Excessive daytime sleepiness and narcolepsy

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Objectives

1. Understand the causes of excessive daytime sleepiness
2. Determine when sleepiness is abnormal
3. Decide what diagnostic test to order
4. Develop a better understanding of narcolepsy
Pathologically sleepy?

• **Circumstances Matter.**
  • Ask about classroom, meetings, reading
  • driving
  • Naps- this helps separate fatigue from EDS
• **Questionnaires-**
  • Epworth Sleepiness Scale
  • Stanford Sleepiness Scale
  • Karolinska Sleep Scale
## Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations? Use the following scale to choose the most appropriate number:

<table>
<thead>
<tr>
<th>Activity</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting and reading</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watching television</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting inactive, in a public space</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lying down to rest in the afternoon when circumstances permit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting and talking to someone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting quietly after a lunch without alcohol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>As a passenger in car for an hour without a break</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In a car, while stopped for a few minutes in traffic</td>
<td></td>
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</tr>
</tbody>
</table>

**Total Score:**
MSLT or NAP TEST
Don’t ask how much sleep you get.....

• Most patient’s answer 6-8 hours...
• Instead:
  • What time do you go to bed
  • How long until you fall asleep
  • How often do you wake up during the night
  • What time do you get out of bed? Do you need an alarm?
• Now ask all the same questions for the weekend!
General sleep duration recommendations

• Children 3-5 years old: 10-13 hours (including naps)
• Children 6-12 years old: 9-12 hours
• Teens 13-18 years old: 8-10 hours
• Adults 7-8+ Hours
Screen for other sleep disorders

- Insufficient sleep
- Obstructive Sleep Apnea
- Insomnia
- Circadian Rhythm Sleep-Wake Disorders
- Sedating Medications
Narcolepsy: Symptoms

- Excessive daytime sleepiness (EDS)
- Cataplexy
- Hypnagogic hallucinations
- Sleep paralysis
- Disturbed nocturnal sleep

Currently divided into two types:

- **Type 1**: associated with CSF hypocretin deficiency and/or the symptom of cataplexy
- **Type 2**: objective findings of REM sleep disturbance in the absence of cataplexy

Narcolepsy Is Characterized By Sudden Transitions From Wakefulness To REM Sleep

- Central EEG
- Occipital EEG
- LOC
- ROC
- Chin EMG
- R. + L. AT EMG
- ECG
- HR
- $V_{TRIP}$

- Rapid Eye Movements
- Decreased chin muscle tone
Clinical Tetrad: Sleep Paralysis and hypnagogic hallucinations

• Sudden inability to move on falling asleep or on awakening
• Episodes are generally brief and benign
• Can cause significant anxiety
• May be accompanied by hypnagogic hallucinations
Cataplexy

• Muscle weakness triggered by emotions
  • Joking, laughter, excitement, anger
  • Brief duration, mostly bilateral
• May affect any voluntary muscle
  • Knee / leg buckling, jaw sagging, head drooping, postural collapse
• Consciousness maintained at the start
Triggers for Cataplexy (Narcolepsy Type 1)

Quality of Life

# Sleepiness While Driving

<table>
<thead>
<tr>
<th></th>
<th>Narcolepsy</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you drive?</td>
<td>48%</td>
<td>63%</td>
</tr>
<tr>
<td>Fall asleep driving</td>
<td>66</td>
<td>6</td>
</tr>
<tr>
<td>Cataplexy driving</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Sleep paralysis driving</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Frequent near accidents</td>
<td>67</td>
<td>0</td>
</tr>
<tr>
<td>Led to accidents</td>
<td>37</td>
<td>5</td>
</tr>
<tr>
<td>Higher insurance</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Suspended license</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

From Broughton et al 1981
Narcolepsy type 1: Prevalence

Age of Onset of Symptoms

Pathophysiology of Narcolepsy
Loss of orexin/hypocretin neurons results in narcolepsy symptoms

- Orexin/Hypocretin is a neuropeptide of the lateral and posterior hypothalamus that excites the arousal systems of the brainstem and hypothalamus as well as the cortex directly.
- Severe loss of the orexin/hypocretin neurons resulting in instability of the wake and sleep states.


Low CSF hypocretin/orexin levels in narcolepsy with cataplexy (narcolepsy type 1)

The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias." Archives of neurology 59(10): 1553-1562.
The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias." Archives of neurology 59(10): 1553-1562.
Support for an auto-immune cause of narcolepsy

- There is a strong association of narcolepsy type 1 with HLA class II DQB1*06:02
- Genetic abnormalities in the regulation of the immune response has resulted in narcolepsy symptoms
- Strong associations with disease onset and upper airway infections
  - *Streptococcus pyogenes*
  - Influenza A virus/H1N1 vaccination and infection


Diagnostic Criteria
ICSD-3 Criteria for Narcolepsy

Narcolepsy Type 1

Diagnostic Criteria. Criteria A and B must be met

A. Sleepiness for at least three months.
B. The presence of one or both of the following:
   1. Cataplexy and a mean sleep latency of $\leq 8$ minutes and 2 or more SOREMPs on a MSLT. (A SOREMP on the polysomnogram may replace one SOREMP.
   2. CSF hypocretin-1 concentration, measured by immunoreactivity, is either $\leq 110$ pg/mL or $<1/3$ of mean values obtained in normal subjects with the same standardized assay.

Not clinically available
ICSD-3 Criteria for Narcolepsy

Narcolepsy Type 2
Diagnostic Criteria- Must meet A-E

A. Excessive daytime sleepiness for at least three months.
B. A mean sleep latency of $\leq 8$ minutes and 2 or SOREMPs are found on a MSLT. (A SOREMP on the polysomnogram may replace one SOREMP.
C. Cataplexy is absent.
D. Either CSF hypocretin-1 concentration has not been measured or is normal.
E. EDS not better explained by other causes such as insufficient sleep, obstructive sleep apnea, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal.
It is challenging to get an accurate sleep PSG/MSLT!

- Diagnosis requires-
  - Polysmnogram and Mean Sleep Latency Test (MSLT) with at least 6 hours of sleep and no OSA
  - At least 7-8 hours of sleep prior to study for 7-14 days measured by actigraphy or sleep logs
  - No REM suppressant medications
    - TCA, SSRI, stimulants, narcotics, beta-blockers, anti-psychotics held for 14 days or 5 half-lives)
  - Toxicology Screen

Criteria= is a sleep latency of 8 minutes or less and 2 sleep onset REM periods
So many things can go wrong!

Start of the patient’s naps

What else have I seen??

- Lot’s of positive drugs screens
- All-night study sessions
- Chronic partial sleep deprivation
- Erratic sleep schedules
- Unknown obstructive sleep apnea
Treatment= Symptom management

**Goal:** Individual tailoring of therapy to improve alertness, productivity, quality of life, and reduced risk of injury.

1. Behavioral
2. Pharmacologic
3. Polypharmacy is common

Requires regular follow-up and monitoring of symptoms

- Sleepiness
- Sleep Fragmentation
- Cataplexy
- Sleep paralysis and hypnopompic hallucinations


Napping and Improving Sleep Hygiene

• Naps –scheduled 1-3 times a day
• Adequate and regular sleep patterns
• Avoiding exacerbating factors such as:
  • Shift work
  • Alcohol and other recreational drugs


Potential Wake-Promoting Systems

<table>
<thead>
<tr>
<th>Neurotransmitters</th>
<th>Pharmaceutical Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Dopamine</td>
<td>• Amphetamine-like compounds</td>
</tr>
<tr>
<td>• Histamine</td>
<td>• H3 receptor agonists (Pitolisant Not on market yet)Compounds)</td>
</tr>
<tr>
<td>• Hypocretins</td>
<td>• Hypocretin agonists (Future compounds)</td>
</tr>
<tr>
<td></td>
<td>• Sodium oxybate</td>
</tr>
</tbody>
</table>

Action of Stimulants

Presynaptic

Methylphenidate and possibly modafinil
Block re-uptake

tyramine → dopa → dopamine

GHB reduces cell firing but does not inhibit dopamine synthesis

Amphetamine-like stimulants inhibit VMAT, increase

Postsynaptic
Wake-prompting agents

- Modafinil and Armodafinil
- Methylphenidate
- Amphetamine-dextroamphetamine
- Amphetamine
- Dextroamphetamine
Modafinil and Armodafinil

• Dosing
  • **Modafinil 200-400 mg in the morning**
  • No clear data that 400 mg is more effective. Take in once dose in AM or second dose early afternoon
  • **Armodafinil 150 -250 mg in the morning**

• Side effects
  • Hypertension
  • Headaches
    • 34%
  • Decreased appetite
  • Decreased serum concentration of oral contraceptive pills
Methylphenidate- often a combination of immediate and sustained formulations

**Methylphenidate**

**Immediate release** Initial: 5 mg twice daily before breakfast and lunch; maximum dose: 60 mg daily (in 2-3 divided doses).

**Extended release - Sustained release:** convert the immediate release dose to extended release dose maximum: 60 mg daily.
Amphetamine—often a combination of immediate and sustained formulations

- **Dextroamphetamine** - Single salt
  - 5 mg to maximum 60 mg

- **Dextroamphetamine-amphetamine mixed salts**
  - 5 mg to maximum 60 mg

- **Lisdexamfetamine** - Off label use-prodrug of dextroamphetamine
  - 20 mg to maximum 70 mg

"It keeps you awake because it takes 5 hours to finish drinking it."
Stimulant Side Effects

• Headache, nervousness, nausea, insomnia, reduced appetite, cardiovascular effects, hypertension, priapism
• Abuse
• Michigan now requires MAPS for every script
Sodium Oxybate

Active on all symptoms of narcolepsy

• Initial: 2.25 g at bedtime and 2.25 g 2.5 to 4 hours later (4.5 g per night). Effective dosage range: 6 to 9 g per night.

• *Dose titration:*

  • Increase dose by 1.5 g per night (0.75 g per dose) in weekly intervals (maximum dose: 9 g per night)

  • Take on empty stomach (at least 2 hours)

  • Side effects: respiratory sedation, enuresis, parasomnia, increased salt load, weight loss, obstructive sleep apnea

  • Requires registration to prescribe
Sodium Oxybate

Data from Xyrem International Study Group 2005

Figure 2—Combined median change from baseline Epworth Sleepiness Scale per month for all doses following the double-blind trial. This change was significant after month 1 (denotes p < 0.001) compared to a median score of 18 prior to entry in the previous 4-week double-blind study.
What I do….

• Start with Modafinil or Armodafinil (I usually continue unless adverse side effects)

• Still sleepy?
  • Add methylphenidate (max total dose of 60 mg titrated over a period of time)

• Still sleepy?
  • Switch to Dextroamphetamine-Amphetamine combination salts (max total dose of 60 mg titrated over a period of time)

• Still sleepy?
  • Consider adding Sodium Oxybate

• Only occasionally will I use amphetamine, or dextroamphetamine
Treatment of Cataplexy

• Not all patients require therapy
• Side effects and complications limit use
• Select drug and timing of administration to match its sedating or stimulating effects *(e.g. sedating antidepressants at bedtime)*
• Pregnancy and nursing
Cataplexy and Disassociated REM Sleep Features

• **Consider as first line options**
  
  • Venlafaxine extended release- 37.5-150 mg/day with maximum of 300 mg/day
  
  • Duloxetine 20-40 mg with maximum dose 60mg/day
  
  • Atomoxetine (has stimulant and cataplectic effect)10-60 mg with a maximum of 80 mg/day

• **Tricyclic antidepressants**
  
  • Protriptyline (10 to 60 mg/day)
  
  • Clomipramine / Imipramine (25 to 150 mg/day)
  
  • Anti-cholinergic side effects

• **Selective serotonin re-uptake inhibitors**
  
  • Fluoxetine / Paroxetine (20 to 60 mg/day)
  
  • Better tolerated but higher dose often needed
Fragmented Nocturnal Sleep

- Generally untreated
- If treated, will not normalize daytime alertness
- Hypnotic compounds or sedating antidepressants can be used
- Avoid hypnotics with carryover effects
- Gamma hydroxybutyrate is also effective
Summary-Excessive Daytime Sleepiness

• The most common cause is insufficient sleep

• Consider narcolepsy when other causes have been excluded by a careful clinical history

• The evaluation requires an PSG/MSLT/Toxicology Screen/ Measurement of Sleep patterns

• Treatment is symptomatic and often requires polypharmacy with a combination of immediate and extended release medications
Thank you!