Narcolepsy: Update on Diagnosis and Treatment

Phyllis C. Zee, MD, PhD
Benjamin and Virginia T. Boshes Professor in Neurology
Professor of Neurobiology
Director Center for Circadian and Sleep Medicine
Director Sleep Disorders Center
Northwestern University Feinberg School of Medicine

Solomon A. Briggs
Symptoms of Narcolepsy

- Daytime sleepiness (all patients)
  - Typically moderate to severe
- Cataplexy (50% of patients)
  - Brief episodes of muscle weakness triggered by strong emotions, such as laughter (can be very subtle)
  - Can develop months to years after EDS
- Hypnagogic hallucinations
- Vivid dreams
- Sleep paralysis

- Increased BMI
- Disrupted nocturnal sleep

Andlauer, et al, 2012
Fragmented Sleep Associated with Frequent Unexplained Arousals

Control

Narcolepsy Patient

Normal and narcoleptic 24-h PSG recordings

Adapted from Rogers et al. Sleep. 1994;17:590.
## Disrupted Nocturnal Sleep

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients with Narcolepsy</th>
<th>Comparator</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkes et al., 1998(^{31})</td>
<td>4.5</td>
<td>1.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Rosenthal et al., 1990(^{33})</td>
<td>4.6</td>
<td>1.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Bruck et al., 1996(^{22})</td>
<td>3.3</td>
<td>1.3</td>
<td>&lt; 0.005</td>
</tr>
</tbody>
</table>

In each study, the number of awakenings among patients with narcolepsy was more than twice that reported by the comparator.

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Thomas Roth, Ph.D.\(^{1}\); Yves Dauvilliers, M.D.\(^{2}\); Emmanuel Mignot, M.D., Ph.D., F.A.A.S.M.\(^{3}\); Jacques Montplaisir, M.D., Ph.D.\(^{4}\); Josh Paul, M.A.\(^{5}\); Todd Swick, M.D., F.A.A.S.M.\(^{6}\); Phyllis Zee, M.D., Ph.D., F.A.A.S.M.\(^{7}\)

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Alteration in Sleep Stages

Thomas Roth, Ph.D. ¹; Yves Dauvilliers, M.D.²; Emmanuel Mignot, M.D., Ph.D., F.A.A.S.M.³; Jacques Montplaisir, M.D., Ph.D.⁴; Josh Paul, M.A.⁵; Todd Swick, M.D., F.A.A.S.M.⁶; Phyllis Zee, M.D., Ph.D., F.A.A.S.M.⁷

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Narcolepsy Symptoms Defined According to Sleep-wake Instability

Wakefulness intruding into sleep
  • *Sleep disruption*

Sleep intruding into wakefulness
  • *EDS*

REM/Wake Instability
  • Hypnagogic hallucinations
  • Sleep paralysis
  • Cataplexy

References:
AASM. *International Classification of Sleep Disorders*. 3rd ed. 2014; Darien, IL; American Academy of Sleep Medicine.
Common Associated Disorders

1) Concomitant sleep disorders
   – Obstructive and central sleep apnea in 10-20%
   – Periodic limb movements in 40-60%
   – REM sleep behavior disorder in in 10-30%
   – Sleepwalking, sleep talking, night terrors in ~20%

2) Mild obesity: BMI increased by ~15% on average

3) Depression in ~25%
Comorbidity Prevalence: Targeted Diagnoses

Population prevalence of targeted diagnoses, narcolepsy versus control; For all comparisons versus controls $P<0.0001$
Narcolepsy: Impact on Functioning

Impaired Activities of Daily Living

Impaired Social/Occupational Functioning

- Difficulty maintaining relationships
- Increased risk of domestic and occupational accidents
- Tendency to fail in school and difficulty maintaining employment

Increased risk of domestic and occupational accidents

Pathophysiology of Narcolepsy

Disorder of both sleep and wake: Brain state instability

- Role of hypocretin /orexin cell loss
  - decreased levels
  - receptor mutation (rare)

- Acquired autoimmune disorder

- Genetic Contributions

Lateral hypothalamic brain tissue

Narcoleptic Control

Loss of hypocretin containing neurons

CSF Hypocretin Levels

# Narcolepsy Diagnostic Criteria

<table>
<thead>
<tr>
<th></th>
<th>ICSD-3</th>
<th>DSM-5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1</strong></td>
<td><strong>Type 2</strong></td>
<td><strong>Sleepiness for ≥3 months</strong></td>
</tr>
<tr>
<td>daily periods of irrepressible need to sleep or daytime lapses into sleep</td>
<td>recurrent periods of irrepressible need to sleep, lapsing into sleep, or napping</td>
<td></td>
</tr>
<tr>
<td><strong>Plus one of the following:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cataplexy</td>
<td>also must have positive MSLT</td>
<td>none</td>
</tr>
<tr>
<td>CSF Hypocretin</td>
<td>≤110 pg/ml or ≤1/3 normal values</td>
<td>&gt;110 pg/ml or &gt;1/3 normal values</td>
</tr>
<tr>
<td>MSLT</td>
<td>Positive MSLT</td>
<td>Positive MSLT</td>
</tr>
<tr>
<td>PSG</td>
<td>Short REM latency</td>
<td>Short REM latency</td>
</tr>
</tbody>
</table>

Positive MSLT: mean sleep latency ≤ 8 min and ≥2 SOREMPs

PSG: Short REM sleep latency ≤ 15 min
Summary

• Clinical history is essential
• Cataplexy is pathognomonic
• Disrupted nocturnal sleep (increased number of arousals, WASO and lighter sleep)
• Self report measures
  – Epworth sleepiness scale
  – Swiss narcolepsy scale
• Sleep laboratory tests
  – Polysomnography
  – MSLT-nap series
• HLA Typing
• CSF hypocretin/orexin levels
## 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

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

## Mean ESS Scores in Narcolepsy and Normal Populations

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mean (SD) ESS Score</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narcolepsy (n=13)</td>
<td>17.5 (3.5)</td>
<td>13-23</td>
</tr>
<tr>
<td>Normal subjects (n=30)</td>
<td>5.9 (2.2)</td>
<td>2-10</td>
</tr>
</tbody>
</table>

An ESS of 0-8 = normal, 9-12 = mild, 13-16 = moderate, >16 = severe sleepiness

Swiss Narcolepsy Scale

- The Swiss Narcolepsy Scale (SNS) is a brief subjective questionnaire that screens for the occurrence of several behavioral symptoms that may be associated with narcolepsy with cataplexy.¹

- **Purpose:** Designed to screen for a symptom profile that might be suggestive of narcolepsy with cataplexy¹

- **Population:** Patients with EDS in whom the clinician may want to screen for potential narcolepsy with cataplexy²

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Swiss Narcolepsy Scale

• **Assessments:** Measures frequency of 5 potential symptoms\(^1\):
  
  \(Q_1\) – Inability to fall asleep  
  \(Q_2\) – Feeling bad or not well rested in the morning  
  \(Q_3\) – Taking a nap during the day  
  \(Q_4\) – Weak knees/buckling of the knees during emotions such as laughing, happiness, or anger  
  \(Q_5\) – Sagging of the jaw during emotions such as laughing, happiness, or anger

• **Method:** Patient self-report\(^1\)

• **Time required:** Consists of 5 questions and takes only a few minutes to complete\(^1\)

• [swissnarcolepsyscale.com](http://swissnarcolepsyscale.com)

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Swiss Narcolepsy Scale

- **Scoring:** Frequency for each behavioral complaint is rated on a 5-point scale, from 1, indicating “never,” to 5, indicating “almost always.” Each question is weighted by a positive or negative factor, with the score calculated using the following equation: \((6Q_1 + 9Q_2 - 5Q_3 - 11Q_4 - 13Q_5 + 20)\).\(^1,2\)

- **Interpretation:** An SNS score <0 is suggestive of narcolepsy with cataplexy.\(^1,2\)

- **Validation:** In patients with narcolepsy with cataplexy, an SNS score <0 was shown to have a sensitivity of 96% and specificity of 98%.\(^2\)

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Figure 3. Values of new narcolepsy score in patients with narcolepsy with cataplexy (n = 57) and patients with non-narcoleptic hypersomnia (n = 56).

Goals of Treatment

• Reduce daytime sleepiness
• Control ancillary symptoms:
  – Cataplexy
  – Nightmares and hallucinations
  – Sleep paralysis
  – Disturbed nocturnal sleep
• Improve psychosocial and work functioning
• Improve safety of patient and public
Initial Treatment Considerations

• What is the severity of symptoms?
  - affecting work performance

• Lifestyle of the patient
  • how might that effect their dosing schedule?
    • Is there flexibility in their life?

• Age and comorbidities
  • Hypertension? (dangers of classic stimulant meds and black box warnings)
  • Depression/psych issues?
Multimodal Approach

General

• Assessment and treatment of co-morbid disorders (sleep apnea, restless legs, psychiatric and neurologic disorders)

• Behavioral and environmental factors
  - Sleep hygiene
    - Structured nocturnal sleep and wake times
    - Naps: scheduled and PRN
  - Temperature (night (cooler); Day: core warming and distal cooling
  - Light therapy
  - Exercise
  - Diet

Social Factors

- Personal and family counseling
- Narcolepsy support groups
Sleep Hygiene

• Regular sleep/wake cycle\textsuperscript{1-3}
• Regular exercise in the morning and/or afternoon\textsuperscript{1,3}
• Increase exposure to bright light during the day\textsuperscript{2}
• Avoid exposure to bright light during the night\textsuperscript{1,3}
• Avoid heavy meals or drinking within 3 hours of bedtime\textsuperscript{1}
• Enhance sleep environment\textsuperscript{1,3}
• Avoid caffeine, alcohol, and nicotine\textsuperscript{1,3}
• Relaxing routine\textsuperscript{1-3}
• Temperature regulation

Alerting Agents

Mechanism

- Caffeine: adenosine receptor antagonist
- Sympathomimetic: enhance neurotransmission of dopamine, norepinephrine, serotonin
- Modafinil: specific mechanism remains unclear
- Histamine receptor 3 agonists (H3R)
- Hypocretin stimulation
## AASM Practice Parameters for Narcolepsy: Excessive Sleepiness

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Recommendation Level</th>
<th>Based on:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modafinil</td>
<td>Narcolepsy: <strong>EDS</strong></td>
<td><strong>Standard</strong></td>
<td>4 level 1 studies</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2 level 2 studies</td>
</tr>
<tr>
<td>Sodium oxybate</td>
<td>Narcolepsy: <strong>EDS</strong></td>
<td><strong>Standard</strong></td>
<td>3 level 1 studies</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 level 2 studies</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>Narcolepsy: <strong>EDS</strong></td>
<td><strong>Guideline</strong></td>
<td>3 level 2B studies</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d-amphetamine</td>
<td></td>
<td></td>
<td>4 level 5C studies</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selegiline</td>
<td>Narcolepsy: <strong>EDS</strong>, <strong>cataplexy</strong></td>
<td><strong>Option</strong></td>
<td>2 level 2B studies</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1 level 4C studies</td>
</tr>
<tr>
<td>Ritanserin</td>
<td>Narcolepsy: <strong>EDS</strong></td>
<td><strong>Option</strong></td>
<td>2 level 2B studies</td>
</tr>
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<td></td>
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</tbody>
</table>

**AASM, American Academy of Sleep Medicine.**

Modafinil/Armodafinil Precautions

- Reduces efficacy of oral contraceptives
  - Increases metabolism of ethinylestradiol
- Can cause serious rashes and allergic reactions
## AASM Practice Parameters for Narcolepsy: Ancillary Symptoms

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Recommendation Level</th>
<th>Based on:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium oxybate</td>
<td>Narcolepsy: cataplexy, disrupted sleep, hypnagogic hallucination, sleep paralysis</td>
<td><strong>Standard</strong></td>
<td>3 level 1 studies, 2 level 2 studies</td>
</tr>
<tr>
<td>Tricyclic antidepressants, SSRIs, venlafaxine, and reboxetine</td>
<td>Narcolepsy: cataplexy</td>
<td><strong>Guideline</strong></td>
<td>1 level 2 study, 1 level 4 study, 1 level 5 study</td>
</tr>
<tr>
<td>Tricyclic antidepressants, SSRIs, venlafaxine, and reboxetine</td>
<td>Narcolepsy: sleep paralysis, hypnagogic hallucination</td>
<td><strong>Option</strong></td>
<td></td>
</tr>
</tbody>
</table>

SSRI, selective serotonin reuptake inhibitor.
Sodium Oxybate

- Improves nocturnal sleep;
  - Increases slow wave sleep
  - Reduces arousals and awakenings
- Can eliminate cataplexy
- Reduces vivid dreams, nightmares and hallucinations
- Reduces sleep paralysis
- The only medication that can treat all symptoms of narcolepsy
- Improves overall functioning
Sodium Oxybate Precautions

- Caution in depressed patients

- Should not be used with hypnotics, depressant medications and alcohol

- Some patients may be advised salt restriction

- Has potential for respiratory depression
  - Should not be used in untreated OSA
  - Can be used in OSA with CPAP or other treatments.
Summary: Management Approaches

- Treatment of comorbid disorders
- Excessive daytime sleepiness
  - Structured nocturnal sleep
  - Naps: scheduled and as needed
  - Sympathomimetic stimulants
  - Nonsympathomimetic agents, eg, armodafinil, modafinil, and sodium oxybate
- Cataplexy
  - Antidepressants (TCAs or SSRIs)
  - Sodium oxybate
- Sleep fragmentation
  - Sleep hygiene
  - Hypnotics (limited utility)
  - Sodium oxybate

TCA, tricyclic antidepressant.
Treatment Approaches Under Development

- CBT-Hypersomnia/Narcolepsy
- Non-hypocretin-based therapies
  - Novel monoaminergic reuptake inhibitors
  - Novel SWS enhancers
  - H3R antagonist/inverse agonists
  - TRH analogues
- Hypocretin-based therapy
  - Hypocretin-1
  - Hypocretin peptide agonist
  - Nonpeptide agonist
  - Hypocretin cell transplantation
  - Gene therapy
- Immune-based therapies
  - Steroids
  - IVIG
  - Plasmapheresis
Pitolisant

- A histamine receptor inverse agonist / antagonist.
- Selective for the H3 subtype.
- Available in Europe.

JZP-110

JZP-110 is a wake-promoting agent with dopaminergic and noradrenergic activity.

B)

Average Sleep Latency

Time, Minutes

JZP-110 300 mg/day (N = 33)

Placebo (N = 33)
Questions?