Advances in Narcolepsy and Idiopathic Hypersomnia
Wake Up to Sleep Disorders 2015

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Disclosures

- Jazz Pharmaceuticals
Central Disorders of Hypersomnolence

- Narcolepsy Type 1
- Narcolepsy Type 2
- Idiopathic Hypersomnia
- Kleine-Levin syndrome
- Hypersomnia due to Medical Disorder
- Hypersomnia due to Medication or Substance
- Hypersomnia associated with Psychiatric Disorder
- Insufficient Sleep Syndrome


Narcolepsy

- Disabling disorder characterized by
  - Excessive daytime sleepiness
  - Abnormal REM sleep manifestations
    - Cataplexy
    - Sleep paralysis
    - Hypnagogic hallucinations
    - Disturbed nocturnal sleep
  - Unstable sleep-wake boundaries
Epidemiology of Narcolepsy Type 1

- Prevalence 0.03-0.05% \(^1\)
- 1-2% of narcoleptics with affected 1st degree relatives
- Slight male predominance
- Mean age of onset in mid-20s; bimodal distribution
- Narcolepsy w/o cataplexy (Type 2) & Idiopathic Hypersomnia are less common
- Life events precede onset in >50% \(^2\)
- Diagnostic delay of 14.6 ±14.3 yr implies many undiagnosed cases \(^3\)
- Longer delay in aging, obese, females, absence of cataplexy


Narcolepsy Age of Onset
Peaks at 15 yr & 35 yr

Dauvilliers Y. Neurology 2001; 57: 2029–33.
Intrusion of NREM and REM Sleep into Wake and Fragmentation of Nighttime Sleep

Cataplexy is specific to Narcolepsy: Best diagnostic marker of disease

- More than 1 episode of generally brief usually bilaterally symmetric sudden loss of muscle tone w/retained consciousness
- Precipitated by strong emotions, usually positive (laughter)
- Partial (jaw drop, head nod, facial twitch, dysarthria, dropping things, buckling knees) to complete w/fall
- DTRs transiently abolished
- Frequency from 1/yr to many times daily
- Status cataplecticus rare, usually due to withdrawal of anticataplectic antidepressants
- Presents within 1 yr of EDS in 50%; may present before EDS or >40 yr later

Associated Conditions

- Obstructive sleep apnea: 50%
- Periodic limb movements: 60%
  - Increase with age, in REM, and more likely associated with arousals
- Sleep talking: 17%
- Arousal disorders: 8%
- REM sleep behavior disorder in 7-36%

Morbidity in Narcolepsy

- Obesity
- HTN, HLP, heart, digestive, upper respiratory diseases more common than general population
- Major depression/social anxiety ~20%
- Driving and occupational accidents
- Reduced professional and academic performance
- Unemployment
What is Hypocretin?

- Peptide produced exclusively by in lateral hypothalamus
- Innervates ascending arousal system; projects to cortex, thalamus, hypothalamus, brainstem
- Involved in sleep regulation, energy expenditure, autonomic function
- Loss of HCT-1 neurons destabilizes sleep-wake boundaries


Narcolepsy with Cataplexy is caused by hypocretin (HCT) deficiency

- Mutation in HCT-2 receptor gene causing familial canine narcolepsy identified in 1999
- Striking decrease in HCT-1 in human narcoleptic CSF
- Loss of HCT-1 containing neurons in postmortem human narcoleptic brain tissue
- Cause of HCT cell death is unknown

CSF HCT-1 in Narcolepsy

Low HCT-1: non-Caucasians, higher ESS, more frequent sleep paralysis, SOREMPs, shorter MSL, HLA DQB1*0602 positivity, lower age of onset, longer duration of illness.


Autoimmune Hypothesis

- Strong association with HLA allele DQB1*0602
  - 85-95% w/typical or severe cataplexy
  - 40-60% w/mild, atypical or no cataplexy
  - 75% w/familial narcolepsy
- *0602 homozygosity double-quadruples risk
- 30% of general population are *0602 positive
  - 12% Asians, 25% white, 38% AA
- Other non-HLA gene associations
  - Anti-streptolysin O autoantibodies
  - Tribbles homolog 2 (Trib2) autoantibodies
- Environmental factors

Narcolepsy with H1N1 Pandemrix Vaccine in Finland

12-17 fold increase in narcolepsy in children in Finland with ASO3-adjuvant-containing vaccine.


Secondary Narcolepsy with Cataplexy

- Multiple sclerosis
- Tumors
- Encephalitis
- Ischemia
- Neurodegenerative disorders
  - Niemann-Pick
  - Muscular dystrophy
  - Parkinson’s disease
Diagnostic Criteria: Narcolepsy Type 1

A. Daily periods of irrepresible need to sleep or daytime lapses into sleep occurring for at least 3 mo.

B. The presence of one or both of the following:
   - Cataplexy and a mean sleep latency of ≤8 min and ≥2 sleep onset REM periods (SOREMPs) on MSLT. A SOREMP (within 15 min of sleep onset) on preceding PSG may replace 1 SOREMP on MSLT.
   - CSF hypocretin-1 concentration either ≤110 pg/mL or <1/3 of mean normal values.

Criteria A and B must be met


Diagnostic Criteria: Narcolepsy Type 2

A. Daily periods of irrepresible need to sleep or daytime lapses into sleep occurring for at least 3 mo.

B. Mean sleep latency of ≤8 min and >2 SOREMPs on MSLT. A SOREMP (within 15 min of sleep onset) on preceding PSG may replace 1 SOREMP on MSLT.

C. Cataplexy is absent.

D. Either CSF hypocretin-1 not measured or is either >110 pg/mL or >1/3 of mean normal values.

E. Hypersomnia and/or MSLT findings not better explained by other causes (insufficient sleep, OSA, delayed sleep phase disorder, or medication or substances or their withdrawal).

Criteria A-E must be met

PSG Findings in Narcolepsy

- Decrease total sleep time
- Short sleep latency
- Sleep onset REM (<15 min)
- REM sleep fragmentation
- REM sleep without atonia (RSWA)
- Increased stage 1
- Increase in periodic limb movements

European Narcolepsy Network: 1099 HLA–DQB1*0602 Positive Cases

- MSL 3.9±3.0 min (median 3.0)
- MSL < 8 min in 92%
- MSL significantly shorter in women
  - 3.68±2.7 min vs. 4.10±3.24 min
- SOREMPs in 65.9±27.2% of naps (~3/5)
- No SOREMPs in 3.9%; 1 SOREMP in 5.7%
- 90.3% had MSL <8 and at least 2 SOREMPs
Idiopathic Hypersomnia (IH)

- Poorly elucidated
- Narcolepsy outnumbers IH by 10:1
- Sexes equally affected
- Onset 2nd or 3rd decade
- Normal CSF HCT, inconclusive HLA association
- Symptomatic treatment, although naps not refreshing


Diagnostic Criteria: Idiopathic Hypersomnia

A. Daily periods of irrepressible need to sleep or daytime lapses into sleep for at least 3 mo.
B. Cataplexy is absent.
C. MSLT shows < 2 SOREMPs or no SOREMPs if REM latency on preceding PSG ≤15 min.
D. Presence of at least 1 of following:
   - MSLT shows mean sleep latency ≤ 8 min.
   - Total 24-hr sleep time ≥ 660 min (typically 12–14 hr) on 24-hr PSG after correction of sleep deprivation or actigraphy w/sleep log (averaged over ≥7 d).
E. Insufficient sleep ruled out.
F. Hypersomolence and/or MSLT findings not explained by another sleep, medical or psychiatric disorder, or use of drugs or medications.

Criteria A-E must be met

Pathophysiology of IH

• CSF from IH patients stimulated GABA<sub>A</sub> relative to controls and modestly enhanced BZD-insensitive GABA<sub>A</sub> receptors
• Flumazenil reversed enhancement of GABA<sub>A</sub> signaling and normalized vigilance in 7 patients


Non-Pharmacologic Recommendations for CNS Hypersomnias

• Education - patient, family, teachers, employers
• Good sleep hygiene
• Regular sleep-wake schedule
• Short scheduled naps - 30 min naps can attenuate sleep drive for a few hours
• Strategic caffeine
• Avoidance of heavy meals, alcohol, recreational drugs, CNS depressants
• Avoid driving and other potentially injurious activities when sleepy

Pharmacologic Therapies for Narcolepsy

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<tr>
<th></th>
<th>Excessive Daytime Sleepiness</th>
<th>Cataplexy</th>
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<tbody>
<tr>
<td>XYREM® (sodium oxybate)</td>
<td>FDA-approved</td>
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Wake Promotion

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<th>FDA-approved</th>
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<td>Modafinil/Armodafinil</td>
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Stimulants

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<tr>
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<th>FDA-approved for narcolepsy</th>
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<tr>
<td>Dextroamphetamine</td>
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<td>Methylphenidate</td>
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Antidepressants

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<tr>
<td>Selective serotonin reuptake inhibitor</td>
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<tr>
<td>Serotonin-norepinephrine reuptake inhibitor</td>
<td>Not FDA-approved</td>
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<tr>
<td>Tricyclic antidepressant</td>
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Modafinil & Armodafinil

1st line Treatments for Narcolepsy

- Wake promoting agents w/low abuse potential
- MOA: DA, NE, 5-HT, GABA systems
- Effective in treatment of EDS (AASM Standard)
- Long acting T½ ~14 hrs
- Starting dose: modafinil 200mg; armodafinil 150mg/d
- Mild adverse events: headache, nervousness, nausea
- P450 inducer, increases OCP metabolism

<table>
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<tr>
<th>Measure</th>
<th>Armodafinil 150 mg</th>
<th>Armodafinil 250 mg</th>
<th>Placebo</th>
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<tr>
<td>Mean sleep latency on MWT</td>
<td>12.1 (1.3)</td>
<td>9.5 (2.6)</td>
<td>12.5 (-1.9)</td>
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Sodium oxybate (Xyrem®)

- Approved for EDS & cataplexy in narcolepsy patients ≥16 yrs (AASM Standard)
- Sodium salt of \( \gamma \)-hydroxybutyrate
  - High sodium load (1638 mg in 9 g dose) precludes use in certain clinical settings (HF, resistant HTN, impaired renal function)
- Unknown MOA: GABA\(_B\) and GHB receptors
- Metabolized through Kreb cycle, \( T_\frac{1}{2} =1 \) hr
- BLACK BOX: Should not be used with alcohol, CNS depressants

XYREM (sodium oxybate) PI; AASM Standards of Practice Committee. Sleep 2007;30(12):1705-11

Effect of Sodium Oxybate on Epworth Sleepiness Scale Scores

Over 80% of patients taking concomitant stimulants

B = baseline; E = endpoint (week 8)
Effect of Sodium Oxybate on Cataplexy

No rebound after abrupt withdrawal

Adapted with permission from US XYREM Multicenter Study Group. Sleep 2002;25:42-9

Sodium Oxybate Dosing & Titration Calculator

- Taken in 2 equal doses at night at least 2 hr after eating
- 1 wk between dosage increases; Follow-up every 3 mo
- Monitor for edema, eneuresis, sleep walking

XYREM (sodium oxybate) PI
Cataplexy Pharmacotherapy* 
*not FDA approved


Controlled Substance Schedules

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<tr>
<th>Schedule</th>
<th>Abuse/Dependence Potential</th>
<th>Agents</th>
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| II       | • Drugs with high abuse potential  
          • Accepted medical uses  
          • Abuse may lead to severe psychological or physical dependence | • Dextroamphetamine  
          • Methylphenidate  |
| III      | • Lower abuse potential than Schedule II  
          • Abuse may lead to moderate or low physical/high psychological dependence | • Sodium oxybate*  |
| IV       | • Lower abuse potential than Schedule III  
          • Abuse may lead to limited physical or psychological dependence | • Modafinil  
          • Armodafinil  |

*When used medically.
Future Directions

- Histamine H3 reverse agonists/antagonists
  - Stimulate postsynaptic H1 receptors and promote wakefulness
- Novel monoaminergic reuptake inhibitors
- Hypocretin-1-based therapy
  - IV, intranasal, intracisternal not effective to date
  - Intracerebroventricular
  - Orexin receptor agonists
  - Gene therapy and cell transplantation
- Immunotherapy
  - Steroids, plasma exchange, IVIG not effective to date