Narcolepsy “101”
The Past, The Present, The Future

Todd J. Swick, M.D., FAASM, FAAN
Assistant Clinical Professor of Neurology-The University of Texas School of Medicine-Houston
Medial Advisory Board Member, National Narcolepsy Network
Medical Director, North Cypress Medical Center; Sleep Disorders Center
Medical Director Apnix Sleep Centers
International Sleep Medicine Consultant-Medipert Sleep Medicine Center, Beijing, PRC
Diplomate, American Board of Sleep Medicine
Diplomate, American Board of Psychiatry and Neurology in Neurology and Sleep Medicine
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• Consultant/Advisory Board Membership
  • National Narcolepsy Network
  • Sun Pharmaceuticals
1877 - 1880
Gélineau coined the term "narcolepsy" for patients with sleepiness and muscle weakness.

1877 - 1883
Westphal described sleepiness with muscle weakness.

1877 - 1901
Lowenfeld was first to characterize cataplexy as part of the narcolepsy syndrome.

1877 - 1913
Adie changed the term to "cataplexy" from the Latin word cataplessa which means "to strike down with fear." 1902

1877 - 1919
Henneberg was first to name the attacks of muscle weakness "cataplectic inhibition." 1916

1877 - 1925
Von Economo described sleep as a brain function with localization to the diencephalon and brain stem.

1877 - 1931
Prinzmental and Blooming reported on the use of amphetamines for the Rx of daytime sleepiness.

1877 - 1935
Doyle and Daniels reported the use of ephedrine for Rx of sleepiness in patients with narcolepsy.
1955

Kleitman and Aserinsky described Rapid Eye Movement Sleep (REM sleep)-1955

1958

Dement and Kleitman described the different stages of sleep-1957

1961

Yoss and Daly described the "Narcolepsy Tetrad"-1957

1964

Akimoto reported imipramine for the treatment of cataplexy-1960

1967

Rechtschaffen, Wolpert, Dement et al. described sleep onset REM periods (SOREMPs) occurring in narcoleptics-1963

1970

Hishikawa et al. confirmed the beneficial effects of imipramine and its active metabolite, desipramine in the treatment of cataplexy-1966

1973

Mitler, Dement, et al. reported on a narcoleptic dog-1973

1976

Richardson, Carskadon, et al. codified the MSLT in their paper; "Excessive Daytime Sleepiness in Man: Multiple Sleep Latency measurement in Narcoleptic and Control Subjects" 1978.

1979

Carskadon and Dement reported that shortened sleep onset latency can be useful to show an increased sleep tendency as an objective measure of sleep loss-1977

1982

Juji and Honda, found that 100% of Japanese narcolepsy/cataplexy patients carried the HLA-DR2 and DQ1 genes vs. 25% of normal controls-1983

Narcolepsy Timeline

1955 - 1983

29 years
1998

Sakurai, et al. identified two peptides they named Orexins (Orexin-A and Orexin-B)-1998

Sakuri showed that the Hypocretins and Orexins were the same polypeptides-1998

Chemelli, Scammell, et al. reported narcolepsy/cataplexy-like traits in orexin knockout mice-1999

Nishino, Ripley, Overeem, Lammers and Mignot reported that there is a significant loss or complete absence of Hypocretin (orexin) in the brain/CSF in human narcolepsy-2000

Mignot showed canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene-1999

Modafinil (Provigil®) was approved by the FDA for excessive sleepiness in narcolepsy-1998

de Lecea and Kilduff identified two peptides they named hypocretins (Hypocretin-1 and Hypocretin-2)-1998

Sodium Oxybate (Xyrem®) was approved by the FDA to treat excessive daytime sleepiness and/or cataplexy associated with narcolepsy-2005

Dauvilliers, Montplaisir, Mignot, et al. described the association between post H1N1 infection and/or vaccination with the onset of Narcolepsy Cataplexy-2010

Dauvilliers, Bassetti, Lammers, et al. reported, pilotisant a selective histamine H3 auto-receptor activator improved EDS compared to placebo and was well tolerated compared to modafinil in patients with narcolepsy-2013

1998-2014
Narcolepsy

• Lifelong neurologic/sleep disorder characterized by the disruption of the boundaries between sleep and wake states

• Classic pentad of signs and symptoms:
  • Excessive Daytime Sleepiness (EDS)
  • Cataplexy
  • Hypnogogic hallucinations
  • Sleep paralysis
  • Disrupted nighttime sleep (DNS) [nocturnal sleep fragmentation]
Narcolepsy

• Ancillary symptoms:
  • Automatic behavior
  • Loss of concentration and memory
  • Visual symptoms (blurred vision)

• There are 2 distinct groups of patients with narcolepsy:
  • Those with cataplexy (Type 1 Narcolepsy as per ICSD-3 classification)
  • Those without cataplexy (Type 2 Narcolepsy as per ICSD-3 classification)

• Can coexist with other sleep disorders
  • Obstructive Sleep Apnea
  • Restless Legs Syndrome
  • Periodic Limb Movements in Sleep
  • REM sleep behavior disorder
  • Nocturnal eating disorder
Narcolepsy

• Sleepiness is usually the first symptom
• Commonly mistaken for:
  • Daydreaming
  • Insomnia
  • Drug Abuse
  • Depression/Bipolar disorder
  • Apathy
  • ADD
  • Seizures
Cataplexy

- Episodic weakness without altered consciousness lasting seconds to minutes and precipitated by excitement or emotion
- May occur several times/day or a few times/year
- Sagging of face, eyelid, or jaw; dysarthria (slurred speech—*particularly in children*); head drop; blurred vision; knee bucking; “drop attack”
- Can be unilateral
- Episodic blurring of vision
- Laughter is the most common trigger but can also be triggered by fright, excitement, fear, organism
- Usually develops within 3 years of EDS symptoms, but may develop 10-40 years later
Sleep Paralysis

- The inability to move for a few seconds or minutes during sleep onset or offset
- Often occurs in normal individuals on a relatively rare episodic basis but is far more common and almost universal in narcoleptics
- Paralysis ends spontaneously (fear reaction is most common) or after mild sensory/tactile stimulation
Hypnogogic Hallucinations

- Vivid, “waking dreams” that occur during transitions between sleep and wakefulness
  - Hypnogogic (occurring at sleep onset)
  - Hypnopompic (occurring upon awakening)
- May accompany sleep paralysis or occur independently
- May be tactile or auditory
- Some awareness of surroundings is preserved
- Differentiated from dreaming during sleep
Disrupted Nocturnal Sleep (DNS)

• Common aspect of narcolepsy that differs from DNS in other sleep disorders including insomnia

• Patients report:
  • Frequent arousals
  • Higher wakefulness after sleep onset (WASO)
  • Frequent shifts to wake or increased N1 sleep with reduction in N3 (SWS)
  • Decreased in overall sleep efficiency (SE)
  • Typically there is no prolongation of a return to sleep

• Several studies using PSG suggest that the decreased NREM and slow wave activity are possible mediators of the fragmented sleep

Narcolepsy-Age of Onset of Symptoms

- Onset between ages 15 and 30 in 60% of patients
- Age range from 5 to 63
- Median age of 22
- Onset of cataplexy ages 9 to 68
- Hypnagogic hallucinations ages 9 to 65
- Sleep Paralysis ages 10 to 58

A) Monthly counts of narcolepsy-cataplexy onset over a 15 year period diagnosed at the People’s Hospital, Beijing University

B) Mean of monthly occurrences

C) Yearly counts of narcolepsy onset

The number of yearly 2004-2010 influenza infections documented by government statistics is in blue

Onset of Narcolepsy/Cataplexy on a yearly and monthly basis at The People’s Hospital of Beijing University

Widespread Underdiagnosis of Narcolepsy

- Only 50,000 of the estimated 200,000 Americans with narcolepsy have been correctly diagnosed
- Almost as common as Multiple Sclerosis
- Can go 10 to 15 years after symptoms start before correct diagnosis is made
- A patient with narcolepsy/cataplexy sees an average of 5-7 physicians before a proper diagnosis is made

Narcolepsy and Immunity

• Human leukocyte antigens (HLA) are strongly linked to many autoimmune diseases
• 85% of patients with narcolepsy/cataplexy carry the genes for HLA DQB1*06:02
• <50% of patients with “atypical” or “mild” narcolepsy/cataplexy or those with narcolepsy without cataplexy have the gene for DQB1*06:02
• 12-38% of the general population are HLA DQB1*06:02 positive (the test therefore is not useful as a general screening tool)
Autoimmune Hypothesis

- There is strong epidemiological evidence that susceptible individuals (defined as being HLA DQB1*06:02 positive) have a >100X greater chance of developing Narcolepsy/Cataplexy
- Narcolepsy/Cataplexy has been associated with
  - H1N1 infection and/or immunization
  - As a consequence of streptococcal infection
  - Specific antibodies hypothesized to attack hypocretin cells

Autoimmune Hypothesis*

• Multiple factors contribute to the development of autoimmune diseases
  • Genotype differences at the HLA level
    • HLA DQB1*06:01
  • Hormonal factors
    • Onset at or near puberty
  • Environmental factors
    • Associations with upper airway infections, strep infections, and influenza H1N1-infections and H1N1-vaccinations and by the strong seasonality of disease onset

Hypocretins (Orexins)

• Human narcolepsy/cataplexy is caused by loss of hypocretin (orexin) neurons in the dorsolateral hypothalamus (70,000 neurons in a paired set)

• Thought to be caused by an autoimmune process directed specifically against hypocretin neurons in the hypothalamus (not by a mutated gene)
  • The *canine form* (e.g., Doberman Pinchers) of narcolepsy is caused by a single mutated hypocretin receptor 2 gene in an autosomal recessive pattern

Hypocretin (Orexin) Cell Loss as the cause of narcolepsy vs. normal tissue

Hcrt loss as the cause of narcolepsy

Abnormal structure and severe loss of Hcrt peptide staining

Normal hypothalamus

Normal Hcrt peptide staining
Measuring Sleepiness

- Subjective scales
  - Stanford Sleepiness Scale
  - Epworth Sleepiness Scale

- Objective Testing
  - Polysomnography/Multiple Sleep Latency Testing (PSG/MSLT)
  - Maintenance of Wakefulness Test (MWT)
Objective Tests Used to Diagnose Narcolepsy

• Polysomnogram (PSG)
  • Measures a variety of signals during sleep using electrodes placed on the scalp
  • Test measures the electrical activity of the brain (electroencephalogram) and heart
    EKG (electrocardiogram) and the movement of muscles EMG (electromyogram)
    and eyes EOG (electrooculogram)
  • Also monitors breathing

• Multiple sleep latency test (MSLT)
  • Measures how long it takes patients to fall asleep during the day
  • Patients asked to take four or five naps, each nap two hours apart
  • Observe sleep patterns

• Hypocretin test
  • Levels of hypocretin in CSF (spinal fluid)
    • levels <110 pg/ml are considered significant for the diagnosis of narcolepsy
    • Not FDA approved for commercial testing
PSG/MSLT

• PSG should show at least 6 hours of recorded sleep and sleep time needs to approximate the patient’s habitual sleep time
• 5 naps are standard for the MSLT
• Patients should document at least 8 hours of sleep per night for the preceding week
• Wrist actigraphy is preferable but *adequate sleep over the preceding week* can be documented with a sleep log

PSG/MSLT

- REM suppressant medications need to be discontinued at least 2 weeks prior to the MSLT (4 weeks for medication with long half-life such as fluoxetine)
  - Tricyclic antidepressants
  - MAO Inhibitors
  - Selective serotonin reuptake inhibitors
  - Dual serotonin/norepinephrine reuptake inhibitors
  - Atypical antipsychotics

PSG/MSLT

• Stimulant medications need to be discontinued at least 7 days prior to MSLT
• Sodium oxybate needs to be discontinued at least 4 weeks before MSLT
Classification of Narcolepsy

- DSM-V (American Psychiatric Association-2013)
  - Narcolepsy [with cataplexy]
    - Recurrent periods of irrepressible need to sleep, lapsing into sleep or napping occurring within the same day; occurring 3X per week over the past 3 months
    - Presence of at least one of the following:
      - Episodes of cataplexy (occurring at least a few times/month)
      - Hypocretin deficiency (CSF containing <110 pg/ml)
      - PSG showing an initial SOREMP period <15 minutes or an MSLT with >2 SOREMPs and a mean SOL<8 minutes
      - Note: the PSG/MSLT may not be necessary under this classification if there is "documented cataplexy"
  - Narcolepsy without cataplexy but with hypocretin deficiency
  - Narcolepsy with cataplexy but without hypocretin deficiency (<5% of narcolepsy cases)
  - Autosomal dominant narcolepsy, obesity, and type 2 diabetes (low CSF Hcrt-1 levels)

American Psychiatric Association; Diagnostic and Statistical Manuel of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013
Classification of Narcolepsy

• ICSD-3 (American Academy of Sleep Medicine-2014)
  • Narcolepsy Type 1 [Narcolepsy \textit{with} Cataplexy]
    • Patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for \textgreater 3 months
    • Cataplexy \textit{and} a mean SOL of \textless 8 min and \textgreater 2 SOREMPs on an MSLT (a SOREMP on the preceding night’s PSG can substitute for one of the SOREMPs on the MSLT)
  \textit{OR}
  • CSF HYPOCRETIN-1 concentration of \textless 110 pg/mL

American Academy of Sleep Medicine. International Classification of Sleep Disorders, 3\textsuperscript{rd} ed. Darien, IL: American Academy of Sleep Medicine, 2014.
Classification of Narcolepsy

• ICSD-3 (American Academy of Sleep Medicine-2014)
  • Narcolepsy Type 2 [Narcolepsy \textit{without} Cataplexy] (\textit{All} criteria must be met)
    • Patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for $>3$ months
    • Mean SOL=$<8$ min and $\geq 2$ SOREMPs (a SOREMP on the preceding PSG can count as one SOREMP for the MSLT)
    • Cataplexy is absent
    • CSF has NOT been measured or is $>110$ pg/mL
    • The hypersomnia is not better explained by another sleep disorder, medical, psychiatric or neurological disorder
Classification of Narcolepsy

• ICSD-3 (American Academy of Sleep Medicine-2014)
  • Idiopathic Hypersomnia
    • Patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for $\geq 3$ months
    • Cataplexy is absent
    • MSLT shows $<2$ SOREMPs or no SOREMPs if there was a SOREMP on the preceding night’s PSG
    • MSLT demonstrates a mean SOL=$\leq 8$ minutes
    • Documented long sleep times ($>660$ minutes) per 24 hours
    • Insufficient sleep time is ruled out
Narcolepsy Management

• Treatment of excessive daytime sleepiness (EDS)
  • Stimulants (methylphenidate, amphetamines)
  • modafinil (Provigil®)-racemic mixture of “r” and “s” forms of modafinil
  • armodafinil (Nuvigil®)-pure “r” isomer of modafinil

• Treatment of Cataplexy
  • Tricyclic antidepressants (TCAs)
  • Selective Serotonin Reuptake Inhibitors (SSRIs)
  • Selective Serotonin Noradrenergic Reuptake Inhibitors (SSNRIs)

• Both EDS and Cataplexy
  • Sodium Oxybate (Xyrem®)
Goals of Treatment

• Reduce daytime sleepiness
• Reduce/eliminate cataplexy
• Control ancillary symptoms
  • Nightmares and unpleasant frequent dreams
  • Hallucinations
  • Sleep paralysis
  • Disturbed nocturnal sleep
• Improve cognitive, psychosocial and work functioning
• Improve safety of patient and public
Benefit of Treatment

- “Wake Up Narcolepsy” survey of patients [2013-2014] (n= 2017; data were analyzed of 1697 respondents along with information from their direct care givers)
  - 62% were between the ages of 25-54
  - 78% had narcolepsy symptoms for >3 years (prior to diagnosis)
  - 59% had cataplexy
- “Improved” **EDS** with FDA approved medications: 85.4%
  - 42.3% had improved cognition
  - 51.8% improved fatigue
- Despite treatment most patients continue to struggle with daily symptoms
  - Residual EDS symptoms in 64.8%
  - Constant fatigue 37.4%
  - Cognitive impairment 40.8%
- Cognitive symptoms are very common and are under-appreciated by clinicians

Efficacy of current narcolepsy treatments: are we setting the bar too low? Maski KP et al. Sleep 37: A232; 2014 (abs)
Behavioral Treatment

• Naps
  • 20 min naps 2 or 3 per day (when possible)
  • Avoid driving when sleepy
  • Avoid high carbohydrate foods

• Maintain good sleep hygiene (try NOT to deviate from routine sleep/wake schedules)

• Cataplexy
  • Avoid emotional situations likely to induce cataplexy

• Psychosocial support
  • Family
  • School
  • Job
  • Education
    • Narcolepsy Network
    • Wake Up Narcolepsy
    • National Sleep Foundation
## Modafinil/Armodafinil Adverse Experiences

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Placebo</th>
<th>Modafinil/Armodafinil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>40%</td>
<td>50%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4%</td>
<td>13%</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>8%</td>
<td>11%</td>
</tr>
<tr>
<td>Nervousness</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4%</td>
<td>8%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>1%</td>
<td>5%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1%</td>
<td>5%</td>
</tr>
</tbody>
</table>
## Anticataplectic Compounds

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Normal Dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protriptyline (Vyvactil®) (tricyclic type)</td>
<td>5-60 mg/day</td>
<td>Anticholinergic effects (dry mouth, blurred vision, constipation, sexual dysfunction)</td>
</tr>
<tr>
<td>Imipramine (Tofranil®) (tricyclic type)</td>
<td>10-100 mg/day</td>
<td>Anticholinergic effects (dry mouth, blurred vision, constipation, sexual dysfunction)</td>
</tr>
<tr>
<td>Clomipramine (Anafranil®) (tricyclic type)</td>
<td>10-150 mg/day</td>
<td>Anticholinergic effects (dry mouth, blurred vision, constipation, sexual dysfunction)</td>
</tr>
<tr>
<td>Fluoxetine (Prozac®) [SSRI] Sertraline (Zoloft®) [SSRI]</td>
<td>20 mg/day 50-100 mg/day</td>
<td>Sexual dysfunction, Sleep disturbance</td>
</tr>
<tr>
<td>Venlafaxine (Effexor®) [SSNRI]</td>
<td>37.5-220 mg (XR)/day</td>
<td>Dry Mouth, sexual dysfunction, sleep disturbances</td>
</tr>
</tbody>
</table>
Sodium oxybate (Xyrem®)

- Na⁺ salt of gamma hydroxybuterate (GHB)
- Only drug to be FDA approved to treat both excessive daytime sleepiness and cataplexy in patients with narcolepsy
- ½ life 30-60 min
- Allow at least 2 hours after eating to time of first dose
- Nocturnal dosing (as a split dose)
  - ½ of the full dose at bedtime
  - ½ of full dose 3-4 hours after taking the bedtime dose
- Increases slow wave sleep
- Decreases time to sleep onset and decreases wakefulness after sleep onset
- Needs to be titrated upwards over 4-8 weeks (max total nightly dose=9 gm)
- Cannot be used with other CNS depressants or alcohol
Sodium oxybate precautions

• Caution in depressed patients
  • Ask about suicidal ideation, prior suicide attempts, mood swings, changes in personality
• **Contraindicated** with other hypnotics/sedatives and alcohol
• 9 gm dose has 1.7 Gms of sodium, so some patients may be advised restrict sodium intake
• Has potential for respiratory depression
  • Should not be used in *untreated* OSA
  • Can be used in OSA as long as patient is using CPAP or other treatments
• Treatment can result in weight loss
### Most Common Adverse Events in Controlled Studies of sodium oxybate (Xyrem®)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo</th>
<th>Xyrem®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Somnolence</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Urinary Incontinence</td>
<td>&lt;1</td>
<td>6</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
New Agents Under Research/Development

- Non-hypocretin-based therapies
  - sodium oxybate for children, JZP 13-005 (Jazz Pharmaceuticals—currently enrolling patients ages 7-17)
  - histaminergic H3 antagonist/inverse agonists (pitolisant)
  - JZP-110 (ADX-N05) a novel wake-promoting compound being developed by Jazz
  - Once nightly sodium oxybate “micropump sodium oxybate” Avadel/Flamel technologies
  - GABA-A receptor agonists
    - flumazenil
    - clarithromycin
  - melanin-concentrating hormone (MCH) antagonists
    - The MCH system promotes sleep (REM sleep > Non-REM sleep) so theoretically the antagonism of MCH activity might promote wakefulness/improve cataplexy
Other Agents (”not yet ready for prime-time”)

- Hypocretin-based therapy
  - Hypocretin-1
    - *Intra-cerebro-ventricular administration* has been shown to increase arousal and reduce cataplexy in narcoleptic mice
    - *Intranasal administration of Hcrt-1* (limited human trials showed no effect on wakefulness but there were changes in REM sleep parameters)
  - *Nonpeptide hypocretin agonist* (non-protein, peptide Hcrt agonists that can pass the blood-brain barrier)
  - *Hypocretin cell transplantation* that is immune to further immune attack
  - *Development of vaccine* for hypocretin-specific autoimmune disease is the holy grail but we still have to conclusively determine if Hcrt cell loss is secondary to an autoimmune reaction and then determine the exact mechanisms involved in such a process