

When Dreams Become Nightmares: Pediatric Narcolepsy

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Produced by the Alabama Department of Public Health
 Video Communications and Distance Learning Division

CME DISCLOSURE

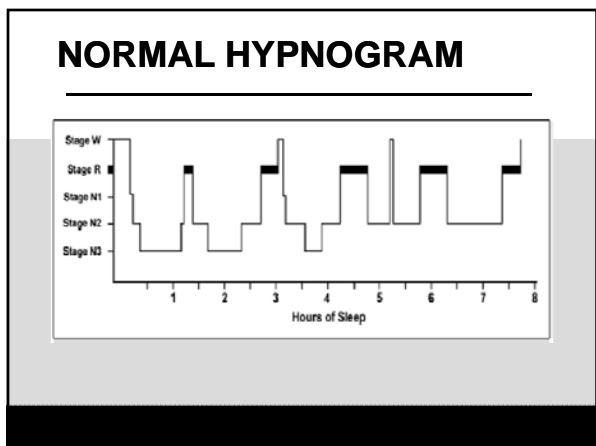
- I have no conflicts of interest to disclose

OBJECTIVES

- Discuss the epidemiology of pediatric narcolepsy
- Review the clinical signs and symptoms of pediatric narcolepsy
- Describe the pathophysiology of narcolepsy
- Highlight the diagnostic testing of narcolepsy
- Highlight treatments for narcolepsy

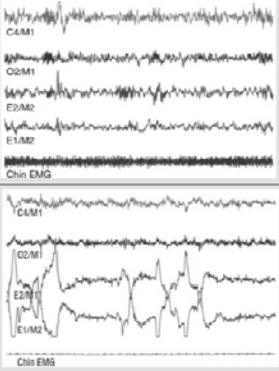
DISCUSSION WITH TWO EXPERTS

- Heather and Lori Thompson

CHARACTERISTICS OF REM SLEEP

- Rapid-Eye Movement
- Skeletal muscle atonia
- Sawtooth EEG pattern
- Dreaming



Principles and Practice of Sleep Medicine, 2015. Chapter 141. Fig 141-2, 141-5.

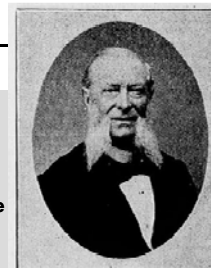
NARCOLEPSY-DEFINED

- Lifelong condition of excessive daytime sleepiness
- May be accompanied with cataplexy
 - Loss of muscle tone while awake



HISTORY

- First described by Gelineau as narcolepsie
 - Brief, recurrent attacks of sleepiness
 - Frequent falls (atasias)
- Daniels in 1930's described the clinical constellation that we identify as narcolepsy
 - Tetrad of symptoms



Dr. JEAN-BAPTISTE-ÉDOUARD GÉLINEAU

Gelineau J. Gaz Hosp (Paris) 1880; 53:626-8
<https://reliawire.com/story-of-narcolepsy/>

INCIDENCE

- Daytime Sleepiness occurs in 10-20% of school-aged children and adolescents
- Adult Incidence in Olmstead County, Minnesota
 - 1.37 per 100,000 persons
 - 1.72 for men and 1.05 for women
 - Prevalence was 56 per 100,000
- Prevalence in Japan: 1 in 600
- Prevalence in Israel 1 in 500,000
- Childhood Prevalence Estimate: 20-60 per 100,000 in the United States



Silber M et al. *Sleep*. 2002;25:197-202
 Honda Y. *Narcolepsy*, 1998: 2457
 Lavie P, et al. *Sleep*. 1987;10:608-9

EPIDEMIOLOGY CONTINUED

- Slight male predominance (1.8 male:1 female)
- Age:
 - Typically presents in late adolescence, post-puberty
 - Median age of onset is 14.7 years
 - 33% report symptoms starting before the age of 15 years
 - 15% prior to the age of 10 years
 - A lag of 5-15 years between onset of symptoms and diagnosis is common
 - 4.6% diagnosed prior to 5 years of age

Challamel MJ, et al. *Sleep* 1994;17S:16-20
 Han, F., et al.. *Annals of Neurology*, 2011; 70(3), 410-417.

EPIDEMIOLOGY CONTINUED

- In China, seasonal variation
 - Highest incidence in April and lowest in November
 - Three-fold increase in narcolepsy in China after the H1N1 influenza pandemic in 2009

Challamel MJ, et al. *Sleep* 1994;17S:16-20
 Han, F., et al.. *Annals of Neurology*, 2011; 70(3), 410-417.

INCIDENCE IN FAMILIES

- Most cases are sporadic
- Risk of narcolepsy with cataplexy in a 1st-degree relative=1-2%
 - 10-40 fold increase from the general population

FINANCIAL COSTS OF NARCOLEPSY

- Compared with controls, narcolepsy subjects had approximately twofold higher annual rates of inpatient admissions (0.15 vs. 0.08)
- Emergency department (ED) visits w/o admission (0.34 vs. 0.17)
- Hospital outpatient (OP) visits (2.8 vs. 1.4)
- Physician visits (11.1 vs. 5.6; all $p < 0.0001$)

Black, J., Reaven, et al. (2014). *Sleep Medicine*, 15(5), 522-529.

FINANCIAL COSTS OF NARCOLEPSY

- The rate of total annual drug transactions was doubled in narcolepsy versus controls (26.4 vs. 13.3; $p < 0.0001$)
 - 337% higher usage rate of narcolepsy drugs
 - 72% higher for non-narcolepsy drugs, respectively (both $p < 0.0001$)
- Mean yearly costs were significantly higher in narcolepsy for medical services (\$8346 vs. \$4147; $p < 0.0001$) and drugs (\$3356 vs. \$1114; $p < 0.0001$).

Black, J., Reaven, et al. (2014). *Sleep Medicine*, 15(5), 522-529.

FORMS OF NARCOLEPSY

TYPE I (NARCOLEPSY WITH CATAPLEXY)

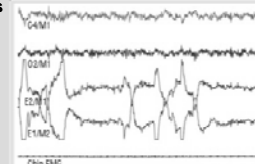
- Excessive daytime sleepiness
- Hallucinations
- Sleep paralysis
- Fragmented nighttime sleep
- Cataplexy
- Loss of orexin

TYPE II (NARCOLEPSY WITHOUT CATAPLEXY)

- Excessive daytime sleepiness
- Hallucinations
- Sleep paralysis
- Fragmented nighttime sleep

FOUR CENTRAL SYMPTOMS OF NARCOLEPSY

- Excessive Daytime Sleepiness
- Cataplexy
- Hypnagogic and hypnopompic hallucinations
- Sleep paralysis
- REM Sleep
- Muscle atonia
- Dreaming
- Muscle atonia



EXCESSIVE DAYTIME SLEEPINESS

- Most common symptom of narcolepsy
 - Seen in 100% of pediatric patients
 - Chief complaint in 85% of pediatric patients
- Overwhelming urge to fall asleep that worsens in situations with low stimulation, but occurs in numerous situations

Aran A, et al. *SLEEP*. 2010;33(11):1457-1464

EXCESSIVE DAYTIME SLEEPINESS

- Occurs despite adequate nocturnal sleep
- Patient may have frequent "microsleeps" throughout the day
- May be accompanied by autonomic behaviors
- Often children labeled as lazy

Aran A, et al. *SLEEP*. 2010;33(11):1457-1464

CATAPLEXY

- Second most common symptom
- Sudden loss of muscle tone in the facial muscles, or thighs, back, neck
- Typically in response to fright, rage, excitement, laughter, or surprise
- Intrusion of REM muscle atonia in the wake state.



Serra, et al. *Movement Disorders*. 2008

CATAPLEXY

- Caused by the hyperpolarization of the spinal alpha motor neurons
- Results in the inhibition of skeletal muscle tone
- Suppression of tendon reflexes
- Suppression of the monosynaptic H-reflex

https://www.youtube.com/watch?v=W9_IChX0Vm0

<https://www.youtube.com/watch?v=1PuvXpv0vDM>

HALLUCINATIONS

- Hypnagogic = Sleep onset
- Hypnopompic = At awakening from sleep
- Hallucinations that are caused by intrusions of REM into the Wake state
- Occurs in 50% of pediatric narcolepsy patients
- 25% of normal adults have hypnagogic hallucinations
- 18% of normal adults have hypnopompic hallucinations

Aran A, et al. *SLEEP* 2010;33(11):1457-1464

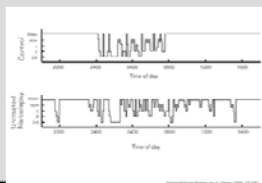
SLEEP PARALYSIS

- Momentary inability to move or speak that occurs at sleep onset or offset
- May be accompanied by eye-fluttering, moaning, or autonomic symptoms
- Ends spontaneously or if touched.
 - Occurs in 40-80% of adults with narcolepsy
 - Occurs in 55% of pediatric narcolepsy patients
 - Occurs in 3-5% of the general population

Aran A, et al. *SLEEP* 2010;33(11):1457-1464

OTHER SYMPTOMS: DISTURBED NOCTURNAL SLEEP

- Sleep fragmentation and disruption is very common in narcolepsy
- 90% of adults and 92% of pediatric patients
- Frequently sleep fragmentation with periodic limb movements seen on the sleep study



OTHER SYMPTOMS: AUTONOMIC BEHAVIORS

- Frequent staring spells
- Repetitive behaviors are common
- Often misdiagnosed as seizures or ADHD

OTHER FEATURES

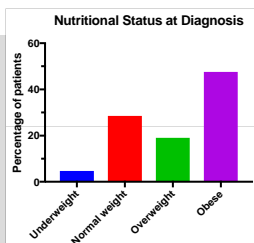
- Increased anxiety, depression
- Impaired academic performance
- Decreased academic performance
- Increase in headaches
- Precocious puberty
 - 17% of narcolepsy patients

NARCOLEPSY AND OBESITY

- Obesity may occur near the onset on narcolepsy – cataplexy
- Found in 50 to 74% of pediatric patients with narcolepsy
 - Inocente (2013): 50% children with narcolepsy with Z-score >2.0
- May be due to loss of nocturnal leptin rise
 - Leptin is an appetite suppressant hormone
- May be due to decreased basal metabolic rate
 - Children may gain 20-40 pounds at onset (Scammell, NEJM, 2015)

NARCOLEPSY AND OBESITY IN ALABAMA

- Retrospective review
- 21 patients between 4-18 years of age
- Mean BMI%: 82.63%
- Only 28.6% were at normal weight at diagnosis



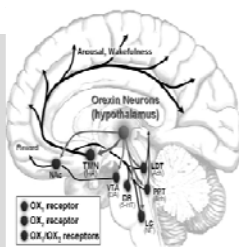
Slide courtesy of Valerie Tarn, MS, RD, LD

PATHOPHYSIOLOGY

- Association between narcolepsy and histocompatibility leukocyte antigen (HLA) DR2
- Stronger association with HLA DQB1*0602 and HLA DQA*0102
 - Found in 95-100% of patients with narcolepsy and 12-38% of the general population
- HLA DQB1*0102 was linked to shorter REM latency, increased sleep efficiency, and decreased N1 sleep

HYPOCRETIN

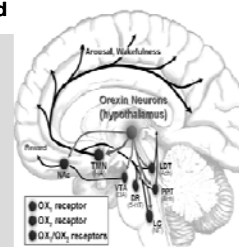
- Discovered in canine narcolepsy
- Hypocretin-containing neurons are found in the dorsolateral hypothalamus and have widespread projections
 - Project to the basal forebrain, amygdala, reticular formation, pontine nucleus, raphe nucleus, and dorsal spinal cord



<http://pharmrev.aspetjournals.org/content/64/3/389>

HYPOCRETIN

- Hypocretin stimulate food intake, increase basal metabolic rate, and promote arousal
- Canine models demonstrate narcolepsy with a decline in hypocretin receptor density.



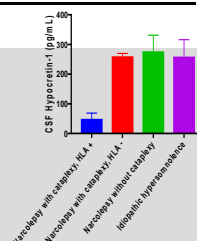
<http://pharmrev.aspetjournals.org/content/64/3/389>

PATHOPHYSIOLOGY

- Narcolepsy with cataplexy is linked to a low level of CSF hypocretin-1 or orexin
- Neurons in the hypothalamic region that have widespread projections
- Decrease in the amount of hypocretin-1 strongly correlates with narcolepsy with cataplexy
- Leads to downregulation of noradrenergic and dopaminergic pathways and upregulation of the REM facilitating pathways

TWO HIT HYPOTHESIS

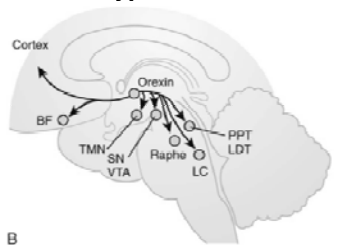
- Genetic susceptibility and stress
- Twin studies with HLA DQB*0602
 - One with narcolepsy at 12 years
 - One with narcolepsy at 44 after emotional stress and sleep deprivation
- Major life event, systemic illness, injury or bereavement seen in 82% of narcolepsy patients versus 44% of controls.



Adapted from Kanbayashi T, et al. J Sleep Res. 2002;11:91-93.
 Orellana C, et al. Sleep. 1994;17(S1):50-53.

ANATOMY OF NARCOLEPSY

- Located in the hypothalamus



McGinty D, et al. Principles and Practice of Sleep Medicine, 2015. Chapter 7.

EVALUATION

- History and Physical
- Standardized scales and instruments
- Diagnostic testing

MEDICAL HISTORY

- Assess for head trauma, neurologic diseases
- Family history
- Behavioral assessment
- Obtain developmental history

SLEEP HISTORY

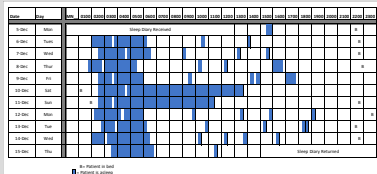
- Ask about:
 - Bedtime Problems
 - Excessive Daytime Sleepiness
 - Awakenings During the night
 - Regularity and duration of sleep
 - Snoring



Mindell JA, Owens JA. A Clinical Guide to Pediatric Sleep, Diagnosis and Management of Sleep Problems. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.

EVALUATION TOOLS

- Sleep Diary
- Formal Sleepiness Scales
 - Epworth Modified Sleepiness Scale
 - Pediatric Daytime Sleepiness Scale
 - Cleveland Adolescent Sleepiness Scale



NPSG/MSLT

- Diagnostic studies done in sleep lab
- Nocturnal PolySomnoGraphy and the Mean Sleep Latency Test
- NPSG rules out other causes of daytime sleepiness
 - OSA
 - PLMS
 - Document a good night of sleep

MEAN SLEEP LATENCY TEST (MSLT)

- Diagnostic gold standard for diagnosis of narcolepsy
- Standardized assessment to determine the patient's ability to fall asleep
- 5 Nap Opportunities
 - Patient should not be taking any stimulants during MSLT
- Measures the Time to Sleep Onset
 - Normal MSLT (adult): 11.6 \pm 5.2min
 - Narcolepsy: 3.1 \pm 2.9 min
- Assesses the Presence of Sleep Onset REMS (SOREMs)

MSLT VARIES WITH TANNER STAGES

Stage of Development	Mean Sleep Latency (min)	Standard Deviation (min)
Tanner Stage I	18.8	1.8
Tanner Stage II	18.3	2.1
Tanner Stage III	16.5	2.8
Tanner Stage IV	15.5	3.3
Tanner Stage V	16.2	1.5
Older adolescents	15.8	3.5

Carskadon M. 1982

CSF HYPOCRETIN-1/OREXIN LEVEL

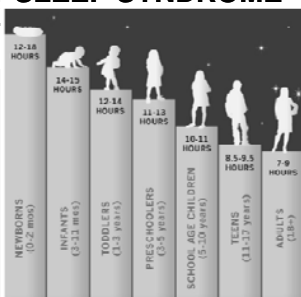
- Lumbar puncture to obtain CSF levels of hypocretin-1
- Levels are low in patients with narcolepsy with cataplexy

DIFFERENTIAL DIAGNOSIS

- Insufficient sleep syndrome
- Abnormal sleep hygiene
- Circadian rhythm disorders
- Psychiatric disorders
- Conversion disorder
- Drug Abuse
- Nocturnal seizures
- Brain tumors
- Klein-Levin syndrome
- Post-concussion syndrome
- Idiopathic hypersomnolence

INSUFFICIENT SLEEP SYNDROME

- Most teenagers do not get enough sleep
- Median sleep time: 6.5 to 7 hours



<https://sleepfoundation.org/sites/default/files/microsite/assets/how-much-sleep-do-we-really-need-infographic.png>

THE 24/7 LIFESTYLE

- 100 adolescents (12-18 years old) in Philadelphia studied 2007-2008
 - Median household income \$53,000
 - 66% had TV in bedroom, 90% had cell phone, 79% had MP3 player
- Engage in 4 electronic activities after 9:00PM
- Sleep
 - 79.1% had <8 hours sleep
 - 33% fell asleep during school

ABNORMAL SLEEP HYGIENE

- Use of stimulants (caffeine, ADHD medications)
- 85% report drinking caffeine
 - Median intake 144 mg (27% less than 100 mg/day)
- Using the bed and bedroom for activities other than sleep



Image from www.time.com

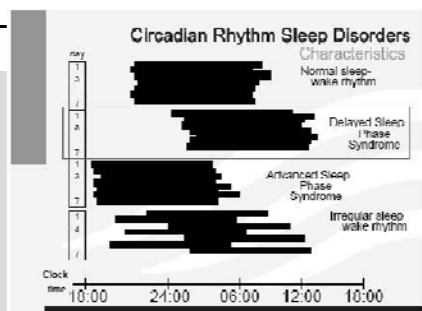
POOR SLEEP HABITS

- Excessive time in bed
- Daytime napping
- Irregular sleep-wake exposure
- Exposure to late night blue wavelength light
 - LED-screens
- Phone calls and social media use late-night and early morning



Rogers R. Chest. 2011;140:572

CIRCADIAN RHYTHM DISORDERS



<http://www.melatonincheck.nl/background.asp>

KLEIN-LEVIN SYNDROME

- Rare disease of hypersomnolence
- Occurs in adolescents
- Male >Female
- 16-20 hours asleep per day for several days in a row up to 2-3 months followed by periods of normality
- Often with hyperphagia and hypersexual behavior

IDIOPATHIC HYPERMORNOLENCE

- **Excessive Daytime sleepiness**
- **Have MSLT with mean sleep onset less than 8 minutes but fewer than 2 Sleep Onset REM**
- **Often short naps are not restorative**
- **May experience "Sleep drunkenness"**
 - **Prolonged confusion with awakenings**

ICSD-3 NARCOLEPSY TYPE I

- **Periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months**
- **Presence of one or both of the following:**
- **Cataplexy and <8minutes and two SOREMP on MSLT (A SOREM within 15 minutes on the NPSG may count for one)**
- **CSF Hypocretin-1 concentration, measured by immunoreactivity, is either <110pg/mL or 1/3 of mean vales in normal subjects within the standardized assessment**

ICSD-3 NARCOLEPSY TYPE 2

- **Periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months**
- **Absence of cataplexy**
- **Presence of one or both of the following:**
- **Cataplexy and <8minutes and two SOREMP on MSLT (A SOREM within 15 minutes on the NPSG may count for one)**
- **CSF Hypocretin-1 concentration, measured by immunoreactivity, is either <110pg/mL or 1/3 of mean vales in normal subjects within the standardized assessment**

TREATMENT/MANAGEMENT

- **Creation of an Individualized Treatment Plan**
- **Education**
- **Healthy Sleep Habits**
- **Behavioral changes**
- **Medications**

EDUCATION

- **Discuss the diagnosis and disease with patient, friends, and family members**
- **Include other impacted individuals**
 - **Coaches, teachers**
- **Notify school officials**
 - **504 Accommodation Plans or IEP**

HEALTHY SLEEP HABITS

- **Maintain good sleep schedule**
- **Keep a set wake time**
- **Short, 15-minute naps are helpful**
 - **May lessen sleep pressure and daytime sleepiness**
- **Use the bed for sleep only**
- **Limit screen time prior to bedtime**

BEHAVIORAL CHANGES

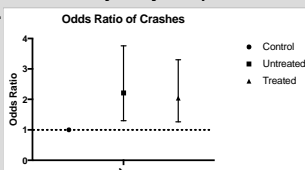
- Limit caffeine and alcohol use
- Incorporate exercise in the daily routine
 - Enhances alertness and may counteract weight gain
- Stop nicotine use

DANGEROUS ACTIVITIES

- Certain Activities of Daily Life are more dangerous with narcolepsy
 - Cooking
 - Swimming
 - Driving

DRIVING

- French study of patients with narcolepsy
- Was modulated by subjective sleepiness level (Epworth scale and naps).
- The risk of car accidents of patients treated for at least 5 years was not different to healthy subjects (OR = 1.23 95%CI = [0.56-2.69]).



Adapted from Pizza, F., et al. (2015). *PLoS One*, 10(6), e0129386.

DRIVING

- Narcoleptics reported :
 - falling asleep while driving (66% vs. 6.2%),
 - Cataplexy while driving (29% vs. 0%),
 - Sleep paralysis while driving (11.5% vs. 0%),
 - frequent near accidents (67% vs. 0%),
 - motor vehicle accidents (37% vs. 5.3%),
 - Increased insurance rates (16% vs. 1%)
 - suspended driver's license (6.1% vs. 3.9)

Broughton R., et al. *Can J Neurol Sci* 1981 ;8:299-304

DRIVING

- Aldrich reported a 1.5- to 4.0-fold increase in auto accidents associated with demonstrated hypersomnia
- The proportion of patients with narcolepsy reporting sleep-related auto accidents was greater than four times that of controls

Broughton R., et al. *Can J Neurol Sci* 1981 ;8:299-304

MEDICATIONS

- Address therapy to sleepiness or to cataplexy symptoms
- None of the pharmaceuticals that I came about to talk about have an FDA-approval for the treatment of narcolepsy in children
- Recommendations are based on scientific evidence where available and on consensus when no data is available.

MEDICATIONS FOR SLEEPINESS

- Treatment is stimulants (sympathomimetic amines)
- Cause increased release and inhibition of dopamine reuptake
 - Norepinephrine effects are also important for the amphetamines

MEDICATIONS FOR SLEEPINESS

- Medications:
 - Methylphenidate 5 mg PO BID-TID
 - Dexroamphetamine 2.5-5 mg po QD-BID
 - Mixed amphetamine salts 5-10 mg po BID
 - OROS-methylphenidate 18-54 mg QAM
 - Extended-release amphetamine salts 5-30 mg PO QD
 - Lisdexamfetamine dimesylate 20-70mg po QAM

SIDE EFFECTS OF STIMULANTS

- Loss of appetite
- Nervousness
- Tics
- Headache
- Insomnia
- Arrhythmias
- Development of tolerance, dependence and addiction

MODAFINIL/ARMODAFINIL

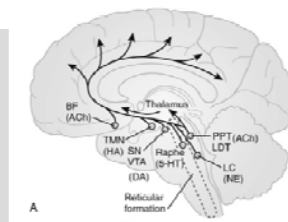
- Dose: 50-200 mg PO QAM/150-250 po QAM
- Unknown mechanism of action
- At least partially inhibits the active transport of dopamine and dopamine reuptake
- First line therapy for adults with EDS from narcolepsy
- Less side effects than other stimulants, but slightly less efficacious

MODAFINIL/ARMODAFINIL

- Low risk of abuse and addiction
- Side effects: disturbed sleep, nausea, diarrhea, decreased appetite, headaches, anxiety and depression, Stevens-Johnson syndrome
- Results in decreased efficacy of hormonal based birth control

TREATING CATAPLEXY

- Cataplexy is mediated by cholinergic pathways in the brainstem
- Treatment: Medications with anti-cholinergic properties
- SSRIs are useful



McGinty D, et al. Principles and Practice of Sleep Medicine, 2015. Chapter 7.

MEDICATIONS FOR CATAPLEXY

- **SSRI:**
 - Venlafaxine 37.5-50mg PO QD
 - Fluoxetine 10-30 mg po QAM
 - Sertraline 25-100 mg po QD 25-100mg po QD div twice per day
 - Side effects: Weight loss, headaches, dizziness, insomnia
- Clomipramine 25-100 mg po QD divided twice per day
 - Side effects: Weight gain, constipation, xerostomia, nervousness

GAMMA HYDROXYBUTYRATE

- Approved by the FDA for treatment of EDS and cataplexy in patients >16 years
- Gamma-aminobutyric acid B (GABA-B) receptor agonist
- Increases Slow Wave (N3) sleep
- Short half life: 40-60 minutes
- Dosing: Children 60 mg/kg up to 3-6g per night in 2 divided doses
 - Adolescents: 4.5-9 g per night in 2 divided doses

SIDE EFFECTS OF SODIUM OXYBATE

- Nausea, vomiting
- Weight loss
- Tremor
- Constipation
- Anxiety
- Suicidal ideation
- High salt load and can be respiratory depressant
- Significant potential for abuse

PSYCHOLOGICAL AND OTHER IMPACT

- <https://www.youtube.com/watch?v=VA6FeiGgLF0>

PSYCHOLOGICAL IMPACT

- 33% felt others did not understand or were intolerant of disease
- Sleep attacks in conversation lead to alienation
- 50% report decreased grades due to narcolepsy
- 30% report embarrassment of symptoms in classroom

Beuchart, et al. 2005.

STRUGGLES DUE TO NARCOLEPSY

- Mental foginess that makes it hard to concentrate
- Memory issues and automatic behavior that can lead to feelings of uncertainty about daily events and self-doubt
- Sleepiness that causes unintentional napping at school or work, which can be embarrassing and problematic

Harvard Sleep Health, 2018

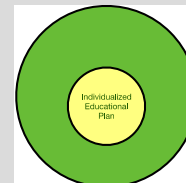
STRUGGLES DUE TO NARCOLEPSY

- **Narcolepsy can also impact social interactions.**
People living with narcolepsy may:
 - Strain to stay awake during social activities such as watching a movie with friends
 - Be confused or grumpy upon waking
 - Need to take naps at inconvenient times
 - Have hallucinations during conversations
 - Experience cataplexy at awkward times, such as when laughing with friends at a party

Harvard Sleep Health, 2018

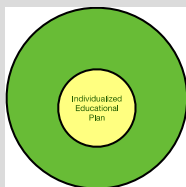
SCHOOL ISSUES

- Individualized Educational Plans
 - Plan or program developed to ensure a child with a disability identified under the law and attending an elementary or secondary educational institution **receives specialized instruction and related services**
- Individuals with Disabilities Education Act



SCHOOL ISSUES

- 504 Plan
 - Plan or program developed to ensure a child with a disability identified under the law and attending an elementary or secondary educational institution **receives accommodations that will ensure their academic success and access to the learning environment**
 - Broader definition of disability: limit one or more basic life activity



IEP VS 504 PLAN

	IEP	504 Plan
Description	Blueprint for special ed experience at school	Blueprint for access to learning at school
What it does	Provides individualized special education and services to meet unique needs of child	Provides services and changes to learning environment to meet needs of child as adequately other students
Eligibility	One of 13 disabilities in IDEA that affect the educational performance	Any disability that interferes with ability to learn in a general educational classroom
Review	Annual	Varies by state
Funding	No charge to student. States receive funding for eligible students	No charge to student. States do NOT receive extra funding for eligible students. Can lose federal funding if non-compliant

CONTENT

IEP

- Sets learning goals and describes services
- Written document
- Specifies current performance
- Annual education goals
- Services to receive
- Accommodations to environment
- Modifications to curriculum
- Standardized test participation

504 PLAN

- Does not have to be written
- Specific accommodations, supports, or services
- Names of who will provide services

RESOURCES

- **Narcolepsy Network- www.narcolepsynetwork.org**
- **Wake Up Narcolepsy- www.wakeupnarcolepsy.org**
- **Pediatric Pulmonary Center Sleep Education Web Modules**
 - <http://ppc.mchtraining.net/ppc-sleep>
- **Clinical Guide to Pediatric Sleep: Diagnosis and Management of Sleep Problems**
 - Jodi A Mindell and Judith A. Owens