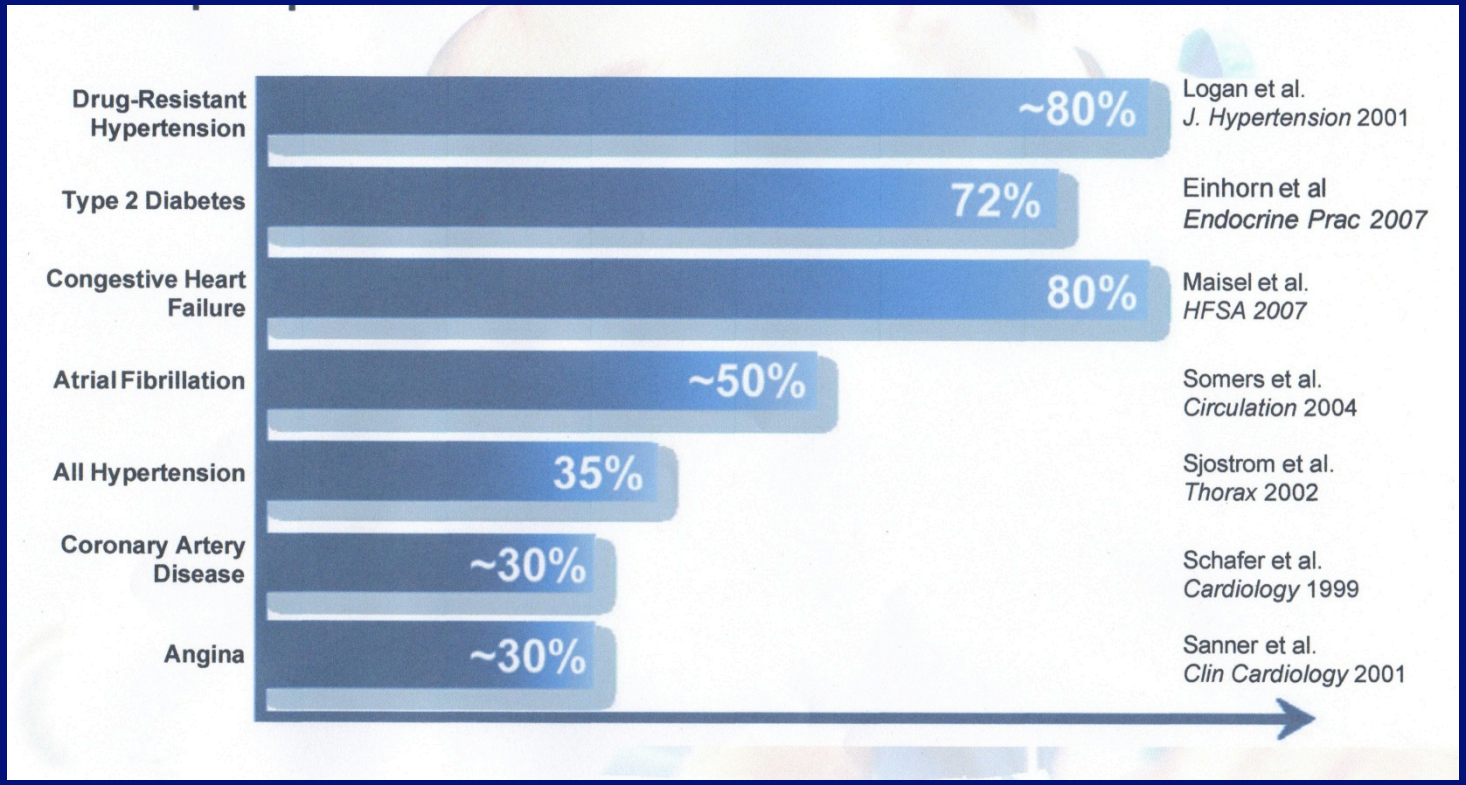
  # apneas + hypopneas per hour of sleep

Prevalence of Sleep Apnea



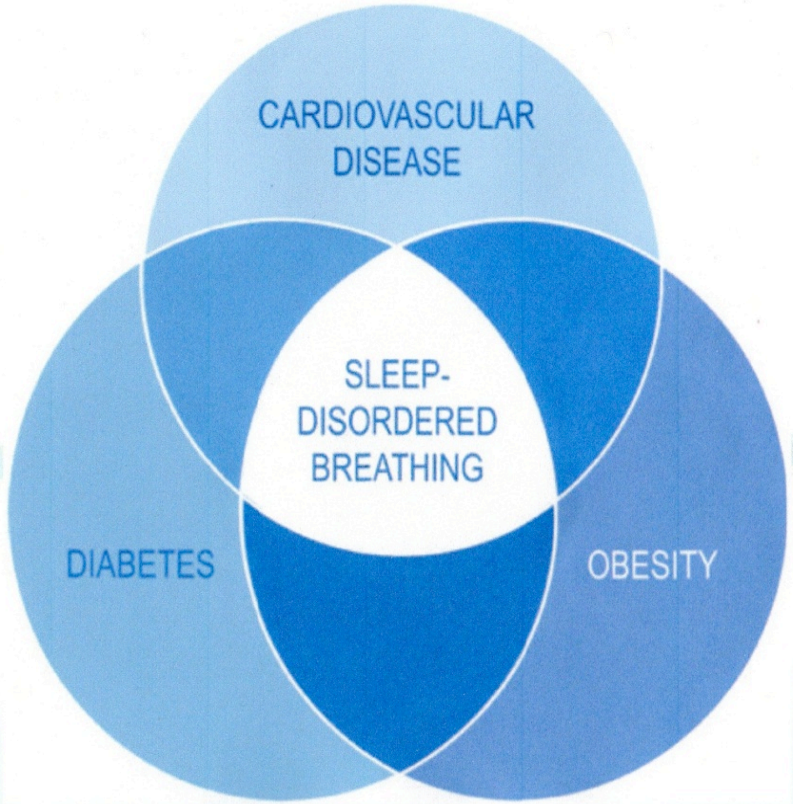
Adapted from Young T et al. N Engl J Med 1993;328.

Prevalence in Co-Morbid Patients

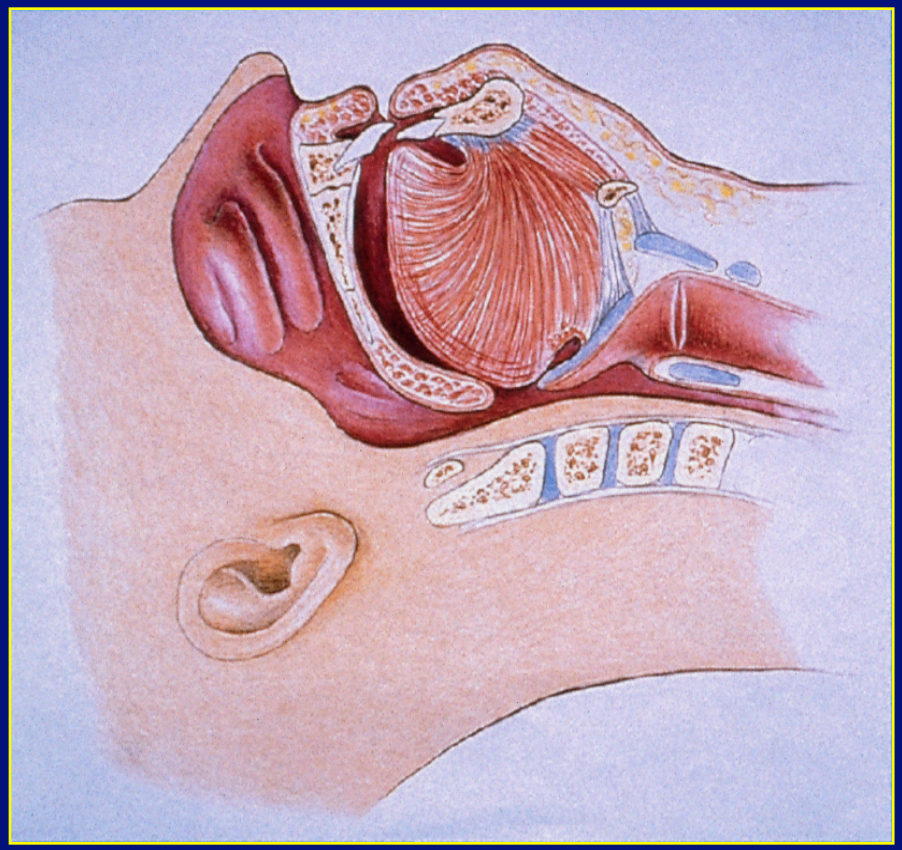


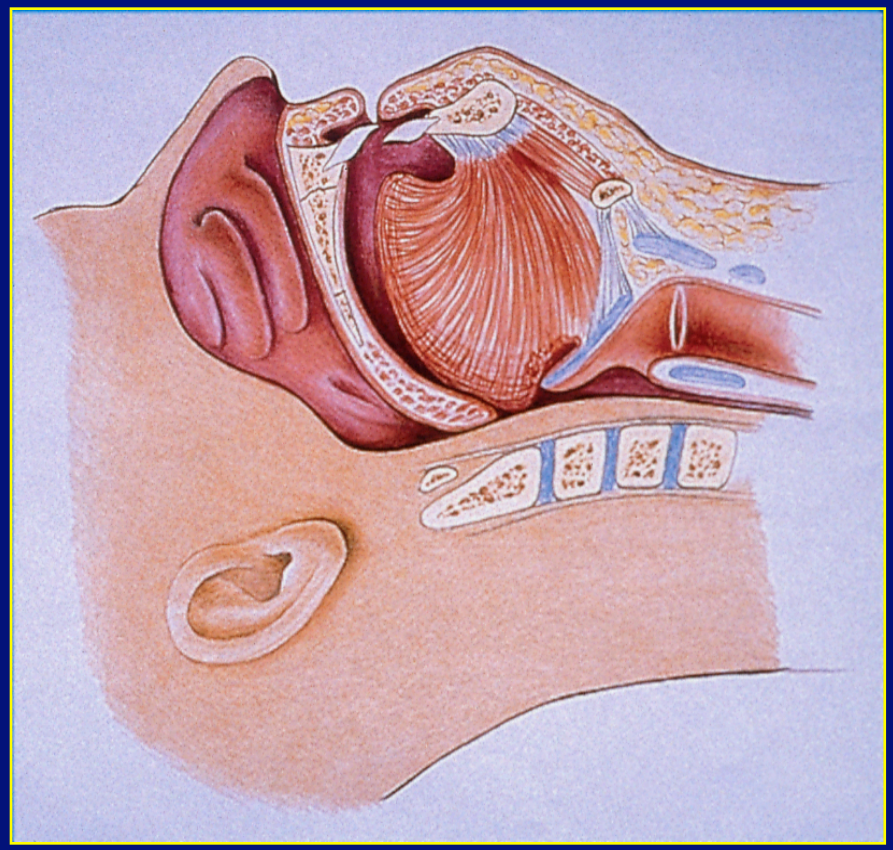
Sleep Apnea & Metabolic Syndrome

- Sleep-disordered breathing is at the center of Metabolic Syndrome
- Treating SDB may improve co-morbidities

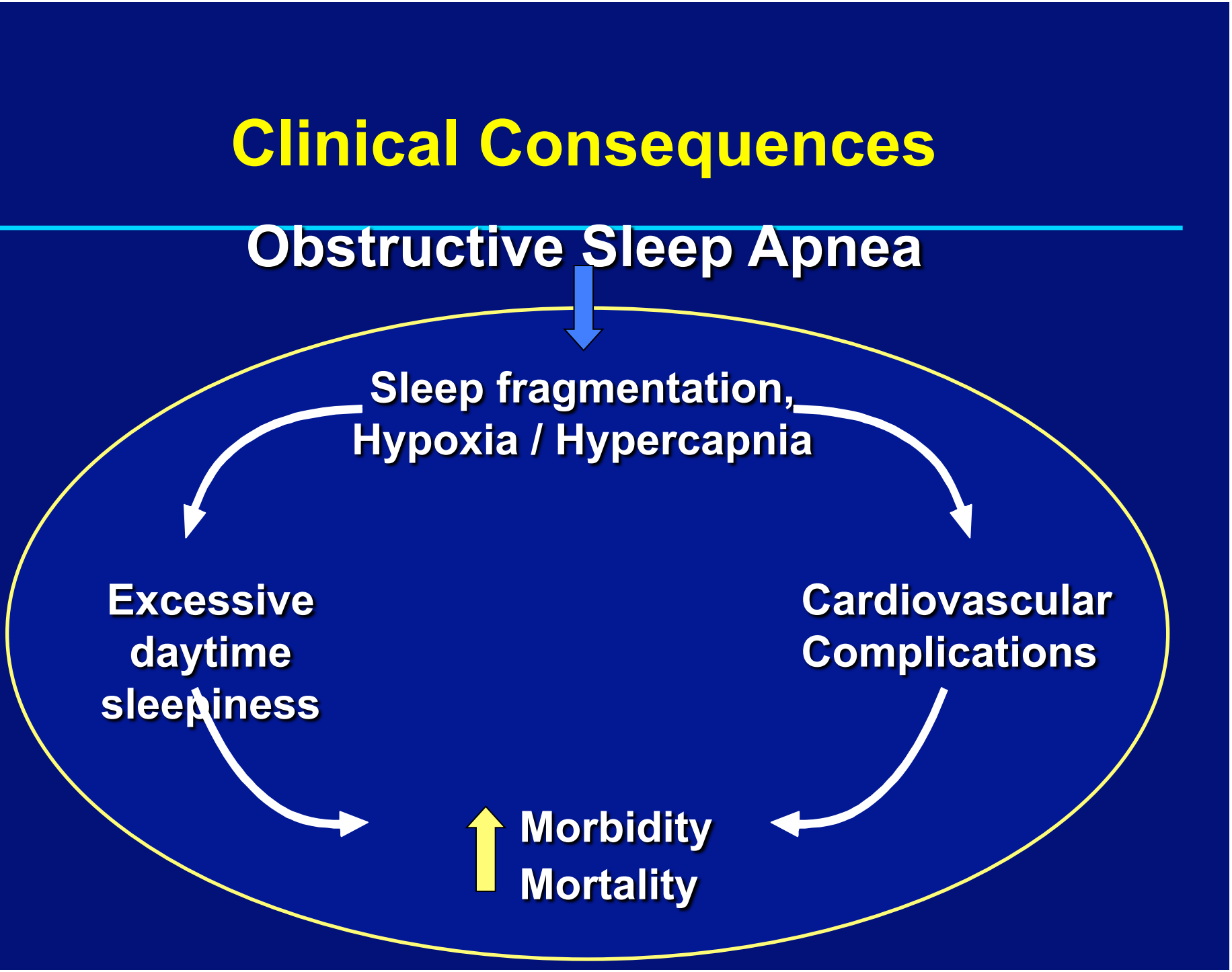


Pathophysiology of Obstructive Sleep Apnea





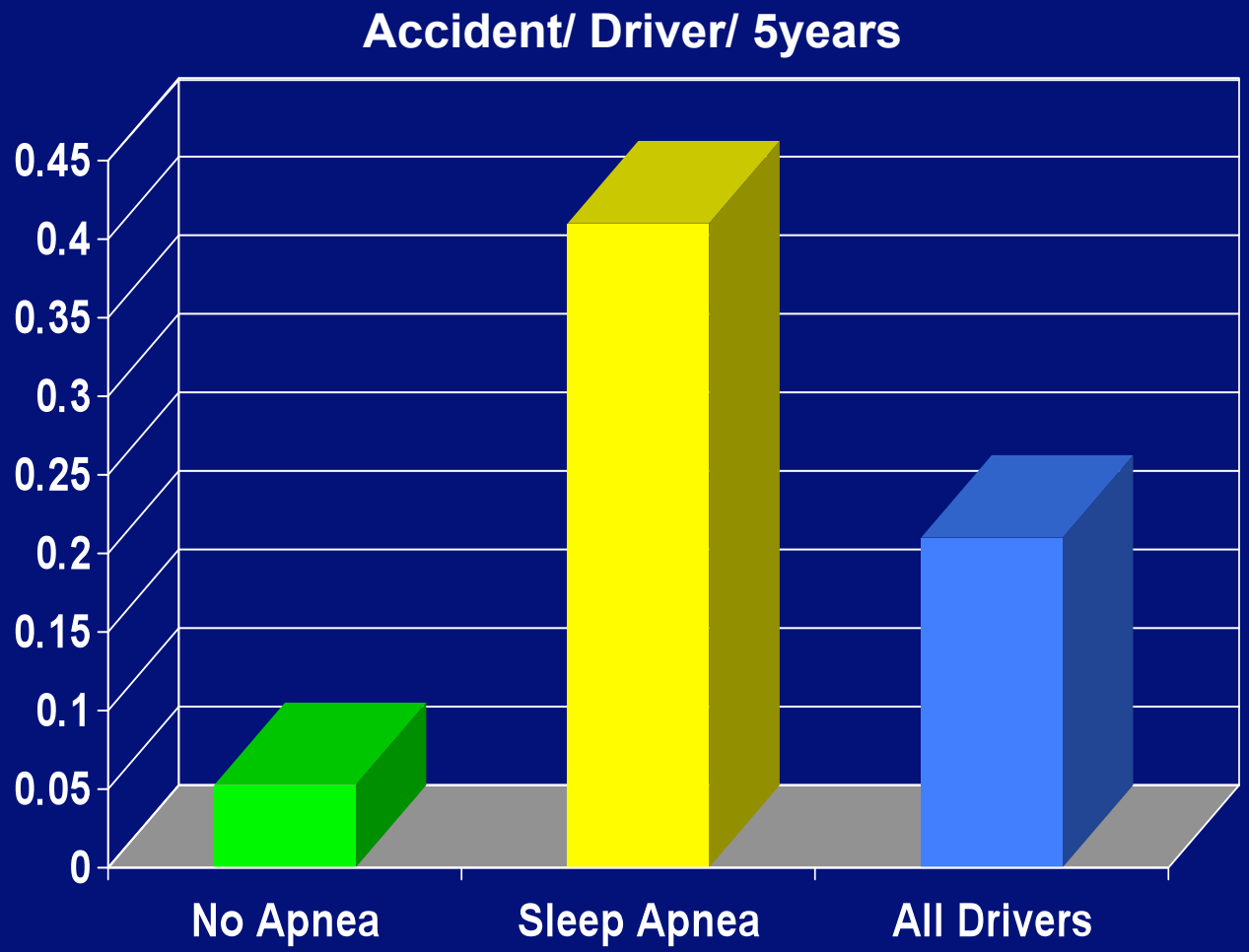
Clinical Consequences



Clinical Consequences: Excessive Daytime Sleepiness

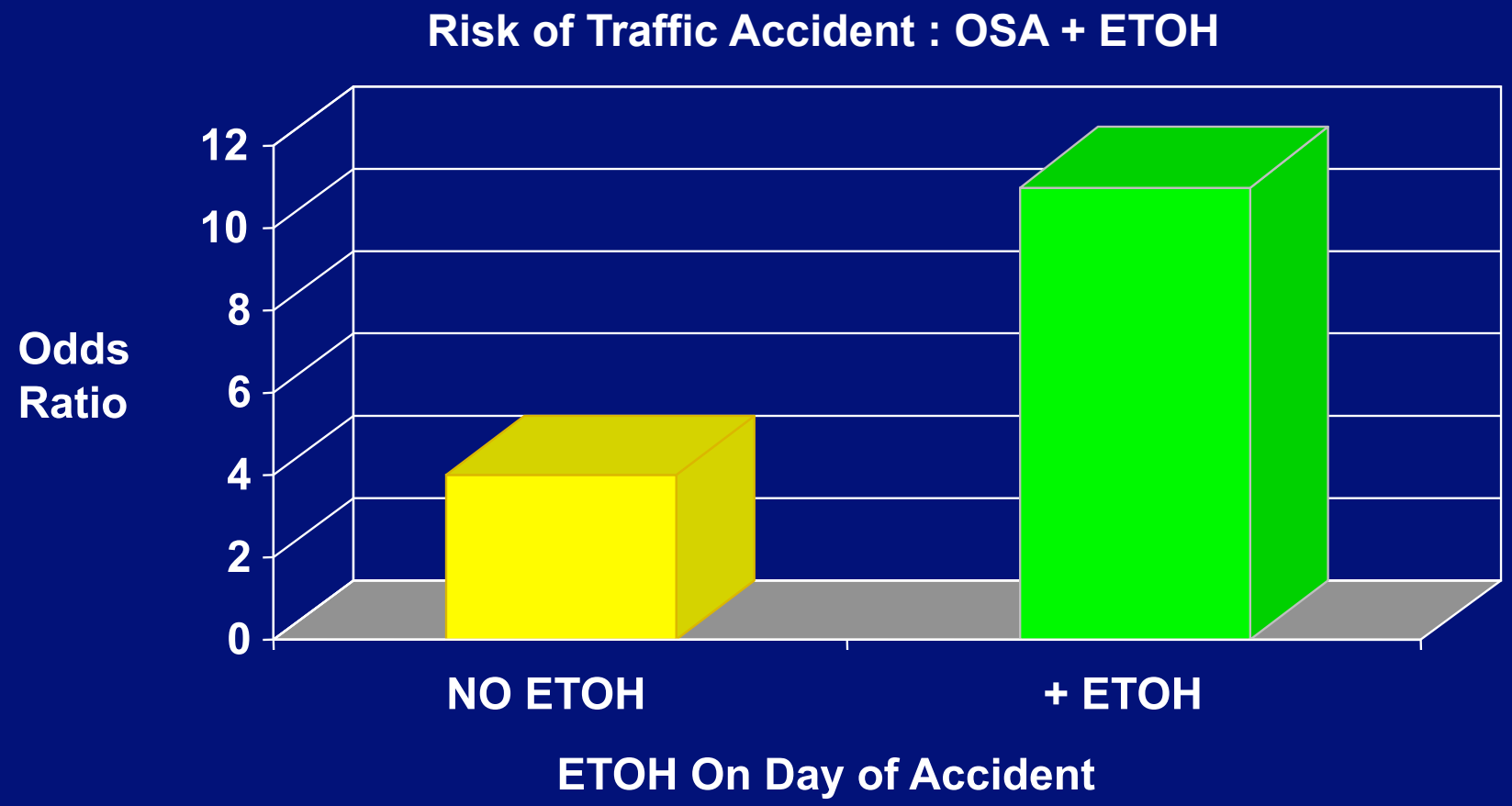
- Increased motor vehicle crashes
- Increased work-related accidents
- Poor job performance
- Depression
- Family discord
- Decreased quality of life

Consequences: Automobile Accidents



Adapted from Findley LJ et al. Am Rev Respir Dis 1988;138.

Consequences: Automobile Accidents



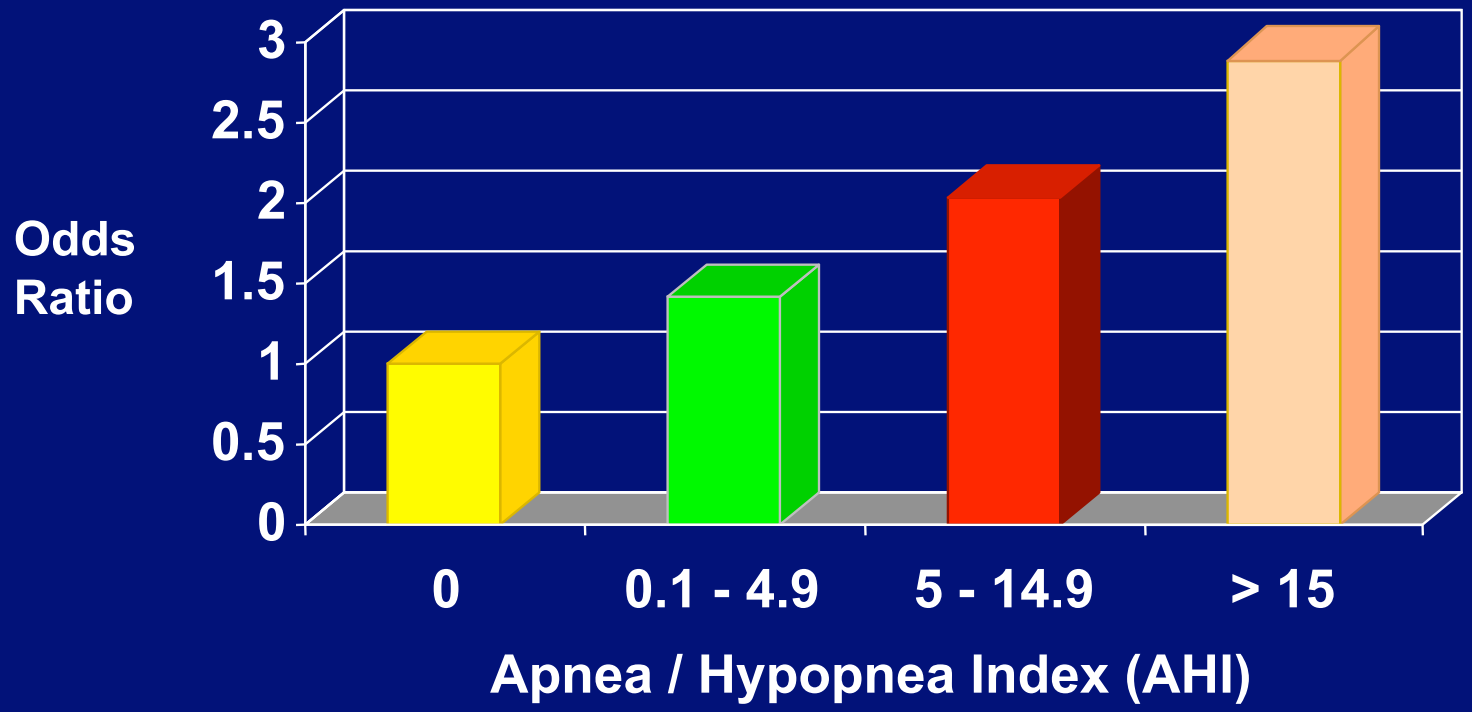
Adapted from Teran-Santos J et al. N Engl J Med 1999;340.

Clinical Consequences: Cardiovascular

- Systemic hypertension
- Cardiac arrhythmias
- Myocardial ischemia
- Cerebrovascular disease
- Pulmonary hypertension

Cardiovascular Consequences: Hypertension

Prospective Study of Association between OSA and Hypertension

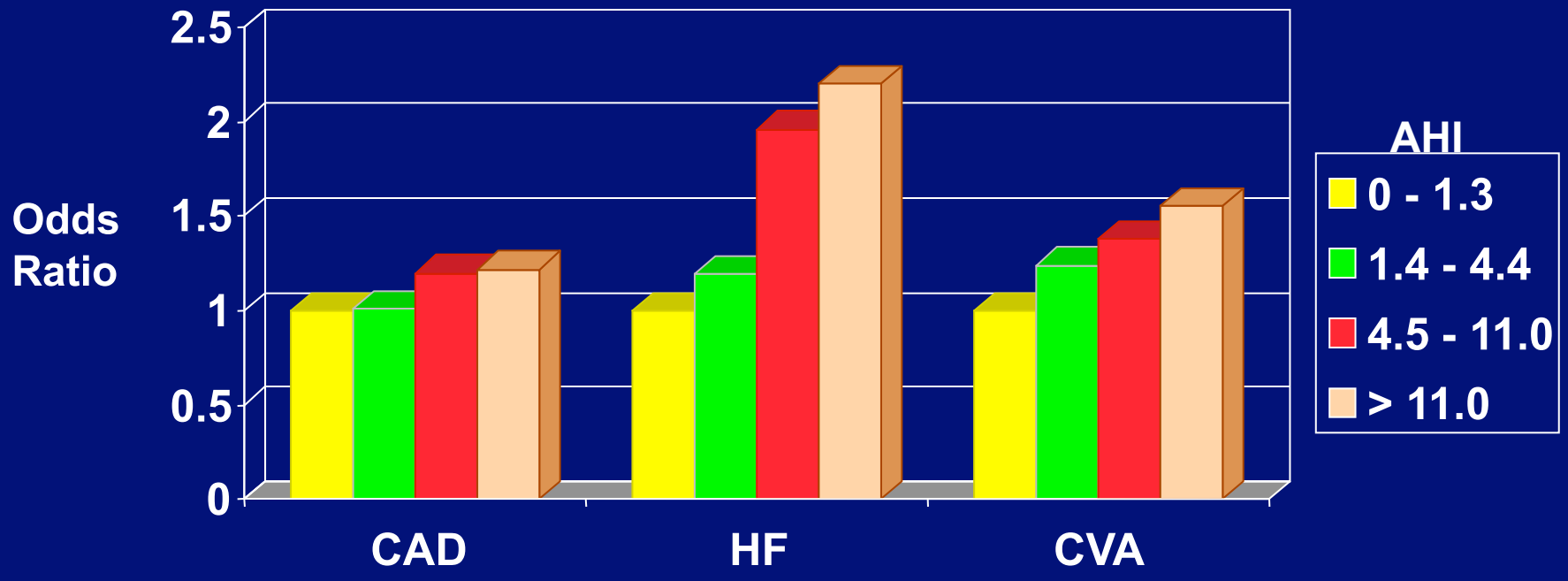


Adjusted for age, sex, BMI, neck circ., cigs., ETOH, baseline HTN.

Adapted from Peppard PE et al. N Engl J Med 2000;342.

Consequences: Cardiovascular Disease

Cross Sectional Study of Association between OSA and CVD



Adjusted for age, sex, race, BMI, HTN, cigs., Chol.

Adapted from Shahar E et al. Am J Respir Crit Care Med 2001;163.

Diagnosis: History

- Snoring (loud, chronic)
- Nocturnal gasping and choking
  - Ask bed partner (witnessed apneas)
- Automobile or work related accidents
- Personality changes or cognitive problems
- Excessive daytime sleepiness
- Risk factors

Sleep Apnea Risk Factors

- Obesity
- Increasing age
- Male gender
- Anatomic abnormalities of upper airway
- Family history
- Alcohol or sedative use
- Smoking

Diagnosis: Physical Examination

- Upper body obesity / thick neck
  - ≥ 17” males
  - ≥ 16” females
- Hypertension
- Obvious airway abnormality

Behavioral Interventions

- Lose weight
- Avoid alcohol and sedatives
- Avoid sleep deprivation
- Avoid supine sleep position
- Stop smoking

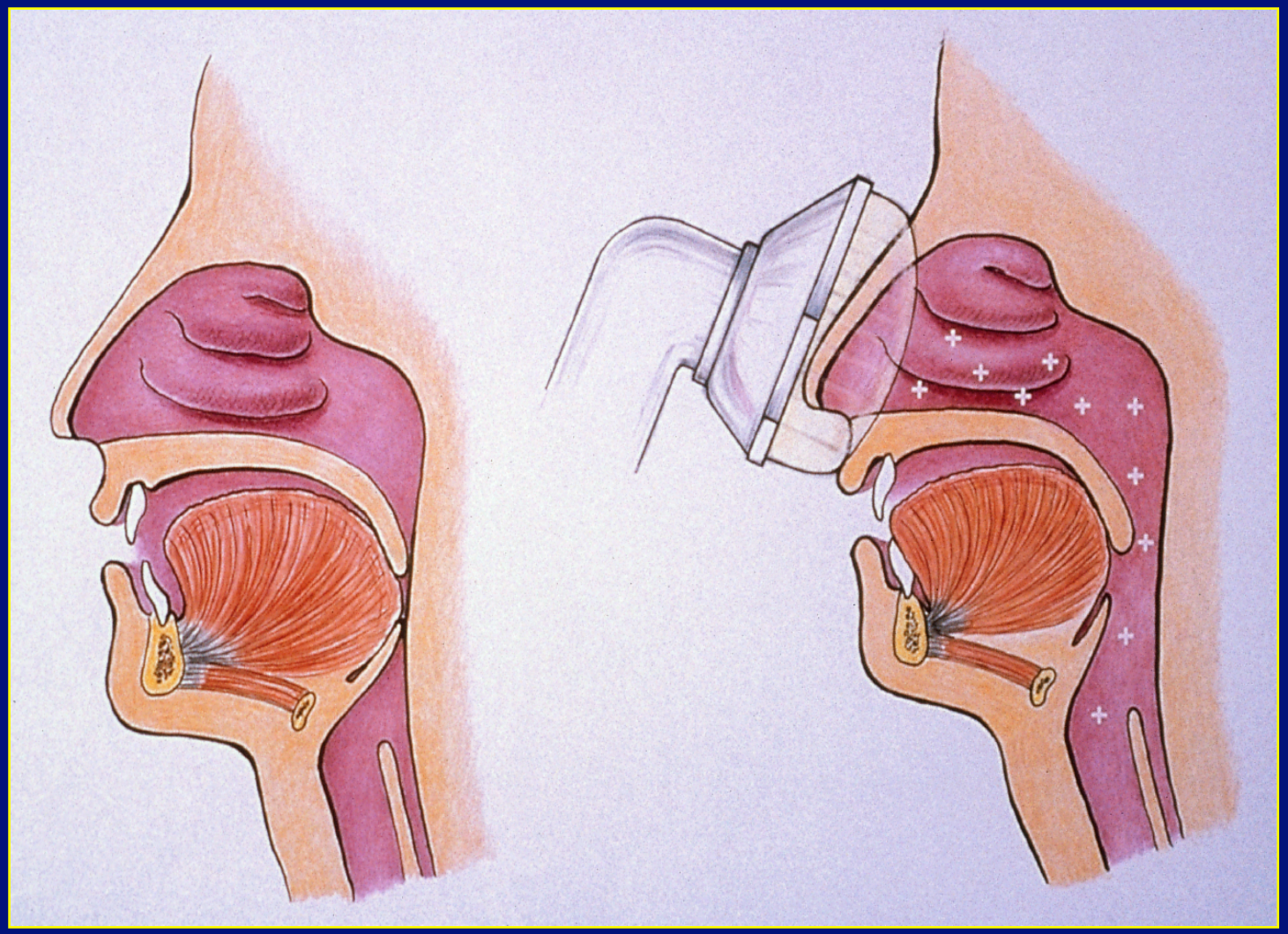
Weight Loss

- Should be prescribed for all obese patients
- Can be curative but has low success rate
- Other treatment is required until optimal weight loss is achieved

Medical Interventions

- Positive airway pressure
  - Continuous positive airway pressure (CPAP)
  - Bi-level positive airway pressure
- Oral appliances
- Other (limited role)
  - Medications
  - Oxygen

Positive Airway Pressure



Surgical Alternatives

- Reconstruct upper airway
  - Uvulopalatopharyngoplasty (UPPP)
  - Laser-assisted uvulopalatopharyngoplasty (LAUP)
  - Radiofrequency tissue volume reduction
  - Genioglossal advancement
  - Nasal reconstruction
  - Tonsillectomy
- Bypass upper airway
  - Tracheostomy

Insomnia

A complaint of:

- Difficulty falling asleep
- Difficulty staying asleep
- Poor quality sleep

Associated with:

- Distress
- Impaired function

Insomnia: Daytime Complaints

- Fatigue, sluggishness
- Sleepiness
- Somatic complaints (aches & pains)
- Stress about poor sleep
- Mood disturbances
- Poor concentration
- Impaired performance

Insomnia
Pathophysiology

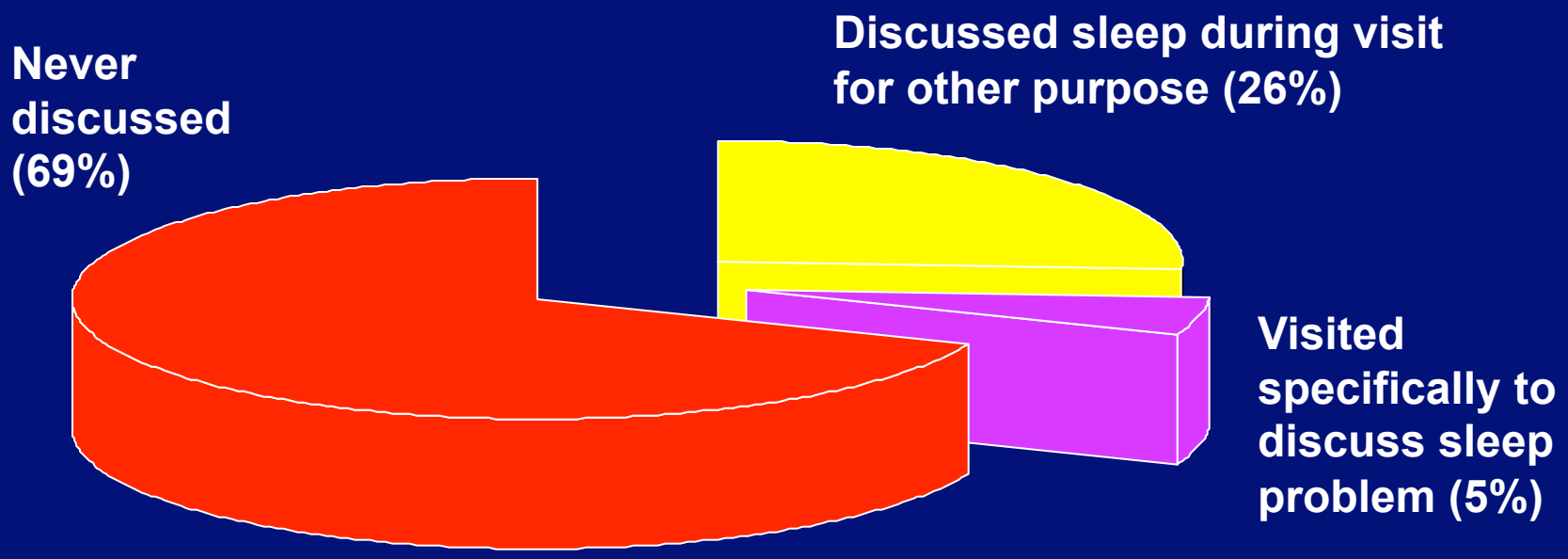
- **Increased physiological arousal**
  - Metabolic rate
  - Sympathetic activation
  - Hypothalamic-pituitary-adrenal axis
- **Increased alertness**
  - Conditioned state of hyperarousal
  - Decreased sleep efficiency
  - Normal MSLT

Insomnia
Consequences

- Decreased quality of life
- Increased healthcare costs
- Increased absenteeism
- Decreased productivity
- Increased risk for developing psychiatric disorders
- Increased accident risk

Insomniacs Under-Report Sleep Problems to Physicians

Percent of insomniacs who discussed any sleep problems with their physicians

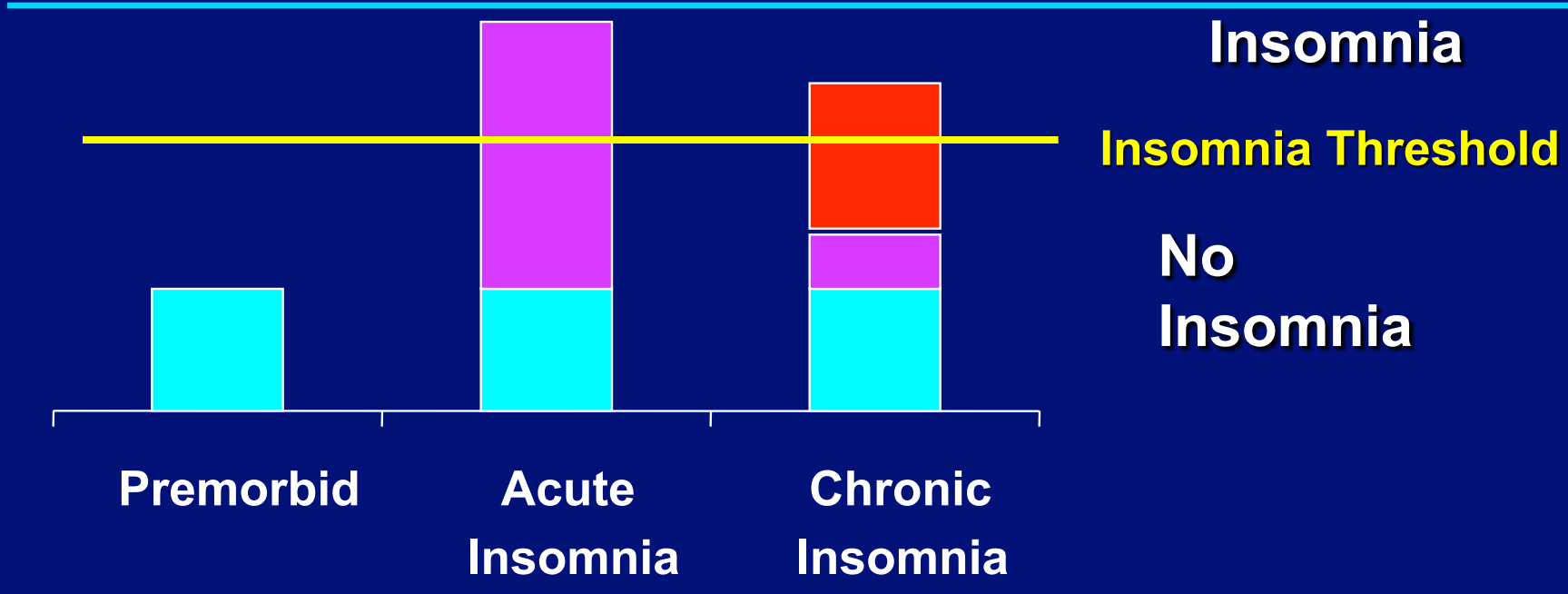


Adapted from Ancoli-Israel S et al. SLEEP 1999;22.

Insomnia
Major Risk Factors

- Previous history of insomnia
- Increasing age
- Female gender
- Psychiatric symptoms and disorders
- Medical symptoms and disorders

Evolution of Insomnia



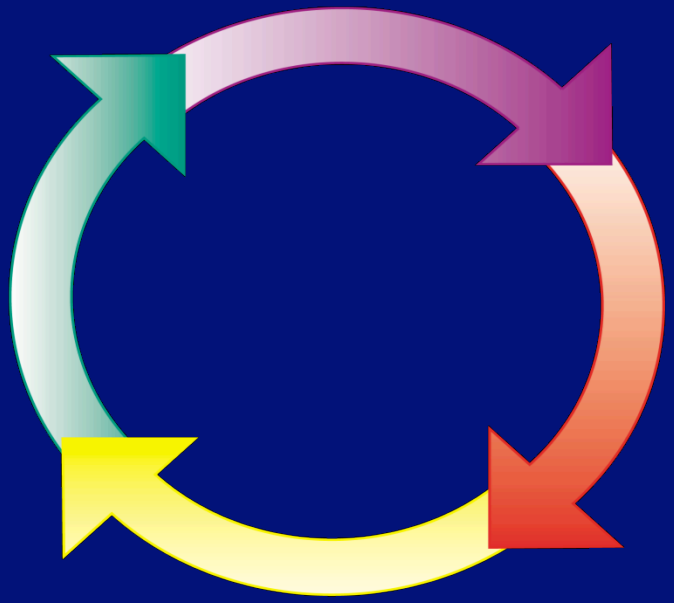
Adapted from Spielman AJ et al. In: Principles and Practice of Sleep Medicine, 3rd ed. Philadephia: W. B. Saunders Company, 2000.

Insomnia
Etiology-Based Classification

- **Secondary insomnia**
  - Acute psychological, social stressors
  - Medical, neurological, psychiatric disorders
  - Medications, substances
  - Specific sleep disorders (e.g. sleep apnea, restless legs syndrome)
- **Primary Insomnia**
  - Psychophysiological
  - Sleep state misperception
  - Idiopathic

Psychophysiological Insomnia

Difficulty falling asleep
or maintaining sleep



Frustration, fear of
sleeplessness

Physiological activation

Behavioral and
cognitive efforts
to promote sleep

Behavioral Treatment:
Sleep Hygiene

- Regular sleep / wake schedule
- Avoid stimulants and stimulating behavior
- Establish relaxing bedtime routine
- Provide conducive sleep environment
- Limit daytime naps
- Reduce or eliminate alcohol and caffeine
- Obtain regular exercise
- Avoid clock watching

Behavioral Treatment:
Stimulus Control

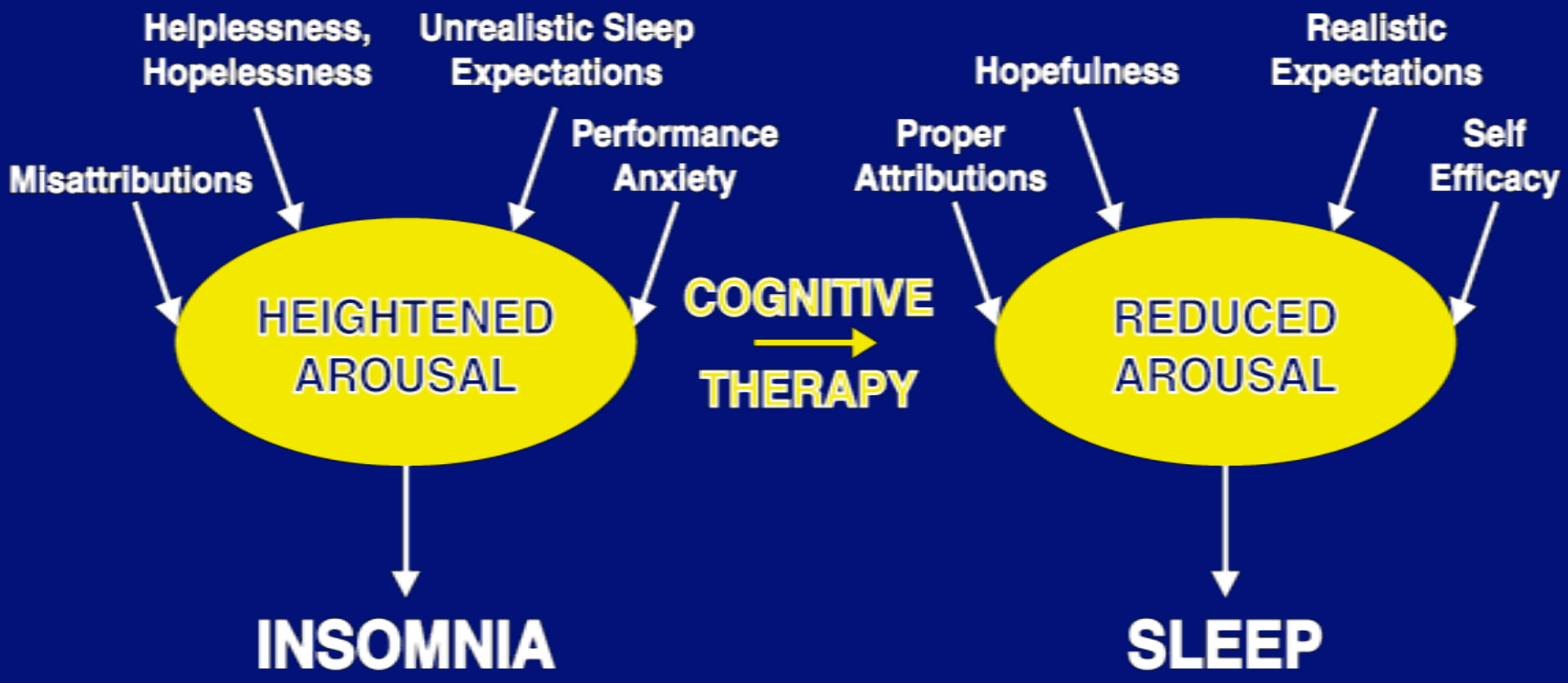
- Use bed for sleep (and sex)
- Go to bed only when sleepy
- Get out of bed when unable to sleep
- Wake up at a consistent time (including weekends)
- Do not take daytime naps

Behavioral Treatment:
Sleep Restriction

- Determine average time asleep
- Set time in bed = time asleep
- Consistent wake-up time
- No daytime naps
- If time asleep $\geq$ 90% of time in bed then increase time in bed (15-30 minutes)
- If time asleep < 80% of time in bed then decrease time in bed (15-30 minutes)

Spielman AJ et al. SLEEP 1987;10.

Behavioral Treatment:
Cognitive Therapy



Adapted from Morin CM. J Psychosom Res 1999;46.

Insomnia
Pharmacotherapy

- Benzodiazepine
- Non-Benzodiazepine receptor agonists
- Antidepressants
- Antihistamines
- Melatonin
- Others

Pharmacotherapy:
Benzodiazepine Receptor Agonists

Benzodiazepines

- Estazolam (Prosom)
- Flurazepam (Dalmane)
- Quazepam (Doral)
- Temazepam (Restoril)
- Triazolam (Halcion)

- Clonazepam(Klonopin)
- Lorazepam (Ativan)
- Alprazolam (Xanax)
- Diazepam (Valium)

Non-benzodiazepines

Zolpidem(Ambien)

Zaleplon(Sonata)

Eszopiclone(Lunesta)

Insomnia
Pharmacotherapy Guidelines

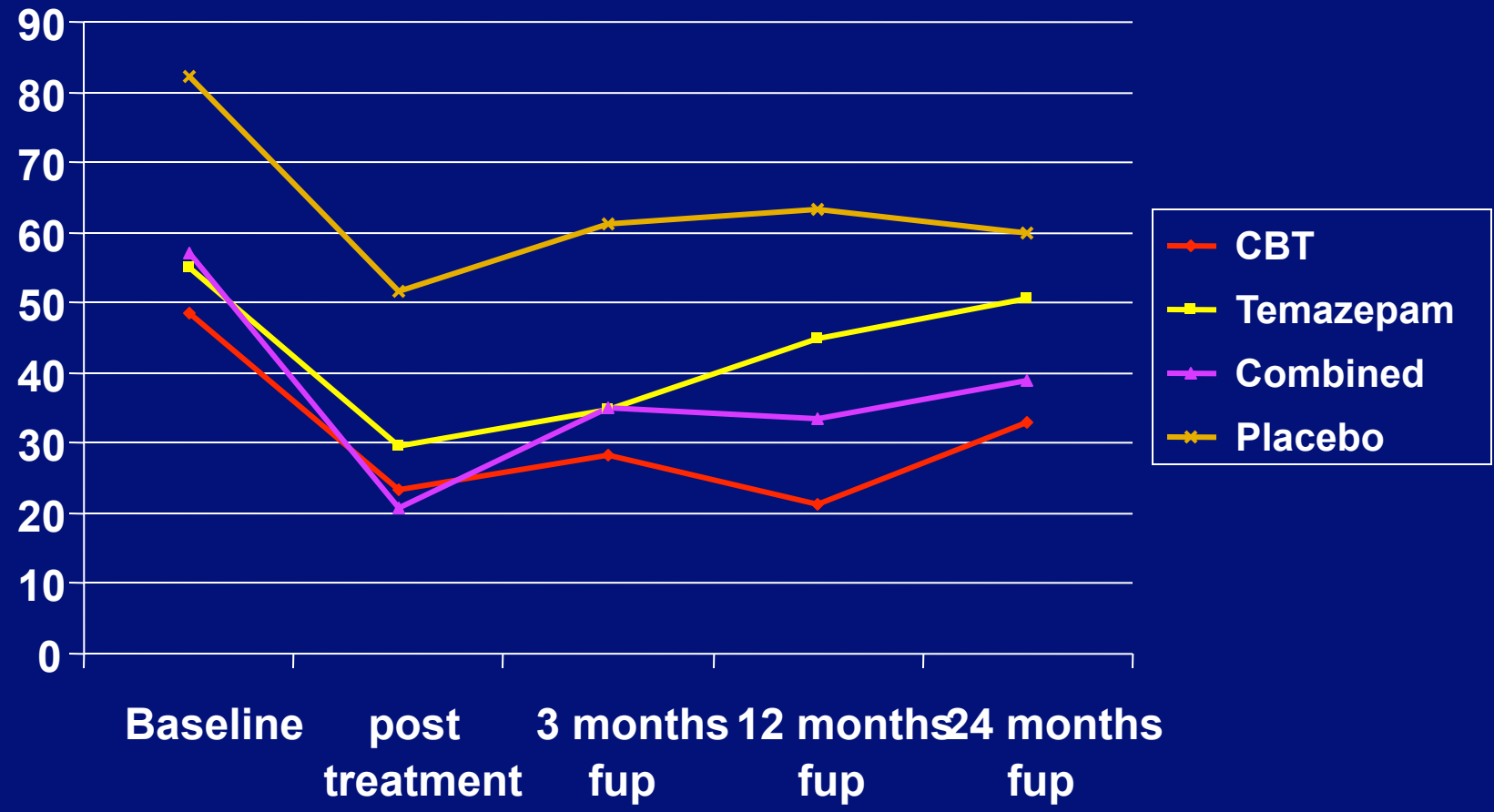
- Select appropriate medication
- Use lowest effective dose
- Use at bedtime (or later, if indicated)
- Duration of therapy
  - Use as needed for 2 to 4 weeks
  - Reduce dose as tolerated
  - Intermittent use suggested
  - Reassess and adjust approach
- Combine with behavioral strategies

Insomnia
Pharmacologic Treatment

Specific Populations

- **Sleep apnea**: consider antidepressant rather than benzodiazepine receptor agonist
- **Elderly**: low-dose, short-acting benzodiazepine receptor agonist
- **Substance abuse history**: antidepressant preferred
- **Co-morbid depression or anxiety disorder**:
  - SSRI + benzodiazepine receptor agonist
  - SSRI + trazodone
  - Nefazodone, mirtazapine

Insomnia Treatment
Comparative Efficacy:
CBT, Temazepam, and Their Combination



Adapted from Morin CM et al. JAMA 1999;281.

Restless Legs Syndrome

A neurological movement disorder characterized by an irresistible urge to move the legs accompanied by uncomfortable sensations that often occur in the evening or when at rest

Allen et al. *Sleep Med*. 2003;4:101-119.

Key Diagnostic Criteria for RLS

Key RLS Diagnostic Criteria*	Supportive Features*
✓ **Urge to move the legs**—usually accompanied or caused by uncomfortable leg sensations	– Sleep disturbances
✓ **Temporary relief with movement**—partial or total relief from discomfort by walking or stretching	– Involuntary leg movements
✓ **Onset or worsening of symptoms at rest or inactivity**, such as when lying or sitting	– Positive family history for RLS
✓ **Worsening or onset of symptoms in the evening or at night**	– Positive response to dopaminergic therapy

* Diagnostic criteria developed by the International RLS (IRLS) Study Group in collaboration with the National Institutes of Health (NIH).

Allen et al. *Sleep Med.* 2003;4:101-119.

Restless Legs Syndrome (RLS)

- Affects approximately 10% of US adults
- Sleep disturbance is often the primary reason patients seek medical attention
- Common onset after age 40
- More prevalent in women
- Positive family history in 40-50%

RLS-Pathophysiology

- A leading hypothesis is brain dopamine dysfunction. This could involve changes in:
  - Dopamine receptors and their function
  - Uptake of dopamine
- There is evidence for brain iron deficiency in early-onset RLS
  - Iron is vital to the function of the brain's dopamine systems
- There is a strong genetic component in early-onset RLS, with several family studies demonstrating an autosomal-dominant hereditary pattern

Secondary RLS

It is important to rule out other underlying conditions that are associated with secondary RLS:

- Low serum ferritin levels or iron deficiency
- Consider other medications that may be contributing to RLS symptoms
- Renal failure
- Pregnancy
- Peripheral neuropathies

RLS Treatment
Non-pharmacological

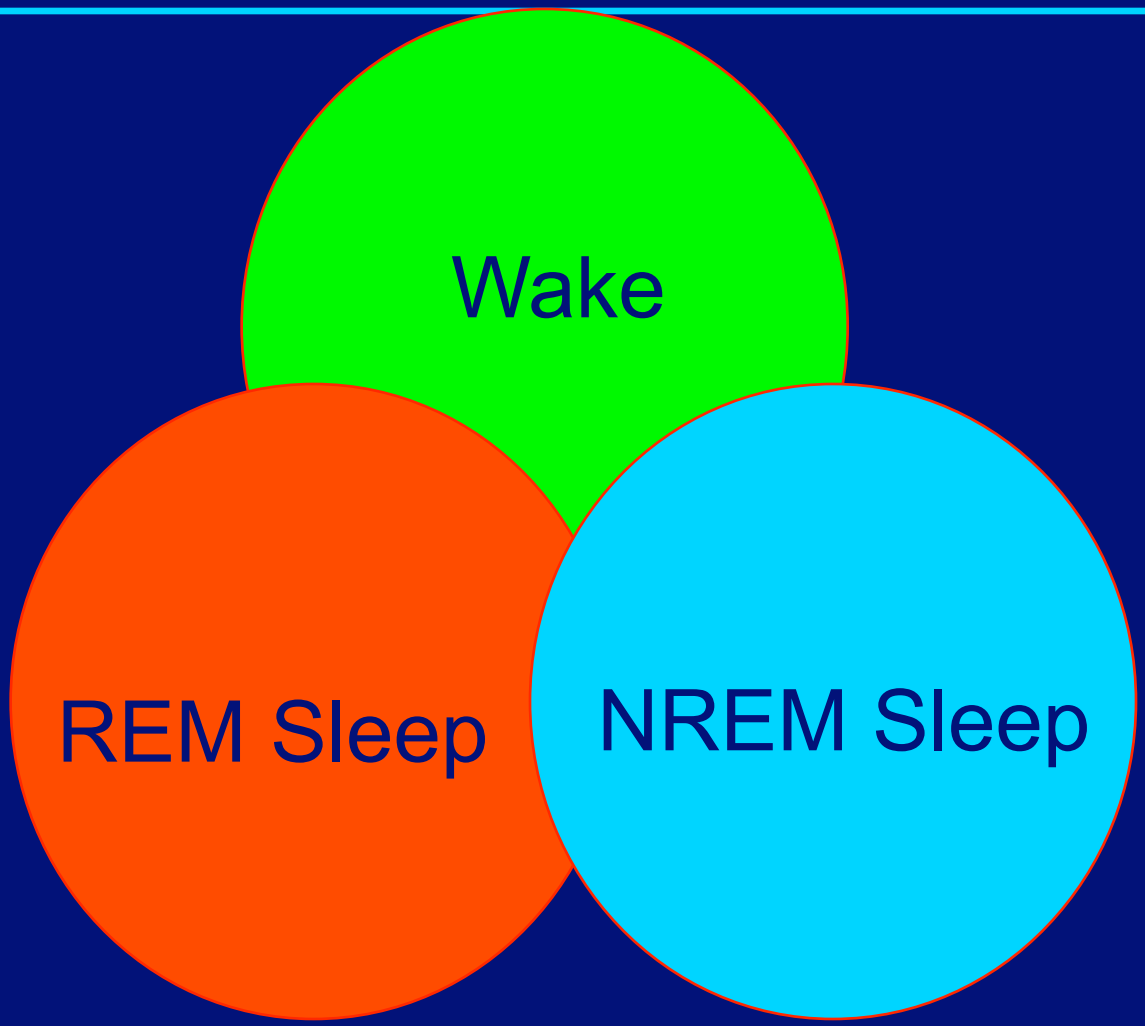
- Avoid Caffeine, Nicotine, and Alcohol.
- Consider effect of medications that may enhance RLS: all antidepressants except Welbuterin, neuroleptic agents, antinausea agents, and sedating antihistamines.
- Iron replacement if serum Ferritin level less than 40 µg/L.

RLS Treatment Pharmacological

- Dopamine Agonists are the drugs of choice in most patients with RLS (Pramipexole, Ropinirole).
- Low potency opioids such as propoxyphene
- Opioid Agonist such as Tramadol
- Benzodiazepines
- Gabapentin
- High potency Opioid (Methadone) for refractory cases

Parasomnias

Dissociated States of Wakefulness and Sleep



REM-Sleep Behavior Disorder
(Wake-REM Dissociation)

Definition:

Intermittent absence of REM sleep atonia, allowing acting out of dreams

REM-Sleep Behavior Disorder (RBD)

Clinical Features:

- Older male predominance
- Progressive course, preceded by prolonged prodrome
- Dramatic, potentially violent, motor behavior during sleep, emerging >60-90 min after sleep onset.
- Chief complaint: injury to self or bed partner during sleep.
- Dream-enacting behavior always correlates with reported dream. Completely discordant with waking personality.

RBD - Altered Dreams

- Vivid, intense, full of action, unpleasant.
- Dreamer is being threatened or attacked by unfamiliar people, animals, insects.
- Dreamer is rarely the primary aggressor.
- Fear and anger are predominant moods.
- Dreamer is often defending his wife in a dream while actually beating her in bed.

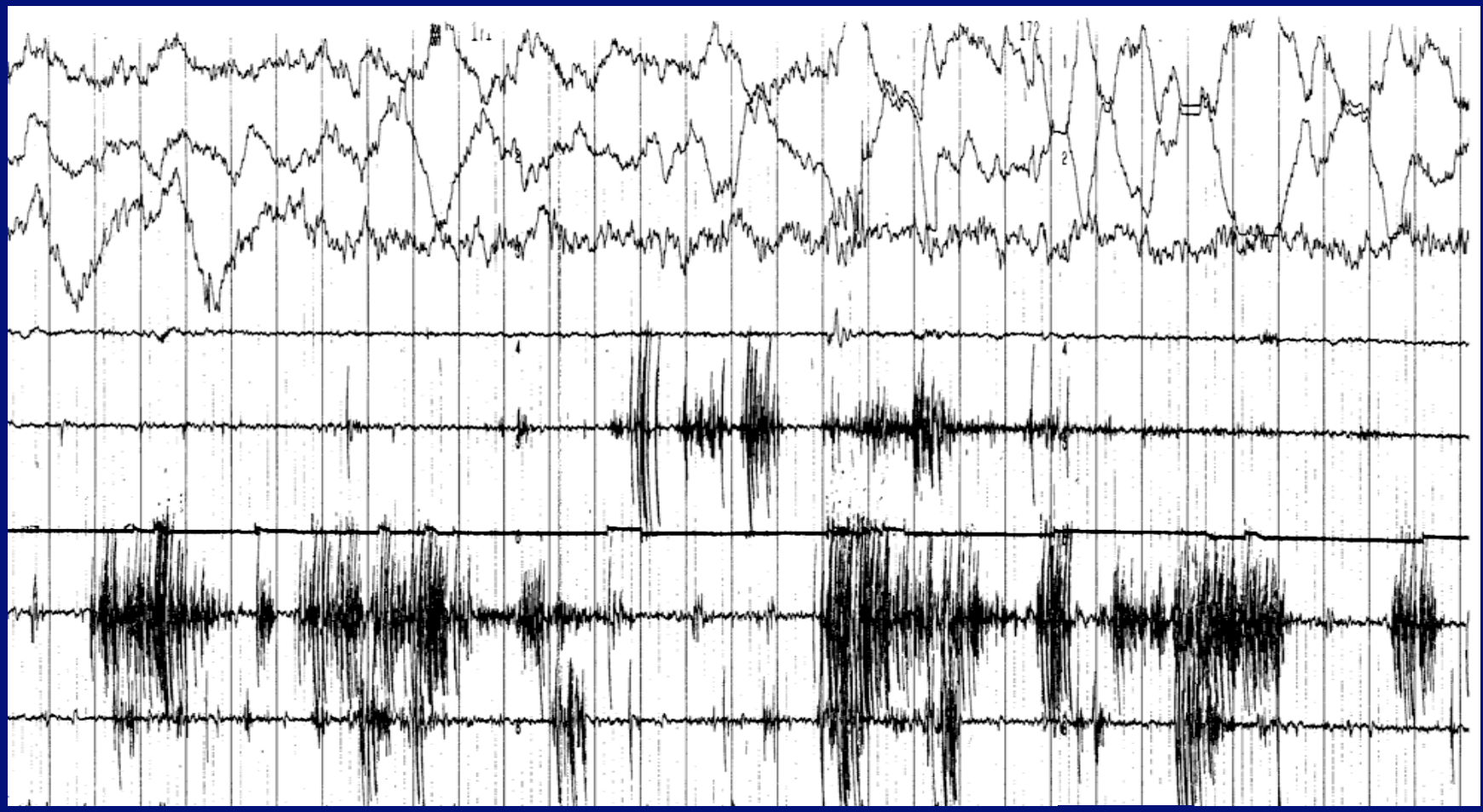
RBD - Sleep-Related Injury

- Bruises
- Lacerations
- Fractures (including C2 “hang man”)
- Subdural hematomas
- Dislocations
- Abrasions/rug burns
- Tooth chipping, hair pulling

RBD - Prevalence

- 0.8% prevalence in the general population
- 87% of patients are men, with a mean age of onset of 52 years
- Typically a disorder of middle-aged and older males, but females and any age group can be affected

RBD - Polysomnography



REM Sleep without Atonia

Acute RBD

- Alcohol/Drug/Medication withdrawal
- Drug intoxication (Anti-cholinergic agents, Tricyclic antidepressants, MAOIs)
- Relapsing multiple sclerosis

Chronic RBD

- Idiopathic (52%)
- Associated with Neurologic Disorders (40%)
- Medication-induced: Beta-blockers, SSRIs, Venlafaxine (Effexor), Mirtazapine (Remeron), Tricyclic antidepressants– BUT NOT Bupropion (Zyban, Wellbutrin), a dopaminergic antidepressant.

RBD, Parkinsonism, and Dementia

- 45% of RBD patients develop Parkinson's disease several years after the diagnosis with a mean of 11.5 years (range 5-23) from the onset.
- 64% of RBD patients develop Synucleinopathy : Parkinson's disease, Muliple System Atrophy, or Lewy body Dementia.
- Men 50 years of age and older with idiopathic RBD should be told about the high risk for future Parkinsonism and Dementia.

Treatment of RBD

- Secure the environment.

- Clonazepam 0.5 – 1.5 mg is most effective; results in rapid control of problematic sleep behaviors and altered dreams in 90% of patients.

- Melatonin (3 – 12 mg) can be effective

- Other options: Carbamazepine, Clonidine, Gabapentin, and Donepezil.