Narcolepsy: To Sleep or Not to Sleep – That is Not an Option

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Objectives:
• Describe the pathophysiology of narcolepsy
• Recognize the clinical features of narcolepsy
• Review the tests used to diagnose narcolepsy
• Recommend treatment management of patients with narcolepsy
Narcolepsy: To Sleep or Not To Sleep, That is Not an Option

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Disclosures

- I have absolutely nothing to disclose
Objectives

• Review the neuroanatomy of wakefulness in relation to narcolepsy
• Discuss important clinical elements of narcolepsy
• Explain diagnostic approach to narcolepsy
• Review management and treatment of narcolepsy
Definition

- Excessive daytime sleepiness that typically is associated with cataplexy and other rapid eye movement (REM) sleep phenomena such as sleep paralysis and hypnagogic hallucinations.
- Essentially narcolepsy is an instability of wake and sleep stages
- However, there are different forms of narcolepsy
  - With cataplexy
  - Without cataplexy
  - Due to medical condition
History of Narcolepsy

- Westphal and Fisher published reports of patients with sleepiness and episodic muscle weakness in 1877-78
- The term narcolepsy was first coined by Gélineau in 1880
- The term cataplexy was coined by Loëwenfeld in 1902
- In 1930 von Economo identified the posterior hypothalamus as a key region for the promotion of wakefulness
- Daniels associated daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations in the 1930s
- Yoss and Daly and Vogel reported sleep-onset REM periods in 1960
- In 1998 two different groups (DeLecea, Sakarai) discovered that a hypothalamic peptide neurotransmitter (hypocretin/orexin) played a major role in wakefulness
- In 1999 Stanford group found an autosomal recessive mutation in the hypocretin receptor-2 gene (HCRTR2) responsible for narcolepsy in canines
- Subsequently in 2000 loss of hypocretin-1-containing cells in the hypothalamus was found to be present in narcolepsy with cataplexy in humans
Animal models

- First reported by Knecht and Mitler in 1973 in two dogs
- Autosomal recessive transmission with full penetrance
  - Doberman pinschers, Labrador retrievers, and dachshunds
  - Cataplexy elicited with appetizing food or while at play
    - Few seconds duration
    - Preferentially affect the hind legs, neck or face but may involve complete muscle paralysis with loss of reflexes
    - Food-elicited cataplexy test to quantify degree of cataplexy
- Due to mutations in hypocretin receptor-2
Neuroanatomy of wakefulness

**Ascending Reticular Activating System (ARAS)**

- Originates in rostral pons and runs through midbrain reticular formation.
- Dorsal route through the thalamus
- Ventral route through the hypothalamus and basal forebrain
- Includes the following structures and neurotransmitters that promote wakefulness:

<table>
<thead>
<tr>
<th>Structure</th>
<th>Neurotransmitter</th>
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<tbody>
<tr>
<td>Locus coeruleus (LC)</td>
<td>Norepinephrine (NE aka NA)</td>
</tr>
<tr>
<td>Pedunculopontine nuclei (PPT)</td>
<td>Acetylcholine (ACh)</td>
</tr>
<tr>
<td>Laterodorsal tegmental nuclei (LDT)</td>
<td>Acetylcholine (ACh)</td>
</tr>
<tr>
<td>Dorsal raphe nuclei</td>
<td>Serotonin (5-HT)</td>
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<tr>
<td>Ventral periaqueductal gray matter (vPAG)</td>
<td>Dopamine (DA)</td>
</tr>
<tr>
<td>Tuberomamillary nucleus (TMN)</td>
<td>Histamine (His)</td>
</tr>
</tbody>
</table>

BF = basal forebrain
LH = lateral hypothalamus
Neuroanatomy of wakefulness

**Hypocretin (aka Orexin)**

- Produced in the lateral hypothalamus
- Projects to multiple other arousal-promoting neurons
- Helps stabilize wakefulness to prevent unwanted wake-to-sleep transitions
- Hypocretin-1 deficiency associated with narcolepsy w/ cataplexy

Staining of hypocretin-1 neurons in the lateral hypothalamus shows deficiency of these neurons in narcolepsy.
Demographics

- Approximately 1 in 2000 people have some form of narcolepsy.
  - 1 in 4000 people in Western Europe and U.S.
  - 1 in 600 people in Japan
  - 1 in 500,000 people in Israel
- May run in some families, but most cases are not clearly genetic.
  - Narcolepsy is sporadic in 99% of patients.
  - Risk of 1st-degree relative developing narcolepsy is 1-2%.
    - 10-fold to 40-fold increase in risk.
- Usual onset between the ages of 15 to 25.
  - Symptoms may worsen after the first few years.
- Extremely rare in children, especially before 5 years of age.
- Slight male preponderance.
Clinical Features

- Excessive daytime sleepiness
- Cataplexy
- Sleep paralysis
- Hallucinations
- Sleep disruption

All of these symptoms can occur in any person who is severely sleep deprived except cataplexy.
Excessive Daytime Sleepiness (EDS)

- Usually the most disabling symptom and first to occur
- Sleep attacks = sudden onset of sleep or involuntary sleep episodes
  - Varies from a few seconds to several minutes to over an hour
- Sleepiness can result in poor school or work performance, memory lapses, social isolation, automatic behavior
  - Patient continues an activity in a semiautomatic fashion without memory or consciousness
- Brief 15-20 minute naps are generally refreshing for one to several hours
  - Contrast with idiopathic hypersomnia in which patients take long and unrefreshing naps
Cataplexy

- 60-70% of narcoleptic patients have cataplexy
  - Typically develops within a year but may precede sleepiness or commence up to 40 years later
- Abrupt and reversible decrease or loss of muscle tone of certain muscles or entire voluntary musculature
  - Jaw sags, head falls forward, arms drop to the side, knees buckle
  - Extraocular muscles rarely involved – blurred vision
  - Speech may be broken or slurred
  - Short breathing pauses can occur
  - Complete body collapse is rare but can lead to injury
  - Transient reversible loss of deep tendon reflexes is a very strong, but rare, diagnostic finding
- Awareness is preserved
- Typically elicited by emotions
  - Laughter, pride, surprise, elation, anger
  - Occurs rarely without precipitating emotion, especially if patient is sleepy
- Duration from a few seconds to 30 minutes
  - Usually 30 seconds to 2 minutes
  - Status cataplecticus can last hours and can be observed following withdrawal of anti-cataplectic medications
Cataplexy

- Physiology of REM muscle atonia
  - Cholinergic neurons from the PPT activate glutamatergic REM-on cells in the pontine reticular formation
  - Glutamatergic neurons activate glycine in the medulla
  - Glycine produces hyperpolarization and is an inhibitory transmitter that causes decreased muscle tone
  - This prevents people from acting out dreams
- Cataplexy = intrusion of REM atonia in wakefulness
Sleep Paralysis

- Transient, generalized inability to move or to speak during the transition between sleep and wakefulness
- Occurs upon falling asleep or awakening
- Often accompanied by hallucinations and sensation of inability to breathe
- Patients aware but unable to move or open their eyes
- Resolves spontaneously within a few minutes or less
- Experienced by 40-80% of narcoleptic patients
- 3-5% of the general population may have sleep paralysis
Hallucinations

- Hypnagogic (sleep onset) or hypnopompic (awakening)
- Recurrent hypnagogic hallucinations in 40-80% of patients with narcolepsy with cataplexy
- Visual or auditory, other senses seldom involved
  - Elementary censethopathic feelings (picking, rubbing, light touching)
  - Changes in location or body parts (arm or leg)
  - Feelings of levitation or extracorporeal experiences
  - Abrupt spinal cord motor neuron inhibition may decrease CNS feedback that gauges position of the body and the relation of limb segments to each other
- Patient may act on hypnopompic hallucinations
- Patients have been mistakenly diagnosed with psychosis
- ~4% of the normal population experiences recurrent sleep paralysis or hypnagogic hallucinations
Sleep Disruption

- Nocturnal sleep is often disrupted by repeated awakenings, sometimes with nightmares
- Occurs in about 50% of narcoleptics
- Insomnia (usually sleep-maintenance) with EDS may be the initial complaint
- Periodic limb movements of sleep (PLMS) are more common in narcoleptics and may contribute to disrupted sleep
  - May be a side effect of medication related to increase in muscle tone during sleep
  - Dopamine agonists may be useful treatment
- REM behavior disorder is more common in narcoleptics
  - May reflect state-boundary control abnormality
  - Tricyclics and SSRIs eliminate or decrease the muscle atonia of REM sleep
Other Issues

- Weight
  - Narcolepsy with cataplexy is often associated with increased BMI, especially when untreated
  - Monitor for the development of obstructive sleep apnea, especially if the degree of sleepiness worsens or previously effective medication regimen loses efficacy
- Depression is common
- Type II diabetes may occur more often
Onset of Symptoms

- Often around puberty
- Peak age is 15-25 years old
  - As early as 2 years
- A second, smaller peak of onset between 35-45 years and near menopause in women
  - 21% of patients have first symptoms after age 30
- Rarely develops at age 60 years or older, and if it does, cataplexy is the most common initial presenting symptom
- Delay of 10+ years (mean 15 years) between symptom onset and diagnosis, especially without cataplexy
  - Cataplexy can occur up to 20 years later but occasionally precedes abnormal sleep episodes
- Symptoms might abate with time but don’t completely resolve
  - Cataplexy has a tendency to decrease in frequency with aging
Diagnosis

- Evaluating Sleepiness
  - Subjective scales
    - Stanford Sleepiness Scale
      - Quantifies sleepiness throughout the day with self-rating every 15-20 minutes
    - Epworth Sleepiness Scale
      - Likelihood of dozing in 8 different daytime situations
      - Maximum score is 24, scores ≥ 10 indicative of pathologic sleepiness
    - Pediatric Daytime Sleepiness Scale
      - Validated in children and teenagers
  - Objective measure
    - MSLT
Diagnosis

- **Multiple Sleep Latency Test (MSLT)**
  - Four-to-five 20 minute nap opportunities 2 hours apart beginning ~2 hours after morning awakening
  - Measures sleep onset latency which is then averaged over the 4-5 naps
    - Diagnostic criteria is ≤ 8 minutes
    - Up to 1/3 of general population have sleep latency of ≤ 8 minutes
    - Most people with narcolepsy fall asleep in an average of 3 minutes
  - Measures sleep onset REM periods (SOREMPs)
    - REM sleep that occurs within 15 minutes of sleep onset
    - Seen in 2 or more naps
    - Sensitivity 0.78, specificity 0.93 for narcolepsy
    - 4-9% of general population may have multiple SOREMPs on routine MSLT
  - Sleep latency and SOREMP criteria may be too stringent in older patients
    - ~15% of patients with narcolepsy may have normal or borderline MSLT especially if older than 36 years of age
  - Moscovitch et al found that 84% of patients with sleepiness and cataplexy had 2+ SOREMPs
    - 100% had 2+ SOREMPs on at least 1 MSLT when MSLT repeated daily x 4
MSLT Requirements

- In-lab PSG the night before the MSLT
  - Verify adequate sleep time (at least 6 hours)
  - Rule out other sleep disorders, ie sleep apnea, which could cause EDS
  - Sleep latency of < 10 minutes and SOREMP are common (25-50% have SOREMP)
  - Increase in N1 sleep and frequent awakenings common
- Abstain from medication for a sufficient period, usually 15 days (or at least 5 times the ½-life of the drug)
  - REM suppressing medications: carbamazepine, phenytoin, SSRIs, TCAs, lithium, venlafaxine, chlorpromazine, haloperidol, progesterone, beta blockers, clonidine, diphenhydramine, loratadine, promethazine, barbiturates, benzodiazepines
- Sleep diaries or actigraphy to verify that sleep-wake schedules are stable for at least 7 days before the test
MSLT Details

- 4-5 nap opportunities at 2-hour intervals beginning 1.5-3 hours after PSG
- Central EEG, occipital derivations, EOG, mental/submental EMG, and ECG
- Should not perform if < 6 hours of sleep or SDB on PSG and should not perform after split-night study
- Urine toxicology testing either morning of MSLT or after final nap
- Patient should be asked if he/she needs to use the restroom or needs other adjustments for comfort before each nap
- Biocalibration before each nap
- Instructions: “Please lie quietly, assume a comfortable position, keep your eyes closed, and try to fall asleep.”
MSLT Details (continued)

• Between naps the patient should be advised to:
  • Not sleep
  • Stop smoking at least 30 minutes before each nap opportunity
  • Avoid vigorous physical activity and stop any stimulating activity at least 15 minutes before each nap opportunity
  • Abstain from all caffeine and avoid any unusual exposure to bright sunlight
• A nap session ends after 20 minutes if no sleep, in which case sleep latency is reported as 20 minutes
• Sleep onset is defined as the 1st epoch of greater than 15 seconds of cumulative sleep
• Test continues for 15 minutes after the 1st epoch of sleep
• Report should include start and end times of nap opportunities, sleep latency of each nap, mean sleep latency over 4-5 naps, and number of SOREMPs
CSF Hypocretin/Orexin

- Hypocretin neurons are selectively damaged in patients with narcolepsy for unclear reasons
  - Loss of approximately 50,000 to 100,000 neurons
  - Neuronal loss in hypothalamus has been seen in some narcoleptics by proton MRI spectroscopy
- CSF hypocretin-1 levels less than 110 ng/L have a 94% positive predictive value for narcolepsy with cataplexy
  - Highly specific and sensitive, rarely seen in controls or other pathologies
  - 296/300 narcoleptics with low CSF hypocretin-1 are HLA DQB1*0602 positive
- Most accurate diagnostic technique but normal levels seen in ~9% of narcoleptics
  - Negative test doesn’t exclude diagnosis
- Other causes of low CSF hypocretin
  - Guillain-Barré syndrome, brain tumors, encephalitis, vascular diseases, brain trauma
Genetics: human leukocyte antigen (HLA)

- HLA genes present antigens to the rest of the immune system, most HLA associated disorders are autoimmune in nature
- HLA subtype DQB1*0602 is most specific marker for narcolepsy across all ethnic groups
  - DR2/DRB1*1501 subtype in Caucasians and Asians but not African-Americans
- 95% of people with narcolepsy with cataplexy carry this haplotype
  - 40% of narcolepsy without cataplexy are positive
  - 18-35% of the general population is positive
    - 25% Caucasian, 12% Japanese, 38% African-American
- This HLA association suggests an autoimmune process targeting hypocretin neurons
  - Most commonly reported triggers are head trauma, abrupt change in sleep-wake patterns, sustained sleep deprivation, or unspecified viral illness
Autoimmune Hypothesis

- Seasonal occurrence of narcolepsy peaks 5-7 months after influenza infection in China
  - 6.7-fold increase in narcolepsy after 2009 H1N1 winter influenza pandemic
- Recent narcolepsy outbreak associated with Pandemrix H1N1 vaccination in Europe and Canada
  - 4- to 17-fold increased risk in various countries
  - Swedish study (Szakacs A et al, 2013)
    - 28 children developed narcolepsy in 2009-2010 post-vaccination (from 2000-2009 only 8 children diagnosed)
    - Incidence jumped from 0.25/100,000/year to 6.6/100,000/year
    - 25-fold increased risk
    - Majority of children (19/28) developed symptoms within 12 weeks
    - 17 of 28 children had HLA-DQB1*0602 testing and all 17 were positive
The graph illustrates the decline in the number of hypocretin cells over time. It shows:

- An environmental factor(s) affecting the number of hypocretin cells.
- A genetic predisposition (e.g., HLA) affecting hypocretin-producing neurons.
- A subsequent damage to hypocretin-producing neurons.
- The onset of symptoms at the end of the process.
ICSD-2 Diagnostic Criteria
Narcolepsy with Cataplexy

A. EDS occurring almost daily for at least 3 months
B. A definite history of cataplexy is present
   ▪ Must be triggered by strong emotions, be brief and bilateral with preserved consciousness
C. Should be confirmed by PSG/MSLT with a mean sleep latency of ≤ 8 minutes and 2+ SOREMPs. Alternatively, hypocretin-1 levels in the CSF are ≤ 110 pg/mL
D. The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.
Narcolepsy without Cataplexy

- Patients without cataplexy or with atypical or doubtful cataplexy but with positive MSLT
  - Examples of cataplexy-like episodes
    - Muscle weakness in the context of exercise or sex
    - Weakness when stress or tensed
    - Feeling the need to roll on the floor when laughing uncontrollably
- Anywhere from 10-50% of narcoleptic population
  - 0.02% of general population
- 40% are HLA DQB1*0602 positive
  - HLA typing should therefore not be used to diagnose narcolepsy without cataplexy
  - May be used in young patients at risk of developing more definitive narcolepsy with cataplexy
- 10-20% are hypocretin-1 deficient, almost always in those who are HLA DQB1*0602 positive
  - May be useful in the setting of other sleep disorders or patients on psychotropic medications that may affect MSLT results
ICSD-2 Diagnostic Criteria
Narcolepsy without Cataplexy

A. EDS occurring almost daily for at least 3 months
B. Typical cataplexy is not present, although doubtful or atypical cataplexy-like episodes may be reported
C. Confirmed by PSG/MSLT with a mean sleep latency $\leq 8$ minutes and 2+ SOREMPs
D. The hypersomnina is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.
Narcolepsy due to a Medical Condition

- Narcolepsy with Cataplexy
  - Hypothalamic tumor
  - Hypothalamic sarcoid
  - MS affecting hypothalamus
  - Anti-Ma2 paraneoplastic syndrome
  - Neimann-Pick type C
  - Coffin-Lowry Syndrome
  - Norries disease

- Narcolepsy without Cataplexy
  - Head trauma
  - MS
  - Myotonic dystrophy
  - Prader-Willi syndrome
  - Parkinson’s disease
  - Multiple system atrophy

Treat OSA 1st
ICSD-2 Diagnostic Criteria
Narcolepsy due to Medical Condition

A. EDS occurring almost daily for at least 3 months

B. One of the following is observed:
   i. A definite history of cataplexy
   ii. If cataplexy is not present or is very atypical, PSG/MSLT demonstrate a mean sleep latency of $\leq 8$ minutes with 2+ SOREMPs
   iii. Hypocretin-1 levels in the CSF are $< 110$ pg/mL

C. A significant underlying medical or neurological disorder accounts for the daytime sleepiness

D. The hypersomnia is not better explained by another sleep disorder, mental disorder, medication use, or substance use disorder
Pediatric Narcolepsy

- Extremely rare prior to the age of 4 years
  - Single case of 6-month old who was HLA negative but had prepro-hypocretin mutation
- Obesity frequently develops, especially if abrupt onset and untreated
- Typically presents with reappearance of regular daytime naps in a child who had previously discontinued napping
- Sleepiness at school or may manifest as ADHD
- May be difficult to confirm presence of hypnagogic hallucinations or sleep paralysis
- Sudden episodes of cataplexy may be misdiagnosed as epileptic or non-epileptic seizures
- If cataplexy isn’t present initially, it could develop over time, especially if hypocretin-1 deficiency
- Diagnosis made clinically based on presence of cataplexy, with assistance of MSLT or CSF hypocretin-1 levels
  - Most common cause of short sleep latencies, often with multiple SOREMPs, in peri-pubertal children and adolescents is chronic sleep deprivation and DSPS
Differential Diagnosis

- EDS due to another cause
  - OSA
  - PLMD
  - Insufficient sleep syndrome
  - Severe insomnia
- Idiopathic hypersomnia with or without long sleep time
  - Long, unrefreshing daytime naps
  - Mean sleep latency on MSLT is $6.2 \pm 3$ minutes
- Cataplexy should be differentiated from hypotension, TIA, drop attacks, akinetic seizures, neuromuscular disorder, vestibular disorders, psychological or psychiatric disorders, sleep paralysis
- Malingering to obtain stimulant medications
Behavioral Treatment

• Patient support groups
  • National Sleep Foundation, www.sleepfoundation.org
  • Narcolepsy Network, www.narcolepsynetwork.org
• Career counseling
  • Avoid shift-work, on-call schedules, driving and transportation industry, monotonous long jobs
• Regular sleep-wake schedule with appropriate amount of nighttime sleep
• Scheduled short naps
• Regular exercise
• Avoid heavy meals and alcohol intake
• Driving precautions
<table>
<thead>
<tr>
<th>Medications for Sleepiness</th>
<th>Medications for Cataplexy (not FDA approved)</th>
</tr>
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<tbody>
<tr>
<td>• Modafinil</td>
<td>• Venlafaxine</td>
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<tr>
<td>• Armodafinil</td>
<td>• Fluoxetine</td>
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<tr>
<td>• Methylphenidate</td>
<td>• Viloxazine</td>
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<tr>
<td>• Atomoxetine</td>
<td>• Protriptyline</td>
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<tr>
<td>• Dextroamphetamine</td>
<td>• Imipramine</td>
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<tr>
<td>• Methamphetamine</td>
<td>• Clomipramine</td>
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<td>• Desipramine</td>
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**Sodium oxybate (GHB)**

**(FDA approved)**
Modafinil (Provigil)

- 1st-line agent for EDS and sleep attacks
- Exact MOA unknown, may selectively activate wake-generating sites in the hypothalamus
  - Animal studies suggest dopamine plays a role (inhibition of dopamine reuptake) and dopamine transporters are necessary for the wake-promoting actions of the drug
- Efficacy verified in several multicenter studies
- Improves but doesn’t normalize MSLT findings
- No effect on cataplexy or other REM-related symptoms
- Not addictive, low potential for abuse
- No reported evidence of tolerance
- Side effects
  - Headache is most common
  - Nervousness, nausea, dry mouth, elevated blood pressure, reduced efficacy of OCPs
- ½-life 10-12 hours
- Administered 1-2 times a day, 100-600 mg daily
- Best in stimulant-naïve patients, may have recurrence of symptoms when switching from stimulant to modafinil
Armodafinil (Nuvigil)

- R-enantiomer of racemic modafinil
- $\frac{1}{2}$-life of 10-14 hours
  - Plasma concentrations remain higher later in the day compared to modafinil
- Administered once a day, 50-250 mg daily
- Side effects similar to modafinil
- No direct comparison studies between modafinil and armodafinil
Amphetamines and Amphetamine-Like CNS Stimulants

- Methylphenidate, dextroamphetamine, methamphetamine
- Increase release of dopamine, norepinephrine, and serotonin
  - NE effect may help control cataplexy and sleep paralysis
- Inhibit the reuptake of amines by the dopamine transporter
- Increase sleep-onset and REM sleep latency, reduce sleepiness and % REM sleep
- Have the greatest impact on EDS
- Doses > 60 mg/day do not significantly improve EDS and increase risk for side effects
  - Worsened nocturnal sleep disruption
  - Palpitations, hypertension, nervousness
  - Psychosis, paranoia, psychiatric hospitalization
  - Alcohol or poly-drug abuse
  - Rebound hypersomnia
  - Abuse and tolerance
- Administered 1-3 times a day, 5-60 mg daily, no later than 3 pm
- Methylphenidate is probably comparable in efficacy to modafinil
- Dextroamphetamine is typically more potent
Cataplexy Treatment

- During wakefulness, serotonergic and noradrenergic input inhibits REM-related neurons of rostral pons and caudal mesencephalon.
- Hypocretin has excitatory effect on these REM-off cells.
- Decreased hypocretin could facilitate the manifestations of these REM sleep-associated features into wakefulness.
- Goal of therapy is therefore to restore REM-off cell function.
Pharmacology of Anti-cataplectic Medication

- Based on canine studies
- Inhibition of adrenergic uptake mediates therapeutic effects of antidepressants
  - Not inhibition of dopaminergic or serotonergic uptake
  - Protriptyline, desipramine, and atomoxetine are effective and potent anticataplectic agents
    - Adrenergic-specific uptake blockers
    - No effect on serotonin transmission
  - Escitalopram, fluoxetine, other SSRIs are inactive or only active at relatively high doses
    - Weak adrenergic uptake effects
- Adrenergic transmission is reduced during REM sleep and decreases during cataplexy
Less Familiar Medications

Atomoxetine
- Selective noradrenergic reuptake inhibitor
  - FDA approved for ADHD
- Used for cataplexy and daytime sleepiness
- Most effective in children
- Less effective in teenagers and adults
- 18-100 mg qday or bid

Selegiline
- Irreversible monoamine oxidase-B (MAO) inhibitor
- Active metabolites are L-amphetamine and L-methamphetamine
- Treats cataplexy and daytime sleepiness
- Start at 20 mg/day
- Maximum 40 mg/day
- Adverse effects
  - Sympathomimetic
  - Drug-drug interactions
  - Hypertensive emergencies
Monoamine Nonspecific Uptake Inhibitors

- Monoamines = serotonin, NE, dopamine
- Tricyclics were the first medications used for cataplexy
  - Imipramine, clomipramine, protryptiline
- Inhibit monoamine reuptake and block cholinergic, histaminic, α-adrenergic transmission
- Significant anticholinergic side effects
  - Dry mouth, sweating, constipation, tachycardia, urinary retention, sexual dysfunction (ED in 40%)
- Due to side effects, these are typically last resort
Selective Serotonin Reuptake Inhibitors (SSRIs)

- Active noradrenergic reuptake blocker metabolite
- Fluoxetine starting at 20 mg in the morning and increasing to 60-80 mg in 2 divided doses
- Fluvoxamine at 25-200 mg/day mildly effective
- Less efficacious in treating cataplexy than tricyclics
- Fewer side effects than tricyclics
  - CNS excitation
  - Nausea
  - Sexual difficulties
- Tolerance to this class does not develop
Norepinephrine and Serotonin Uptake Inhibitors

- Effective for cataplexy, sleep paralysis, and hypnagogic and hypnopompic hallucinations
- Greater efficacy and fewer side effects than other drugs mentioned
- Venlafaxine is SNRI with weak inhibition of dopamine reuptake
  - No muscarinic, cholinergic, H₁ histaminergic, or α₁-adrenergic activity
- Typical dose is 75-300 mg/day
Sodium Oxybate, aka Xyrem, aka gamma-hydroxybutyrate [GHB]

- GHB is a natural CNS metabolite in the hypothalamus and basal ganglia
  - Affects dopamine, serotonin, gamma-aminobutyric acid (GABA), endogenous opioids
  - May act through its own receptor and GABA$_B$ receptors
  - Acts as a sedative to consolidate REM sleep
  - Dose-related increase in slow-wave sleep and reduction in nocturnal awakenings
  - Long-term efficacy shown through multicenter studies
- Treats cataplexy, EDS, and disturbed nocturnal sleep
  - MOA in cataplexy is unknown, thought to be related to REM consolidation or secondary interaction with dopamine secretion
  - Decrease in sleep paralysis, hypnagogic hallucinations, and nightmares
Sodium Oxybate

- $\frac{1}{2}$-life is 90-120 minutes
- Taken with patient already in bed to avoid falls
- 2nd dose taken 2.5-4 hours later
- Dosage recommendations
  - Start at 2.25 grams twice a night (sub-therapeutic)
  - Increase dose by 1.5 grams (0.75 grams per dose) per night at 1-2 week intervals to therapeutic effect
  - Effective dose varies from 6-9 grams
  - Maximum dose 9 grams
- Sustained increase in efficacy on cataplexy over 12 months
- Effect on EDS may not be seen for up to 2 months
  - May need to continue other stimulant during this time
- Side effects, generally worse at higher doses
  - Disorientation, enuresis, nausea, sluggishness, respiratory failure
Pregnancy

- Most of these drugs are category C in pregnancy
  - Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
- May lead to respiratory and feeding side effects
- SSRI/SNRI are category C in 3rd trimester, so progressively withdraw medications before that
- Slow withdrawal to avoid rebound cataplexy
  - Usually occurs on day 3 or 4
  - Peaks near day 10 after complete withdrawal
Practice Parameters for the Treatment of Narcolepsy and other Hypersomnias of Central Origin

- AASM report from 2007
- Evidence levels
  I. Randomized, well-designed trials with low alpha and beta error, or meta-analysis of randomized controlled trials with homogeneity of results
  II. Randomized trials with high alpha and beta error, methodologic problems, or high quality cohort studies
  III. Nonrandomized concurrently controlled studies (case-control studies)
  IV. Case-control or cohort studies with methodological problems, or case series
  V. Expert opinion, or studies based on physiology or bench research
- Levels of Recommendations
  - Standard: This is a generally accepted patient-care strategy that reflects a high degree of clinical certainty. The term standard generally implies the use of level 1 evidence, which directly addresses the clinical issue, or overwhelming level 2 evidence
  - Guideline: This is a patient-care strategy that reflects a moderate degree of clinical certainty. The term guideline implies the use of level 2 evidence or a consensus of level 3 evidence.
  - Option: This is a patient-care strategy that reflects uncertain clinical use. The term option implies either inconclusive or conflicting evidence or conflicting expert opinion.
So what does the AASM recommend?

- **Standard recommendations**
  - Modafinil is effective for treatment of daytime sleepiness
    - No formal recommendation on armodafinil
  - Sodium oxybate is effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep

- **Guideline recommendations**
  - Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of daytime sleepiness
  - Scheduled naps can be beneficial to combat sleepiness but seldom suffice as primary therapy
  - TCAs, SSRIs, and venlafaxine may be effective treatment for cataplexy

- **Option recommendations**
  - Sodium oxybate may be effective for treatment of hypnagogic hallucinations and sleep paralysis
  - Selegiline may be an effective treatment for cataplexy and daytime sleepiness
  - TCAs, SSRIs, and venlafaxine may be effective treatment for sleep paralysis and hypnagogic hallucinations
Conclusions

- Narcolepsy is a condition of excessive daytime sleepiness accompanied by features of REM sleep intruding into wakefulness such as cataplexy, sleep paralysis, and hallucinations usually beginning in adolescence or young adulthood.
- The majority of cases of narcolepsy with cataplexy are associated with CSF hypocretin-1 deficiency and HLA DQB1*0602 positivity but this association in other narcolepsy conditions is much weaker.
- Diagnosis is typically made based on suggestive clinical history and MSLT testing showing a mean sleep latency of ≤ 8 minutes and 2+ SOREMPs.
- Treatment typically involves stimulant medication +/- anti-cataplectic medication with the strongest evidence for modafinil and sodium oxybate.