

Narcolepsy

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Objectives

- Define Narcolepsy
- Discuss Epidemiology and Symptoms
- Understand Pathogenesis and Diagnosis
- Review Current Treatments
- Discuss Newest Therapies and Future Therapies



What is Narcolepsy?

- A chronic neurologic disorder
- Characterized as excessive daytime sleepiness (EDS)
- Brain is not able to regulate your body's sleep-wake cycle
- Impairment of both the onset and offset of REM sleep



EPIDEMIOLOGY

Narcolepsy

3%

Of patients
have a 1st
degree relative

50%

Of patients
remain
undiagnosed

70%

Of patients
have cataplexy



Effects

1 in 2,000

Americans

*Narcolepsy Fact Sheet | National Institute of Neurological Disorders and Stroke. (2021).
Narcolepsy. https://www.ninds.nih.gov/health-information/patient-caregiver-education/fact-sheets/narcolepsy-fact-sheet#3201_6*



*"Narcolepsy Link." Narcolepsy Link, Jazz Pharmaceuticals ,
<https://www.narcolepsylink.com/sitemap/>.*

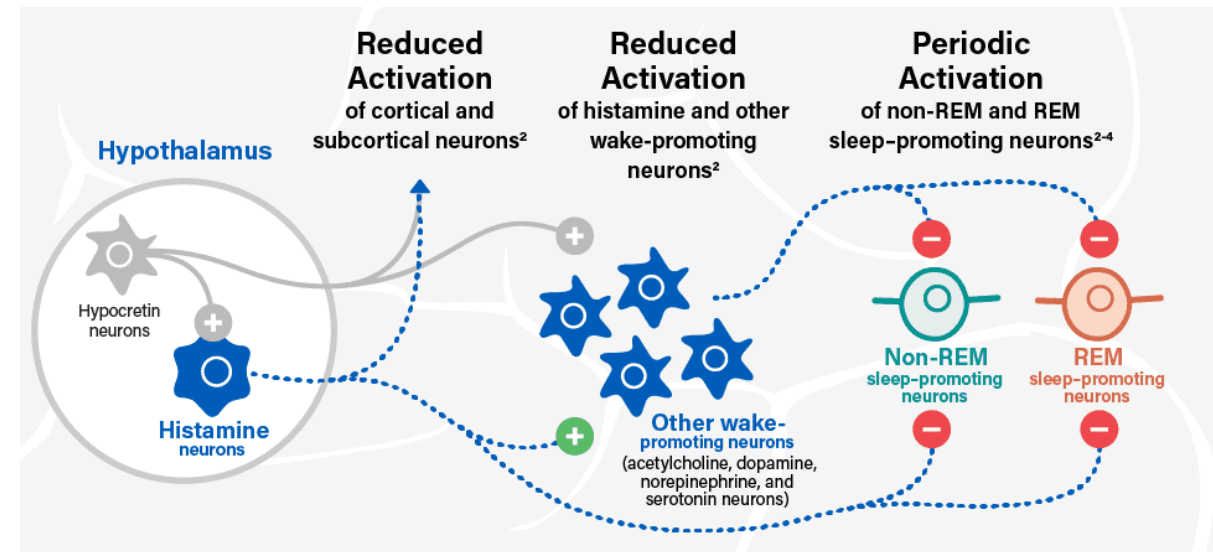
Physiology in patients without Narcolepsy

- Wake promoting neurotransmitters (norepinephrine, serotonin, dopamine, histamine, and acetylcholine) stimulate cortical and subcortical regions of the brain
- GABA works by inhibiting the wake promoting neurotransmitters during sleep
- Hypocretin stabilizes wakefulness by signaling many wake promoting neurons in the cortex, brainstem and forebrain
- Hypocretin increases activity in areas of the brain that suppress REM sleep



Pathophysiology of patients with Narcolepsy

- Wake-promoting neurons fail to activate cortical and subcortical regions
- Fail to inhibit sleep-promoting neurons (GABAergic neurons), resulting in excessive daytime sleepiness
- Loss of hypocretin neurons leads to inconsistent signaling of wake-promoting neurons causing the lack of ability to maintain wakefulness and muscle tone
- Loss of hypocretin neurons leads to the inability to inhibit NREM and REM-sleep promoting neurons



Symptoms (CHES)



- Cataplexy (65%-75%)
 - Most specific of type 1 with sudden onset
 - Brief (<2 minutes) loss of muscle tone with retained consciousness
 - Triggered by strong emotions: laughter, fear, or stress
- Hallucinations (33%-80%)
 - Vivid dreams that occur while falling asleep
- Excessive Daytime Sleepiness (100% of patients)
 - Cardinal symptom and often the most disabling
- Sleep paralysis (25%-50%)
 - Temporary inability to move voluntary muscles or speak
- Sleep Disruption (30%-95%)
 - Frequent awakenings resulting in poor quality sleep

"Narcolepsy Link ." *Narcolepsy Link*, Jazz Pharmaceuticals ,
<https://www.narcolepsylink.com/sitemap/>.

Classifying Narcolepsy

NARCOLEPSY TYPE 1

- Narcolepsy with cataplexy
- Permanent loss of hypocretin neurons
- CSF Hypocretin-1 levels low or undetectable

NARCOLEPSY TYPE 2

- Absent of cataplexy
- Heterogeneous disorder
- Exact cause is unknown
- CSF Hypocretin-1 levels normal or unknown



Diagnosing Narcolepsy

- **Epworth Sleepiness Scale** (Used for screening)
 - Quiz that measures a person's likelihood of dozing or falling asleep in everyday situations, like reading, watching TV or driving
 - **Polysomnogram** (PSG or sleep study)
 - Overnight recording of the brain, muscles, breathing and eye movements. This helps uncover whether REM sleep occurs early in the sleep cycle.
 - **Multiple sleep latency test** (nap test)
 - MSLT assesses daytime sleepiness by measuring how quickly a person falls asleep and if they enter REM sleep
 - Patient takes 4-5 naps in a day
 - Diagnosed if patient falls asleep within less than 8 minutes & goes into REM sleep in two of those nap periods
 - Cerebrospinal fluid (CSF) concentrations of hypocretin-1 can be measured to confirm a diagnosis.
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Diagnosing Narcolepsy- *International Classification of Sleep Disorders (ICSD-3) Criteria*

NARCOLEPSY TYPE 1

- Excessive daytime sleepiness daily for ≥ 3 months
- One or both of the following:
 - Cataplexy and mean sleep latency ≤ 8 minutes and ≥ 2 sleep-onset REM periods (SOREMPs) on multiple sleep latency tests (MSLT)
- Low (≤ 110 pg/mL) or absent CSF Hypocretin-1 levels

NARCOLEPSY TYPE 2

- Same criteria as narcolepsy type 1 but **without cataplexy**
- CSF hypocretin-1 levels are unknown or are above the threshold of narcolepsy type 1
- The hypersomnolence and/or MSLT findings are not better explained by other causes



TREATMENT



Pharmacologic Treatment- Stimulants

Modafinil (Provigil[®]) & Armodafinil (Nuvigil[®])

- Exact MOA unknown
- Schedule IV
- Modafinil Dose: 200 mg/day
- Armodafinil Dose: 150-250 mg/day
- FDA approved for EDS symptoms
- Often 1st line therapy because of fewer side effects and less addiction potential than other stimulants
- No efficacy for cataplectic symptoms
- Side effects: Severe rash, headache, N/V, insomnia, anxiety



Pharmacologic Treatment- Stimulants



Dextroamphetamine/Amphetamine

- Adderall[®] (IR); Adderall XR[®] (ER)
- FDA approved
- 6-12 years: Initial: 5 mg/d (titrate in increments of 5mg)
- ≥12 years: Initial: 10 mg/d (titrate in increments of 10mg)
- When daily dose has been established, switch to Adderall XR 20 am + 10-30 mg regular
- Side effects: Insomnia, Hypertension, Palpitations and irritability
- ❑ Black Box Warning: Substance abuse

Methylphenidate

- Methylin[®] (IR); Ritalin[®], Metadate[®] (CD), Ritalin[®] (LA), Concerta[®] (ER)
- FDA approved
- Start with 5 mg BID (30 minutes before breakfast & lunch)
- Increase by 5–10 mg weekly to control symptoms, then switch to either ER or SR and use IR as add-on at noon for pm sleepiness
- Side effects: Insomnia, irritability, decrease appetite, headache
- ❑ Black Box Warning: Substance abuse

Pharmacologic Treatment

Antidepressants (TCAs, SNRIs, SSRIs)

- Treatment for cataplexy
- Prescribed off-label
- MOA: Blocks neurotransmitter reuptake in the locus coeruleus and raphe. Resulting in suppression of REM sleep.
- Effective in 80% of patients:
 - **Imipramine**
 - **Protriptyline**
 - **Clomipramine**
 - **Fluoxetine**
 - **Nortriptyline**
 - **Venlafaxine**





ANTIDEPRESSANTS CONTINUED

Selegiline (Zelapar[®])

- Potent irreversible MAO type-B inhibitor
- Improves hypersomnolence and cataplexy through REM suppression and increase in REM latency
- Side effects: Constipation, gas, dry mouth, loss of appetite
- Doses of at least 20mg are effective

Atomoxetine (Strattera[®])

- Selective NE reuptake inhibitor
- May improve cataplexy and sleepiness in children
- Less effective than other therapies in adults and older teenagers
- Side effects: Dry mouth, loss of appetite, insomnia, tachycardia
- Doses start at 40mg and titrate (max dose: 95mg)
- ❑ Black Box warning: Risk of suicidal ideation

Xyrem® (sodium oxybate)

- Derived from the inhibitory neurotransmitter (GABA) – Exact MOA is unknown
- 4.5 grams/night PO initially, divided into 2 equal doses of 2.25 grams, the first given at bedtime and the second given 2.5 to 4 hours later
- Schedule CIII controlled substance
- FDA approved in 2002 for treating cataplexy in adults
- FDA approved in 2005 for EDS in adults
- Generally used with daytime stimulants



Xyrem® (sodium oxybate) continued

- “Date rape” drug- Patient must be enrolled in REMs program
- Take in ¼ cup water, lie down immediately after taking and stay in bed
- Sleep onset: 5-15 minutes after first dose
- Side effects: Dizziness, drowsiness, confusion, nausea
- ❑ Black Box warning: Strong CNS depressant; respiratory depression, coma and death can result; risk is increased when taken with other CNS depressants



Why is there a need for advancing Narcolepsy therapy?



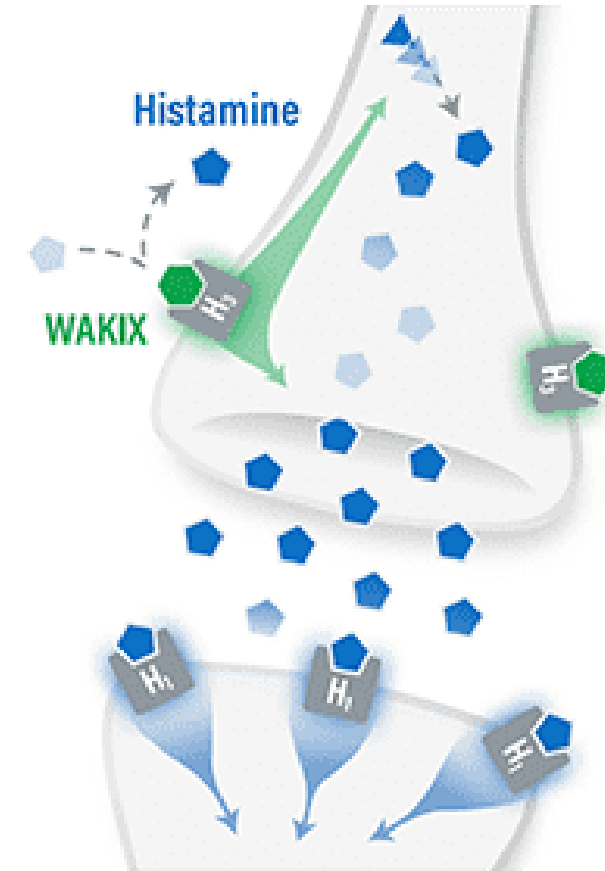
- Medications historically used for treatment of EDS and cataplexy have demonstrated efficacy in managing these symptoms
- However, some patients may have symptoms that are becoming refractory to these agents, or some may have co-morbidities or use concomitant medications that preclude the use of these agents due to drug-disease or drug-drug interactions.
- Advances in the understanding of the underlying mechanisms of narcolepsy have led to the development of new treatments for this disorder

NEW TREATMENTS



Wakix® (Pitolisant)

- Histamine (H3) receptor antagonist/inverse agonist
- First and only Histaminergic treatment for EDS or cataplexy
- Histamine is a neurotransmitter that is important for wakefulness
 - Wakix® blocks histamine from binding to H3 receptors located in the brain
 - Binding to H3 receptors increases histamine synthesis and release
 - Histamine binds to H1 receptors to increase communication to brain regions for sleep and wakefulness



Wakix® (Pitolisant)



- FDA approved (August 2019) for the treatment of EDS symptoms and/or cataplexy
- Approved dose range: 8.9-35.6mg once daily in the morning
 - Starting dose: 8.9mg/d
 - After week 1: increase to 17.8mg/d
 - After week 2: 35.6mg/d
 - Adjust dose based on tolerability
- Side effects: insomnia, headache, nausea, anxiety, irritability



Sunosi® (Solriamfetol)



- Monoamine reuptake inhibitor
- MOA: Dopamine and Norepinephrine reuptake inhibitor
- FDA approved (March 2019) for the treatment of EDS in narcolepsy
- Scheduled IV controlled substance
- Dose: 75-150mg once daily in the morning
- Adverse effects: Headache, decreased appetite, nausea, anxiety, insomnia, dry mouth, constipation



The American Academy of Sleep Medicine clinical practice guidelines - 2021



Table 2—Summary of recommended interventions in adult populations.

Intervention	Strength of Recommendation	Critical Outcomes Showing Clinically Significant Improvement*			
		Excessive Daytime Sleepiness	Cataplexy	Disease Severity	Quality of Life
Narcolepsy					
Modafinil	Strong	✓		✓	✓
Pitolisant	Strong	✓	✓	✓	
Sodium Oxybate	Strong	✓	✓	✓	
Solriamfetol	Strong	✓		✓	✓
Armodafinil	Conditional	✓		✓	
Dextroamphetamine	Conditional	✓	✓		
Methylphenidate	Conditional			✓	

Table 3—Summary of recommended interventions in pediatric populations.

Intervention	Strength of Recommendation	Critical Outcomes Showing Clinically Significant Improvement*			
		Excessive Daytime Sleepiness	Cataplexy	Disease Severity	Quality of Life
Narcolepsy					
Modafinil	Conditional	✓			
Sodium oxybate	Conditional	✓	✓	✓	

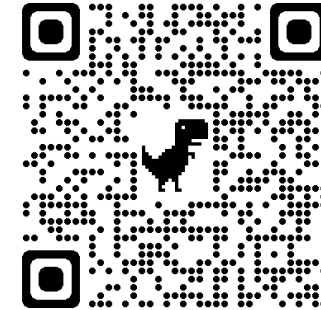
Non-Pharmacologic Therapy

- Take short naps
- Maintain a regular sleep schedule
- Avoid caffeine or alcohol before bed
 - Avoid smoking
 - Exercise daily
- Avoid large, heavy meals right before bed
 - Meditate before bed



What's next?

- FT218 (long-acting sodium oxybate)
 - GABA-B receptor agonist
 - Targets EDS and Cataplexy
 - Phase III
- JZP-258 (low-sodium oxybate formulation)
 - GABA-B receptor agonist
 - Targets EDS and Cataplexy
 - Phase III
- AXS-12 (reboxetine)
 - Monoamine reuptake inhibitor
 - Targets EDS and Cataplexy
 - Phase II
- THN102 (modafinil/flecainide)
 - Non-amphetamine wake promoting agent/ anti-connexin agent
 - Targets EDS
 - Phase II



Use this QR code for more information on upcoming Narcolepsy treatments!



Summary of targeted therapies

Improving wakefulness:

Modafinil
Armodafinil
Stimulants
Solriamfetol

Reducing cataplexy attacks

Sodium oxybate
Venlafaxine

Disturbed nocturnal sleep, sleep paralysis and hallucinations:

Sodium oxybate

EDS and cataplexy:

Pitolisant



Summary



- Narcolepsy has no cure, but drug therapies and lifestyle changes can often help improve symptoms and quality of life
- There are seven drug treatments FDA approved to treat patients with narcolepsy: Xyrem[®] (sodium oxybate), Provigil[®] (modafinil), Nuvigil[®] (amodafonil), methylphenidate, and amphetamine. Wakix[®] (Pitolisant) and Sunosi[®] (Solriamfetol) being the two newest approved therapies.
- There are no FDA-approved drugs specifically for pediatric use in treating narcolepsy.
- Other prescription drugs are also used off-label for narcolepsy, including stimulants, depressants, and antidepressants.
- Lifestyle modifications, such as regular napping, control over diet, and exercise, can also help improve or manage disease symptoms or treatment side effects.

References



Thorpy, Michael J. “Recently Approved and Upcoming Treatments for Narcolepsy.” *CNS drugs* vol. 34,1 (2020): 9-27. doi:10.1007/s40263-019-00689-1

Maski, K., Trotti, L. M., Kotagal, S., Robert Auger, R., Rowley, J. A., Hashmi, S. D., & Watson, N. F. (2021). Treatment of central disorders of hypersomnolence: An American Academy of Sleep Medicine Clinical Practice Guideline. *Journal of Clinical Sleep Medicine*, 17(9), 1881–1893. <https://doi.org/10.5664/jcsm.9328>

WAKIX® (PITOLISANT) tablets: For EDS or cataplexy in adults with narcolepsy. WAKIX® (pitolisant) tablets | For EDS or Cataplexy in Adults with Narcolepsy. (n.d.). Retrieved June 10, 2022, from https://wakix.com/?gclid=EAlaIQobChMIY601ZWj-AIVb8LCBB1NJw13EAAYASAAEgKhRvD_BwE

SUNOSI® (solriamfetol): Excessive daytime sleepiness in OSA or narcolepsy treatment. SUNOSI® (solriamfetol) | EDS in OSA or Narcolepsy Treatment. (n.d.). Retrieved June 10, 2022, from <https://www.sunosi.com/>

“Narcolepsy Link .” *Narcolepsy Link*, Jazz Pharmaceuticals , <https://www.narcolepsylink.com/sitemap/>.

Billiard, Michel. “Narcolepsy: current treatment options and future approaches.” *Neuropsychiatric disease and treatment* vol. 4,3 (2008): 557-66.

Narcolepsy Fact Sheet | National Institute of Neurological Disorders and Stroke. (2021). Narcolepsy. https://www.ninds.nih.gov/health-information/patient-caregiver-education/fact-sheets/narcolepsy-fact-sheet#3201_6