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

EPIDEMEOLOGY

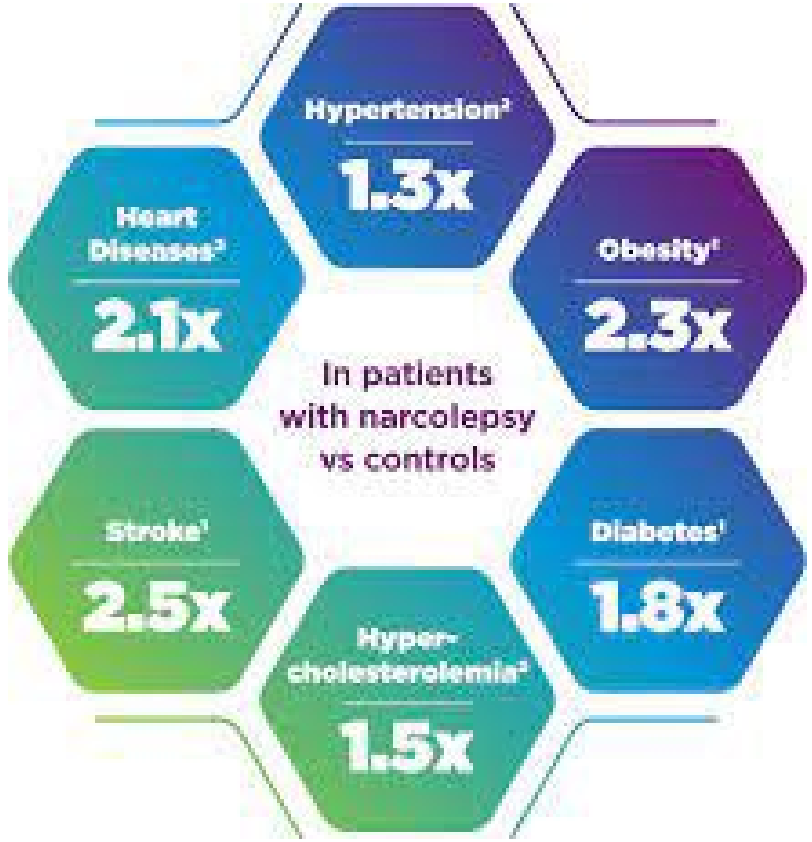
Narcolepsy

3%	50%	70%
Of patients have a 1st degree relative	Of patients remain undiagnosed	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

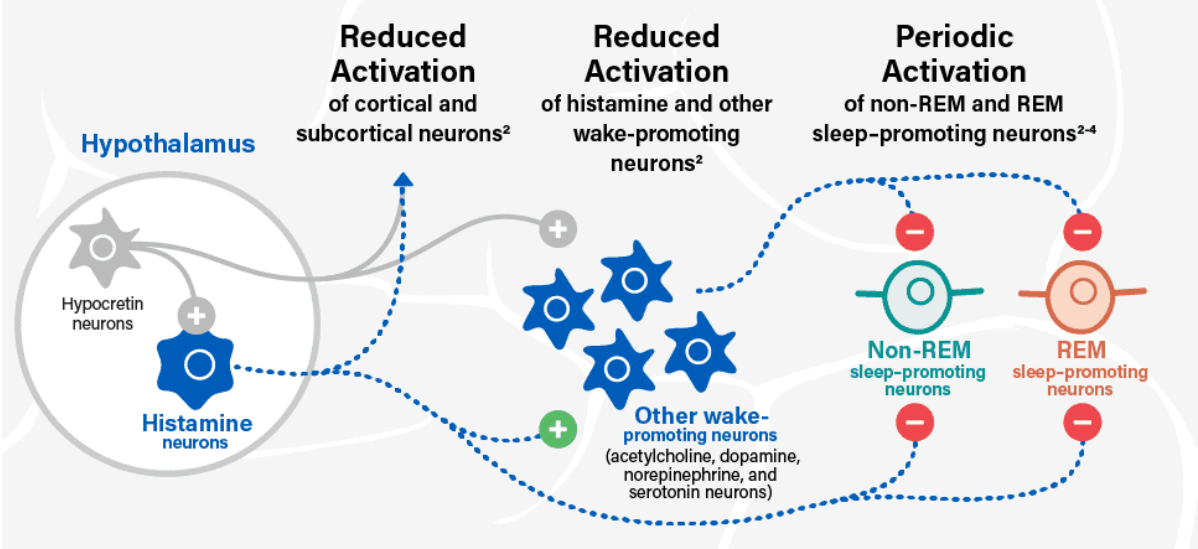
"Narcolepsy Link ." *Narcolepsy Link*, Jazz Pharmaceuticals , https://www.narcolepsylink.com/sitemap/.

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



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=EAIaIQobChMIlY601ZWj-AIVb8LCBB1NJw13EAAYASAAEgKhRvD_BwE

Symptoms (CHESS)

- **C**ataplexy (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
- **H**allucinations (33%-80%)
  - Vivid dreams that occur while falling asleep
- **E**xcessive Daytime Sleepiness (100% of patients)
  - Cardinal symptom and often the most disabling
- **S**leep paralysis (25%-50%)
  - Temporary inability to move voluntary muscles or speak
- **S**leep Disruption (30%-95%)
  - Frequent awakenings resulting in poor quality sleep

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Classifying Narcolepsy

NARCOLEPSY TYPE 1	NARCOLEPSY TYPE 2
• Narcolepsy with cataplexy • Permanent loss of hypocretin neurons • CSF Hypocretin-1 levels low or undetectable	• Absent of cataplexy • Heterogeneous disorder • Exact cause is unknown • CSF Hypocretin-1 levels normal or unknown

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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.

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

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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**
  - **Nortripyline**
  - **Venlafaxine**

Pharmacologic Treatment

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

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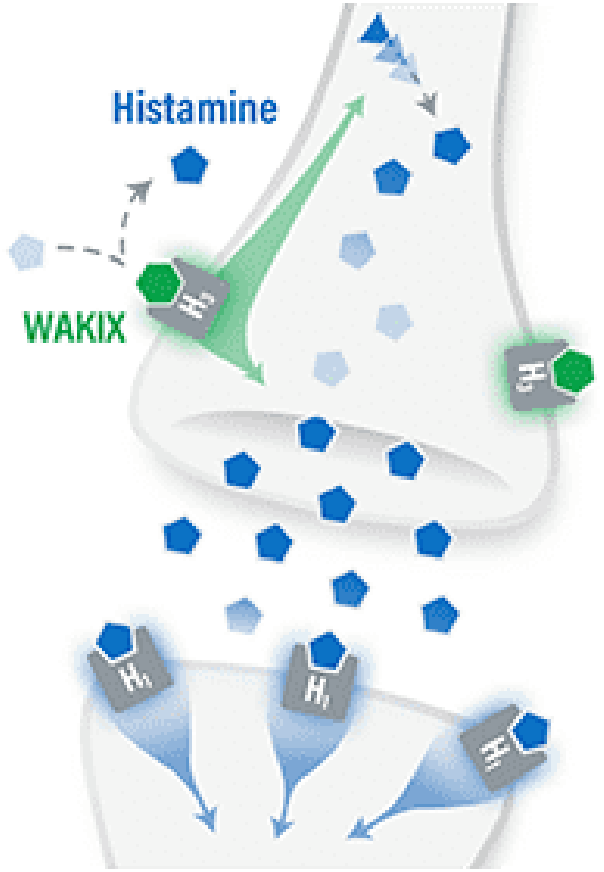
NEW TREATMENTS

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



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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

Wakix® pitolisant tablets

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

SUNOSI™ (solriamfetol) tablets

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	✓	✓	✓	

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

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!

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

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

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