Teaching Course 18

Basics of sleep medicine - Level 1

Primary sleep disorders - symptoms, diagnosis & treatment

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Primary Sleep Disorders – Symptoms, Diagnosis & Treatment

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Goals of Presentation

- To identify definitions and classification of common primary sleep disorders associated with neurological disorders
  - Insomnia
  - REM and NON-REM parasomnia’s,
  - Narcolepsy,
  - Sleep Disordered Breathing (SDB) including OSAS, and
  - Restless Legs Syndrome

Conflict of interest:
The author has no conflict of interest in relation to this manuscript
Why should clinicians show interest into sleep disorders

- **Sleep disorders are common**
  - SDB occurs in >4% of adults
  - Chronic insomnia >6% of adults
- **A significant proportion of neurological pts present sleep disorders**
  - >90% of PD/PD+ present sleep related symptoms/findings
  - >60% of stroke pts present SDB
  - >1/3 of epilepsy pts present nocturnal fits
- **Sleep disorders may be a risk for later neurological /psychiatric disorders**
  - RBD is a significant risk factor for development of PD/PD+
  - Insomnia is associated with later for depression
- **A significant proportion of these disorders are unrecognized**
  - e.g. <20% of narcoleptic/SDB pts are identified.
- **Sleep disorders causes significant burden**
  - SDB strongly associated with morbidity and mortality
  - <50% of narcolepsy pts are employed
  - Sleep disorders causes significant societal burden

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**International classification of sleep disorders**

- The insomnias
- The sleep-related breathing disorders
- The hypersomnias not due to a breathing disorder
- The circadian rhythm sleep disorders
- The parasomnias
- The sleep-related movement disorders
- Isolated symptoms, apparently normal variants and unresolved issues
- Other sleep disorders
Insomnia defined

- Diagnosis requires one or more of the following:
  - difficulty initiating sleep
  - difficulty maintaining sleep
  - waking up too early, or
  - sleep that is chronically nonrestorative or poor in quality
- Sleep difficulty occurs despite adequate opportunity and circumstances for sleep.
- Insomnia is not sleep deprivation, but the two may coexist.

Insomnia defined


Comorbid (secondary) insomnia

- Insomnia associated with another medical, neurological or psychiatric disease
- Impacts quality of life and worsens clinical outcomes\(^1\),\(^2\)
- Predisposes patients to recurrence\(^3\)
- May continue despite treatment of the primary condition\(^4\)
- “Comorbid insomnia” more appropriate than “secondary insomnia,” because limited understanding of mechanistic pathways in chronic insomnia precludes drawing firm conclusions about the nature of these associations or direction of causality. Considering insomnia to be “secondary” may also result in undertreatment.\(^5\)

\(^1\) Roth T, Ancoli-Israel S. Sleep. 1999;22:S354-S358.
Epidemiology of insomnia

- General population: 10-15%
- Clinical Practice: > 50%
- The prevalence and treatment of primary insomnia have been the most studied (less than 20% of cases)\(^1,2\)
- Comorbid insomnia accounts for >80% of cases

Pathophysiology of insomnia

- Changes in sleep-wake structure – the hyperarousal model
- Genetics
- Physiological markers
- Morphological changes
- Psychologic
- Co-morbid conditions
Polysomnographic and power density differences between good and poor sleepers

Figure 1
The relative importance of three types of factors in the course of insomnia
Indicators of hyperarousal in insomnia


Comorbid factor involved in sleep disturbances in the elderly

Constitutional factors, age, gender

Medical-neurological diseases

Social, family factors

Psychiatric diseases

Life style factors

Medication

Sleep disorders
### Meta-analysis of the effects of insomnia for future depression after exclusion of the outliers (fixed-effects meta-analytic model)

<table>
<thead>
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<th>Study name</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
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**Baglioni et al. Journal of Affective Disorders 2011**

### Conditions that can cause insomnia

- Hyperthyroidism
- Arthritis or any other painful condition
- Chronic lung or kidney disease
- Cardiovascular disease (heart failure, CAD)
- Heartburn (GERD)
- Neurological disorders (epilepsy, Alzheimer’s, headaches, stroke, tumors, Parkinson’s Disease)
- Diabetes
- Menopause
Neurological disorders associated with insomnia

- Neurodegenerative disorders
  - PD, MSA, PSP, AD, LBD, narcolepsy
- Stroke
  - Thalamic, hypothalamic, brain stem
- Hereditary diseases
  - MJD, HC, HSP...
- Epilepsy with nocturnal fits
  - Nocturnal frontal and temporal lobe seizures, paroxysmal arousal vs parasomnias/sleep related movement disorders
- Headache
  - Migraine, Cluster Headache, hypnic headache, tension-type headache
- Pain
  - Radiculopathies, mono-polyneuropaties

Mayer, Riemann, Jennum, Sleep Med Rev, 2010

Treatment of primary insomnia

- Pharmacological treatment
  - Benzodiazepines, non-benzodiazepine
  - Melatonin
  - Other
- Non-drug treatments
- Life-style interventions, sleep advices
- Cognitive-behavioral therapy (CBT)
  - Stimulus control
  - Cognitive therapy
  - Sleep restriction
  - Relaxation training
  - Sleep hygiene
Hypersomnia - tiredness

- Excessive daytime sleepiness (EDS)
  Persistent sleepiness, and often a general lack of energy, even after apparently adequate night time sleep
- Fatigue
  A condition characterized by a lessened capacity for work and reduced efficiency of accomplishment, usually accompanied by a feeling of weariness and tiredness

Excessive daytime sleepiness

- Sleep disorders
  - Obstructive sleep apnea
  - Narcolepsy and idiopathic hypersomnia
- Neurological disorders
  - Neurodegenerative, stroke, MS, head injury
- Medical
  - Endocrine
  - Pulmonary, cardiac etc.
- Psychiatric
  - Atypical depression
- Lack of sleep
Fatigue

- Lifestyle problems.
  - Feelings of fatigue often have an obvious cause, such as sleep deprivation, overwork or unhealthy habits.
- Psychological problems.
  - Mental health problems, such as depression, other psychiatric disease, stress, social, incapacity etc.
- Medical problems.
  - Metabolic, immune, renal, hepatic, heart, endocrine, neurological problem.

Narcolepsy

- Narcolepsy is a disabling brain disease, characterized by
  - Excessive daytime sleepiness
  - Hypnogogic and hypnopompic hallucinations and vivid dreams
  - Cataplexy provoked by emotional stimuli
  - Sleep paralysis
  - Primarily due to selective destruction of hypocretinergic neurons in hypothalamus
  - Specific HLA types are strongly associated or protective

Narcolepsy: Mechanisms that stabilize sleep and wakefulness

Proposed mechanism of immunity
### Hypocretin function and consequence of hypocretin deficiency in type 1 narcolepsy

<table>
<thead>
<tr>
<th>Hypocretin function</th>
<th>Associated Narcoleptic symptoms/findings</th>
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</thead>
<tbody>
<tr>
<td>Stabilizing wakefulness</td>
<td>Excessive day-time sleepiness</td>
</tr>
<tr>
<td>Stabilizing REM-NREM switch</td>
<td>REM onset day- and night-time sleep</td>
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<tr>
<td></td>
<td>Sleep transitions ↑</td>
</tr>
<tr>
<td>Stabilizing spinal and cortical motor control</td>
<td>Cataplexy, REM sleep without atonia</td>
</tr>
<tr>
<td>Modulation of autonomic nervous system</td>
<td>Attenuated heart rate response</td>
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<tr>
<td>Pain modulation?</td>
<td>Increased pain reportation</td>
</tr>
<tr>
<td>Spontaneous motor activity (SMA)</td>
<td>Impaired SMA, obesity?</td>
</tr>
<tr>
<td>Feeding and seeking behavior</td>
<td>Impaired reward functioning</td>
</tr>
<tr>
<td>Reward modulation Other?</td>
<td>Psychiatric, mood, other?</td>
</tr>
</tbody>
</table>

| Unresolved issues | Mortality, other comorbidities, CVD? |

### Treatment

- **Stimulants**
  - Methylphenidate
  - Modafinil
  - Pitolisant (2017+)
- **Anticataplectic drugs**
  - Tricyclic antidepressant (imipramine, protriptylin)
  - Serotonergic drugs
  - Anti-adrenergic
- **Gamma-hydroxybutyrate/sodium oxybate**
- **Immune therapy (none proven effective):**
  - IVIG
  - Prednisolone
  - Other?
### Hypocretin level and neurological diseases

<table>
<thead>
<tr>
<th>Hypocretin levels</th>
<th>Diseases</th>
<th>Clinical features</th>
<th>References (selected)</th>
</tr>
</thead>
</table>
| Low/undetectable        | Narcolepsy                | Low in narcolepsy with cataplexy (>90%), Low in 10-30% of narcolepsy without cataplexy | Nishino et al. Arch Neurol. 2002 Oct;59(10):1553-62  
Baumann et al. Neurology. 2004 Jun 22;62(12):2337 |
Baumann et al. Neurology. 2004 Jun 22;62(12):2337 |
|                         | Subarachnoid hemorrhage   |                                                                                   |                                                          |

### Parasomnias

**Disorders of Arousals**
- Confusional arousal
- Sleep terror
- Sleep walking

**REM Parasomnias**
- RBD
- Nightmares

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The International Classification of Sleep Disorders. American Academy Of Sleep Medicine
NREM parasomnias

- Confusional arousals
  - Complex, not stereotypical movements in bed
  - Abnormal movements are absent
  - No walking or terror behaviour
  - Low motor and minimal central nervous system activation

- Sleep terrors
  - Sudden arousals
  - Various degrees of motor activity
  - Screaming, incoherent verbalizations, inconsolable crying
  - Disordered and often intense motor agitation
  - Fear and extreme emotional and autonomic activation

- Sleepwalking
  - A series of complex movements
  - No or poor memory

From state dissociation to status dissociatus

- **Dissociation from prevailing wakefulness** as seen in hypnagogic or hypnopompic hallucinations, automatic behaviors, sleep drunkenness, cataplexy and sleep paralysis

- **Dissociation from rapid eye movement (REM) sleep** as seen in REM sleep behavior disorder, hallucinations, lucid dreaming, and

- **Dissociation from NREM sleep** as seen in the disorders of arousal, e.g. confusional arousal, sleepwalking, sleep terror

Gibbs et al. Sleep Med Rev. 2016 Feb;25:4-20
# Parasomnias

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Sleep terror and walking</th>
<th>Nightmares</th>
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<tbody>
<tr>
<td>Occurrence</td>
<td>First third NREM</td>
<td>Midle and last third REM</td>
</tr>
<tr>
<td>Autonomic activation</td>
<td>Intense</td>
<td>Mild</td>
</tr>
<tr>
<td>Vocalization</td>
<td>’Blood-curling’</td>
<td>Mild scream</td>
</tr>
<tr>
<td>Arousalability</td>
<td>Difficult</td>
<td>Easy</td>
</tr>
<tr>
<td>Motility</td>
<td>Marked</td>
<td>Limited</td>
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<tr>
<td>Recall</td>
<td>Fragmentary</td>
<td>Vivid, detailed</td>
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## Neurodegenerative disorders and sleep
## Common Sleep-wake related phenomena in PD/PD+

- Daytime sleep – micro-sleep pattern
- Hallucination between sleep-wake
- Sleep fragmentation
- Disruption of normal night-daytime pattern
- Restless legs syndrome and (a-)periodic legs movements during sleep
- Respiratory problems: stridor and sleep apnea
- REM sleep behavior disorder (RBD)
  - Loss of REM sleep atonia
  - Dream enacting behavior

## RBD: Diagnostic criteria (ICSD-2, modified)

- **History of**
  - Nocturnal harmful, disruptive or annoying sleep behaviour, and/or
  - Nocturnal hallucinations/dreaming
- **PSG:**
  - REM sleep without atonia (RWA): augmentation of submental or limb EMG during REM sleep
  - Phasic emg activations/non-period and period legs movements
- **Video-PSG:**
  - Limb or body jerking, complex, vigorous or violent movements during REM sleep
  - No paroxysmal activity
RBD episodes

Clinical features of RBD (I)

- Prevalence: ~ 0.5%
- Predominantly males (?)
- Mean age at onset: 5th-7th decade
- Probable prodromal history (for several years) of sleep talking, yelling, or limb jerking, laughing
- Dream content may become more vivid, unpleasant, violent, or action-filled
- Excessive daytime sleepiness if sleep is sufficiently fragmented
RBD etiology

- Idiopathic
- Structural brain stem lesion
- Neurodegenerative diseases
  - Parkinson’s disease
  - Dementia (Alzheimer’s disease, Lewy body disease, corticobasal degeneration)
  - Olivopontocerebellar degeneration
  - Multiple system atrophy
  - Amyotrophic lateral sclerosis
- Hypocretin deficient narcolepsy
- Toxic (medication, alcohol discontinuation)

Schenk et al. Sleep Med 2013; 14:795-806

Neuropathological stages of Parkinson’s disease

Is RBD a preclinical PD stage 2?

Lesional aspects and clinical features

Dysfunction of structure and associated clinical feature

<table>
<thead>
<tr>
<th>OB</th>
<th>TMN</th>
<th>LIH</th>
<th>NIHM</th>
<th>HI</th>
<th>SN</th>
<th>PPN</th>
<th>RN</th>
<th>LC</th>
<th>MLD</th>
<th>MCRF</th>
<th>SO</th>
<th>EBN</th>
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Schematic representation of circuits and pathways regulating muscle activity during “normal” wakefulness and RBD in the rodent brain

Predictive markers for early conversion of iRBD to neurodegenerative synucleinopathy diseases

Predictive markers of neurodegenerative synucleinopathy diseases in iRBD
(A) Nonmotor Symptom Questionnaire (NMSQ),
(B) (B) Scale for Outcomes in Parkinson Disease-Autonomic (SCOPA-AUT), and
(C) (C) dopamine transporter (DAT) tracer uptake of putamen.


Early pre-motor symptoms in PD/PD+

<table>
<thead>
<tr>
<th>Manifestations/symptom</th>
<th>Potential involved nuclei</th>
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<tbody>
<tr>
<td>Constipation</td>
<td>Vagal nuclei</td>
</tr>
<tr>
<td>Smell abnormalities</td>
<td>Olfactoric</td>
</tr>
<tr>
<td>Depression</td>
<td>Raphe/LC</td>
</tr>
<tr>
<td>Dream enacting /hypnagogic hallucinations, RBD</td>
<td>Pontine nuclei, SLD</td>
</tr>
<tr>
<td>Disturbed sleep pattern, sleep episode, fragmented sleep</td>
<td>Several nuclei in brain stem/hypothalamus involving wake-sleep regulation</td>
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### RBD vs frontal lobe seizure

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<th>RBD</th>
<th>Seizure</th>
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<td>Age (y)</td>
<td>&gt;50</td>
<td>&gt;12</td>
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<td>Age of disappearance</td>
<td>lifelong</td>
<td>lifelong</td>
</tr>
<tr>
<td>Occurrence</td>
<td>1-4/night</td>
<td>2-9/night</td>
</tr>
<tr>
<td>Motor pattern</td>
<td>Complex</td>
<td>Stereotypic</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Episode onset</td>
<td>All night</td>
<td>All night</td>
</tr>
<tr>
<td>Sleep stage/EEG</td>
<td>REM / no paroxysmal activity</td>
<td>NREM 1-2/±paroxysmal activity</td>
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</tbody>
</table>

### Differences in RBD between narcolepsy and iRBD/RBD in PD/PD+

<table>
<thead>
<tr>
<th></th>
<th>RBD in Narcolepsy</th>
<th>IRBD/RBD in PD/PD+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of onset</strong></td>
<td>Early (7-25)</td>
<td>Late 40+</td>
</tr>
<tr>
<td><strong>Behavior</strong></td>
<td>Discrete motor activity, Verbalization, not violent, Dream content/hallucination multimodal/severe in NC with cataplexy</td>
<td>Complex motor behavior, Verbalization, laughter, Episodic violent/active</td>
</tr>
<tr>
<td><strong>Pathophysiology</strong></td>
<td>Hypocretin deficiency, Reduced stability of brain stem motor neurons? No/limited brain stem pathology</td>
<td>Destruction of brain stem motor neurons?</td>
</tr>
<tr>
<td><strong>Risk</strong></td>
<td>No increased risk of PD dev./not known</td>
<td>Development of PD/PD+</td>
</tr>
<tr>
<td><strong>Associated symptoms</strong></td>
<td>Reduced smell?, cataplexy, automatic behavior, sleep fragmentation, abnormal REM-NREM switch</td>
<td>Constipation, smell, autonomic symptoms, depression, cognitive impairment, motor symptoms, sleep fragmentation</td>
</tr>
<tr>
<td><strong>Cov-Mort</strong></td>
<td>Mostly low, undetectable</td>
<td>Normal or subnormal</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Stable, little risk for development into PD/PD+</td>
<td>High risk for PD/PD+</td>
</tr>
</tbody>
</table>

### Differential Diagnosis of Nocturnal Events

<table>
<thead>
<tr>
<th>NREM Parasomnia</th>
<th>REM Behavior Disorder</th>
<th>Nocturnal Seizures</th>
<th>Psychogenic Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time of Occurrence</strong></td>
<td>First 1/3 of night. From N3 sleep</td>
<td>During REM; latter 2/3 of night</td>
<td>Any time. From N2 sleep</td>
</tr>
<tr>
<td><strong>Memory of Event</strong></td>
<td>Usually none</td>
<td>Dream recall</td>
<td>Usually none (frontal lobe may have some recall)</td>
</tr>
<tr>
<td><strong>Stereotypical Movements</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>PSG Findings</strong></td>
<td>Arousal from delta sleep</td>
<td>RSWA</td>
<td>Potentially epileptic activity</td>
</tr>
</tbody>
</table>

### Types of sleep disordered breathing

1. Obstructive sleep apnoea syndromes (OSAS) including other disorders with upper obstruction including
2. Central sleep apnoea-hypopnoea syndrome (CSAHS)
3. Cheyne-Stokes Breathing Syndrome - CSBS
4. Sleep related hypoventilation/hypoxemic syndromes

*The American Academy of Sleep Medicine (1999), ICSD-2 (2005)*
Sleep Disordered Breathing - “The basic definition”

Obstructive Sleep Apnea

Central Sleep Apnea

Consequences of sleep apnea

- Physiological changes
- Cognitive disturbances
- Cardio- and cerebrovascular disorders
  - Hypertension
  - Arrhythmias
  - Myocardial infarction
  - Stroke
- Metabolic syndrome
- Family, social and professional problems
- Traffic and professional accidents
OSAS and cardiovascular diseases

- Hypertension
- Myocardiac infarction
- Pulmonary hypertension
- Intracranial hypertension
- Stroke
- RR = 2-3, AHI>20

Positive airway pressure

- Auto /fixed pressure-CPAP – APAP
  - OSA
- Bi-level PAP or Variable PAP VPAP
  - OSA
  - Central søvnnapnø
  - Alvelær hypoventilation
- Positive airway pressure devices for the treatment of Cheyne-Stokes respiration
### Taking a sleep history

- **Nocturnal complaints**
  - Time to bed, wake-up time, circadian factors
  - Snoring, respiratory arrests,
  - Dream, dream content, dream enactment, time of night behavior, motor activity, nocturnal seizures, falls, confusion, paralysis
  - Insomnia (difficulties falling asleep, sleep maintenance)
  - Nocturia, enuresis

- **Daytime symptoms**
  - Sleepiness, fatigue, napping, cataplexy,
  - Sensory and motor symptoms
  - Medication
  - Hereditary factors, familiar issues
  - Relevant medical, neurological, psychiatric history
  - Driving, social, education

### Methods in sleep diagnostics

- **Polysomnography**
  - Recordings of multiple physiological variables during sleep
- **Video-polygraphy**
  - Recordings of multiple physiological variables with video
- **Multiple Sleep Latency Test (MSLT) and Maintaining Wakefulness Test (MWT)**
- **Cardiorespiratory measures**
  - Recording of cardiorespiratory variables during sleep
- **Oxymetry**
- **Actigraphy**
  - Recording of movement, activity, light, temperature
- **Others**
  - Blood samples, lumbar puncture, saliva and urine testing
## Conclusions

- Insomnia, hypersomnias and other sleep disorders are strongly associated with presence of neurological diseases
- The mechanism associated to these symptoms are complex and involves sleep–wake and circadian regulatory mechanism
- The are unmet need in understanding pathophysiology, co-morbidities, health impact and managements of these associations