A Review of Sleep Disorders in Neurology

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Stage I sleep. Vertex waves are focal sharp transients typically best seen on transverse montages (through the midline), and would be missed on this longitudinal bipolar montage if it did not include midline channels (Fz-Cz-Pz). Vertex waves are seen in stages I and II sleep.
Stage I sleep. POSTS are seen in both occipital regions, with their typical characteristics contained in their name: Positive Occipital Sharp Transients of Sleep. They also have the morphology classically described as comparable to a reverse check mark, and often occur in consecutive runs of several seconds, as shown here.
Stage II sleep. On this transverse montage, there is a K-complex in the fifth second, with its typical broad duration (>500 ms), diphasic morphology, and overriding spindle. There are also abundant spindles before and after.
Slow wave sleep. There is predominantly delta activity.
REM sleep. Typical saccadic eye movements are shown, with lateral rectus “spikes” seen just preceding the lateral abducting eye movements.
Generation of REM sleep

Lateral dorsal tegmental (LDT) nuclei

Pedunculopontine tegmental (PPT) nuclei
Biochemistry of REM Sleep

- REM off systems
  - noradrenaline
  - serotonin
- REM on systems
  - acetylcholine

Increased REM sleep pressure
An EEG recording of a 24 year-old lady.
The following description is correct EXCEPT:

- (A) Positive occipital sharp transients (POSTs) usually coexist
- (B) Sleep spindles and K-complexes may follow
- (C) Rapid eye movement is evident in this stage
- (D) Slow eye movement (eye rolling) is evident in this stage
- (E) It can not be taken as epileptiform discharges
DSM-IV Diagnostic Criteria for Primary Insomnia

>1 month of

- Difficulty initiating sleep
- Difficulty maintaining sleep
- Nonrestorative sleep

Causes significant distress or impairment in functioning

Sleep problem cannot be accounted for by another sleep disorder, a medical problem, a substance (drug/medication), or a psychiatric condition.

The Development of Psychophysiological Insomnia

# Insomnia Intensity

## COURSE
- Baseline
- Acute Insomnia
- Short-term Insomnia
- Chronic Insomnia

## Threshold

- **Predisposing Factors**
- **Precipitating Factors**
- **Perpetuating Factors**
Behavioral Treatment of Insomnia

- Sleep hygiene
- Relaxation training
- Stimulus control instructions
- Sleep restriction therapy
## Mechanisms of Sleep-Promoting Agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedatives &amp;</td>
<td></td>
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<tr>
<td>Hypnotics</td>
<td>Barbiturates</td>
<td>Phenobarbital</td>
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<td></td>
<td>Barbiturates</td>
<td>GABA&lt;sub&gt;A&lt;/sub&gt;</td>
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<tr>
<td></td>
<td>Benzodiazepine</td>
<td>Flunitrazepam</td>
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<td></td>
<td>Benzodiazepine</td>
<td>Nitrazepam</td>
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<td></td>
<td>Benzodiazepine</td>
<td>Estazolam</td>
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<td>Imidazopyridine</td>
<td>Zaleplon</td>
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<td>Imidazopyridine</td>
<td>Zolpidem</td>
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<tr>
<td>Anticonvulsant</td>
<td>Gaboxadol</td>
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<td></td>
<td>Tiagabine</td>
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<td></td>
<td>Gabapentin</td>
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<tr>
<td>Antidepressant</td>
<td>Mirtazapine</td>
<td>5HT2&lt;sub&gt;A&lt;/sub&gt;</td>
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<tr>
<td></td>
<td>Trazodone</td>
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<tr>
<td>Antihistamine</td>
<td>Cyproheptadine</td>
<td>H&lt;sub&gt;1&lt;/sub&gt;</td>
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<tr>
<td></td>
<td>Diphenhydramine</td>
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Human Disasters due to Sleepiness
## Epworth Sleepiness Scale (ESS)

<table>
<thead>
<tr>
<th>Situation</th>
<th>Chance of dozing (0–3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting and reading</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Watching television</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Sitting inactive in a public place—for example, a theater or meeting</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>As a passenger in a car for an hour without a break</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Lying down to rest in the afternoon</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Sitting and talking to someone</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Sitting quietly after lunch (when you’ve had no alcohol)</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>In a car, while stopped in traffic</td>
<td>0 1 2 3</td>
</tr>
</tbody>
</table>

**Total Score**


0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing
Multiple Sleep Latency Test

• Series of naps, presented at 2-h intervals, beginning approx. 2-h after initial (morning) awakening.

• Normal MSLT:
  • Mean sleep latency – 10-20 mins
  • < 2 Sleep onset REM period (SOREMP)
MSLT and Age

Average Latency

- Early Adolescents
- Adults
- Elderly
Obstructive Sleep Apnea (OSA)
Case Demo of OSA
Figure 2  A 1-minute epoch from the baseline portion (A) of the study. This figure demonstrates the relationship between the obstructive apnea [characterized by nasal oral (N/O) breathing cessation (φ) in the presence of paradoxical respiratory effort (*), EEG arousal, and hypoxemia] and the arrhythmia. Notice the association of the sinus pause with the onset of hypoxemia associated with this obstructive event. Channels are as follows: electrooculogram (left: LOC-A2; right: ROC-A1), chin EMG, EEG (left central, right central, left occipital, right occipital), electrocardiogram, limb EMG (left leg, right leg), snoring, nasal-oral airflow, respiratory effort (thoracic, abdominal), nasal pressure, and oxygen saturation.
Symptoms of OSA

- Excessive daytime sleepiness
- Habitual snoring
- Witnessed apneic episodes
- Choking or gasping in sleep
- Tiredness upon awakening
- Nocturia
- Morning headache
Continuous Positive Airway Pressure (CPAP)
Mandibular Repositioning Appliance (MRA)
Uvulopalatopharyngoplasty (UPPP)
Mechanisms Associated With Obstructive Sleep Apnea That Potentially Contribute to Risk of Cardiovascular Disease

Obstructive Sleep Apnea
- Hypoxemia
- Reoxygenation
- Hypercapnia
- Intrathoracic Pressure Changes
- Arousals

Intermediary Mechanisms
- Sympathetic Activation
  - Vasoconstriction
  - Increased Catecholamines
  - Tachycardia
  - Impaired Cardiovascular Variability
- Endothelial Dysfunction
- Vascular Oxidative Stress
- Inflammation
- Increased Coagulation
- Metabolic Dysregulation
  - Leptin Resistance
  - Obesity
  - Insulin Resistance

Risk of Cardiovascular Disease
- Hypertension
- Congestive Heart Failure
  - Systolic Dysfunction
  - Diastolic Dysfunction
- Cardiac Arrhythmia
  - Bradycardia
  - A-V Block
  - Atrial Fibrillation
- Cardiac Ischemia
  - Coronary Artery Disease
  - Myocardial Infarction
  - Nocturnal ST-Segment Depression
  - Nocturnal Angina
- Cerebrovascular Disease

Polysomnography of a 46 year-old obese man
The following descriptions are correct EXCEPT:

• (A) Avoid alcohol or benzodiazepine should be suggested
• (B) MSLT is the next step to support the diagnosis
• (C) The treatment of choice is CPAP
• (D) Hypersomnia is a major daytime symptom
• (E) Hypertension is usually associated
Central Apnea with Age

Bixler EO. Am J Respir Crit Care Med 1998;157:144
Lesions for Central Sleep Apnea

A: Chemoreceptors
B: Respiratory groups
C: Cervico-medullary junction
D: Anterior horn cells
E: Phrenic nerve
F: N-M junction
G: Diaphragm
Two Types of CSA

• 1) Normocapnic or hypocapnic CSA (including Cheyne-Stoke breathing, idiopathic central sleep apnea and high altitude central sleep apnea)
• 2) Hypercapnic CSA (sleep—related hypoventilation/Hypoxemic syndrome)
Diagnostic Criteria of CSR

1) Either congestive heart failure or neurological disease with respiratory monitoring that demonstrates at least three consecutive cycles of a cyclical crescendo and decrescendo change in breathing amplitude.

2) Either five or more central sleep apneas-hypopneas per hour of sleep or cyclic crescendo and decrescendo changes in breathing amplitude that have a duration of at least 10 consecutive minutes.
Diagnostic Criteria of SHHS

- Either erythrocytosis, cor pulmonale, pulmonary hypertension, or excessive daytime hypersomnolence not explained by other factors.
- Hypercapnia (PSG shows either an increase in PaCO2 greater than 55 mmHg for at least 10 minutes or an increase in PaCO2 during sleep greater than 10 mmHg from wake values to a value exceeding 50 mmHg for at least 10 minutes).
SHHS not related with Respiratory Diseases

- Disorders of the sensory input systems
- Disorders of the central ventilatory control system
- Defects of the motor output system
MRI (T2WI) at C2-C3 Level
MRI (T2WI) at Medulla Level

- Medial longitudinal fasciculus
- Spinal trigeminal tract and nucleus
- Pyramids
- Nucleus ambiguus
- Solitary nuclei and tract
- Gracile and cuneate nuclei
The following diseases can cause OSA and CSA (including SHVS) EXCEPT:

- (A) Supratentorial stroke
- (B) Brain stem stroke
- (C) Myotonic dystrophy
- (D) Pompe disease
- (E) Cervical spinal cord injury
Narcolepsy (Tetrad)

- Excessive daytime sleepiness (EDS)
- Cataplexy
- Hypnagogic/ Hypnopompic hallucinations
- Sleep paralysis
- (Disrupted nocturnal sleep)
Case Demo of Cataplexy
Onset of Narcolepsy

Age of onset in years

Number of patients

Honda 1988
MSLT Findings in Narcolepsy

- Mean sleep latency < 8 minutes
- Sleep onset REM period (SOREMP) $\geq 2$
Narcolepsy is characterized by a sudden transition from wake to REM sleep (sleep-onset-rapid-eye-movement period, SOREMP)
HLA Typing in Narcolepsy

Chromosome 6p21

Serological Typing

DQ 1

DQ 6

DQ 5

DNA based Typing

DQB1 *0602

DQA1 *0102

Other DQB1*06 and DQA1*01 Subtypes

DRB1 *1502 (Asians)

DRB1*1501 (Caucasians/Asian

DRB1*1503 (African-American

DRB1*1101 (African Americans)
Highly Selective CNS Activity

PROVIGIL promotes wakefulness without generalized CNS stimulation in preclinical models

PROVIGIL  Amphetamine  Methylphenidate

CA = caudate  H = hypothalamus
Data adapted from Lin, Hou, Jouvet, 1996, study in cat.

Treatment of Cataplexy and REM-related Phenomenon

- Tricyclic antidepressant (TCA)
- Selective serotonin reuptake inhibitors (SSRI)
- Sodium oxybate: a naturally occurring neurotransmitter in the brain involved in sleep regulation and a central nervous system depressant is used as a new anti-cataplastic agent with unknown mechanism.
Which of the following statement about narcolepsy with cataplexy is CORRECT?

• (A) In most patients, it is associated with HLAB8
• (B) Orexin/Hypocretin is produced by a group of neurons in the posterior lateral hypothalamus
• (C) CSF orexin/hypocretin level is elevated in most patients with narcolepsy
• (D) Sleep paralysis is usually the first symptom in patients with narcolepsy and cataplexy
• (E) Hypnagogic hallucinations are absent
REM Sleep Behavior Disorder

- 0.5% in the elderly
- Abnormal behavior associated with excess of EMG during REM sleep
- Sleep-related injury
- Male-predominant, age 50 or older
- Idiopathic
- Neurological disorders (alpha-synucleinopathy): Parkinsonism, dementia with Lewy bodies, multiple system atrophy, stroke, antidepressants
Case Demo of RBD
REM Sleep Without Atonia

Pathophysiology of REM sleep behavior disorder

- Lesion in Pons medulla leads to Lack of excitation
- Lack of inhibition in Medullary inhibitory area
- Motor neurons inhibit muscles
- Net effect: Muscle atonia

- Lesion in Pons medulla leads to Lack of excitation
- Medullary inhibitory area excites motor neurons
- Motor neurons inhibit muscles
- Net effect: Lack of muscle atonia
Management of RBD

- Environmental safety
- Clonazepam (Rivotril 0.5-1 mg qhs): highly effective (90% or more)
- Levodopa or dopamine agonist: maybe effective in patients associated with Parkinson’s disease
- Melatonin: case report
Polysomnography of a 68 Year-Old man with RBD
REM sleep behavior disorder can be found in:

- (A) Pontine infarction
- (B) Multiple system atrophy
- (C) Parkinson’s disease
- (D) Dementia with Lewy bodies
- (E) All of above
Disorders of Arousal

- Somnabulism (sleep walking)
- Sleep terror
- Confusional arousals

From ghoulies and ghosties,
And three leggity beasties,
And things that go bump in the night,
Good Lord, deliver us.
*Old Scottish Prayer*
Case Demo of Sleep Terror In a Child
Polysomnography of Somnabulism
Management of Sleep Walking

- Decrease deeper sleep: avoid sleep deprivation
- Decrease source of arousals: sleep-disordered breathing, RLS/PLM, external noise
- Good sleep hygiene
- Benzodiazepines
- Benign neglect: if mild, safe and not common (mostly for children)
- Respond to event: ensure safety, encourage return to sleep
Which of the following sleep disorders is (are) found in the NREM sleep stage?

- A. Sleep walking
- B. Nightmares

- (A) A only
- (B) B only
- (C) Both A and B
- (D) Neither A and B
Epilepsy Misdiagnosed as Sleep Disorders

- Nocturnal frontal lobe epilepsy (NFLE)
  - Paroxysmal arousals (PA)
  - Epileptic nocturnal wandering (ENW)
  - Nocturnal paroxysmal dystonia (NPD)
  - Supplementary motor seizures

- Nocturnal temporal lobe epilepsy
Which of the following statements is CORRECT about the differential diagnosis of nocturnal seizure and parasomnia?

- (A) Parasomnia usually presents as stereotypic behavior
- (B) Parasomnia is usually associated with dystonic or tonic posture
- (C) Patients with nocturnal seizure usually can remember the events
- (D) Nocturnal seizure usually occurs in clusters
- (E) The duration of attack of parasomnia is usually brief but nocturnal seizure is much longer
Restless Legs Syndrome (RLS)

- An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs
- Begin or worsen during periods of rest or inactivity
- Partially or totally relieved by movement, such as walking or stretching
- Worse, or only occur, in the evening or night
- Cause secondary insomnia
Secondary RLS

- Iron deficiency anemia and low ferritin levels
- Polyneuropathy
- Uremia
- Folate/ Vitamin B12 deficiency
- Hypothyroidism
- Pregnancy
- Varicose veins
- Cigarette smoking and caffeine
- Obesity
Medications and Secondary RLS

- Psychotropic agents: dopamine antagonists, antidepressants, lithium (Bupropion with its dopaminergic activity may benefit RLS)
- Antihistamine, Antinausea/Antiemetics
- Alcohol and caffeine
- Beta blockers, CCBs
Periodic Limb Movement in Sleep (PLMS)

- Rhythmic dorsiflexion of the big toe and ankle with occasional flexions of the knee and hip
- Recording tibialis anterior EMG activity
- Duration: 0.5 – 10 seconds
- Intermovement interval: 5 – 90 seconds (most frequently 20 – 40 seconds)
- ≥ 4 leg movements in a series
- The amplitude of the EMG ≥ 25% of the amplitude reached during biological calibration
Case Demo of PLMS
PSG of PLMS (30 seconds)
Treatment for RLS and PLMS

- Dopamine agonists (Ropinirole, Pramipexole)
- Benzodiazepine: Clonazepam
- Anticonvulsant: Gabapentin
- Opiates
Which of the following conditions shows least association with secondary restless legs syndrome?

- (A) Motor neuron disease
- (B) Uremia
- (C) Iron deficiency
- (D) Pregnancy
- (E) Neuropathy
Which of the following medication is NOT indicated for the treatment of RLS?

- (A) Ropirinorole
- (B) Levodopa
- (C) Clonazepam
- (D) Gabapentin
- (E) Trazodone
Kleine-Levin Syndrome

- A rare condition almost exclusive to adolescent males that includes episodes of hypersomnia, cognitive changes, eating disturbances, hypersexuality, compulsions, and depressed mood.
- It can be idiopathic or secondary to infection, trauma, or alcohol consumption.
- When it occurs in females, it is more severe.
- Patients are normal in between episodes and it generally resolves over time.
Clock in the Brain

Suprachiasmatic Nuclei (SCN)

Light

Output Rhythms
Physiology
Behavior
Free-running of Human Circadian Rhythm
Sleep Phase Syndromes

SUMMARY

ASPS: advance sleep phase syndrome
DSPS: delayed sleep phase syndrome
The discovery that bright light (2,500-10,000 Lux) shifts human circadian rhythms and that the size and direction of the shift depends on time of exposure, has been a significant breakthrough in the management of circadian rhythm disorders. Light in the early morning (~6AM) advances rhythms, whereas, light in the evening (6-8 PM) delays circadian rhythms. Bright light therapy has been used successfully in several situations:
Figure 5.3 People traveling east suffer more serious jet lag than people traveling west.
Figure 5.4 The graveyard shift is aptly named—serious industrial accidents usually occur at night, when workers are least alert. Night-shift jobs providing emergency services are essential. But few people want to work permanently at night, so workers rotate among three shifts. As in jet lag, the direction of change is critical. Moving forward—clockwise—is easier than going backward.
Sleep Diary of a 23 year-old woman
Which one is the most likely diagnosis?

- (A) Advanced sleep phase syndrome
- (B) Delayed sleep phase syndrome
- (C) Non-entrained (free-running) sleep-wake disorder
- (D) Irregular sleep-wake disorder
- (E) Primary insomnia
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