

EXCESSIVE DAYTIME SLEEPINESS IN NARCOLEPSY

Taking Steps to Improve Patient Quality of Life

Supported by an educational grant from Harmony Biosciences

Jointly provided by Center for Independent Healthcare Education and Veterans Health

VME

Sleep Homeostasis: Survival

- Decreased alertness
- Microsleeps
- Automatic activity
- Apathy
- Fatigue
- Memory loss
- Mood changes
- Accidents
- Productivity impairment
- Metabolic changes
- Autonomic tone changes
- Immune response

Sleepiness: Impact on Daily Activities

US Adults Reporting That Sleepiness Interferes With Daily Activities

37%

Frequency	Percentage
A few days a month	21%
A few days a week	9%
Every day/almost every day	7%
Rarely/never	63%

National Sleep Foundation. 2002 Sleep in America Poll. AL: <http://www.sleepfoundation.org/2002poll.html>.

Circadian Rhythms and the Suprachiasmatic Nucleus (SCN)

Melatonin (N-acetyl-5-methoxytryptamine)

CC(=O)Nc1ccc2c(c1)nc(C)nc2O

SCN MEL

Adapted from Brzezinski A. *N Engl J Med*. 1997;336:186-195.

Circadian Rhythms

- Ubiquitous among living organisms
- SCN is the "master clock"¹
- In humans, circadian timing modulates daily cycles in^{1,2}:
 - Core body temperature
 - Blood pressure
 - Hormone secretion
 - Immune response
 - Sleep-wake cycle

¹. Turek FE, et al. *Arch Neurol*. 2001 58:1781-1787.
². Mignot E, et al. *Nat Neurosci*. 2002;5(suppl):1071-1075.

Sleep: Neurophysiology

Cortex

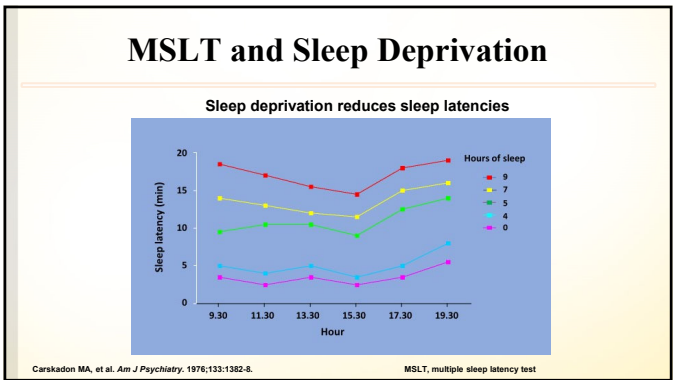
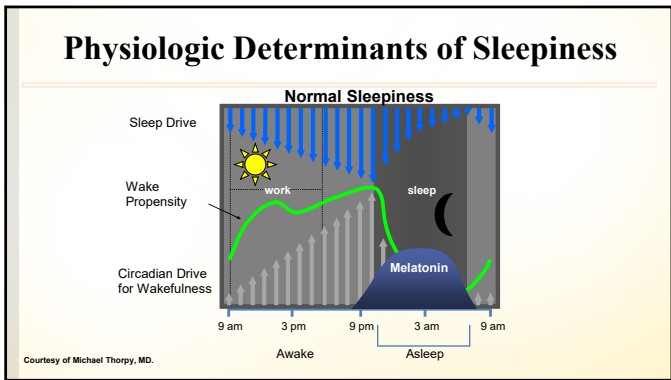
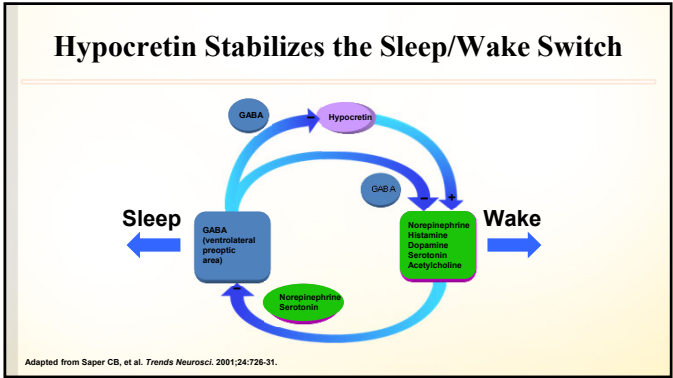
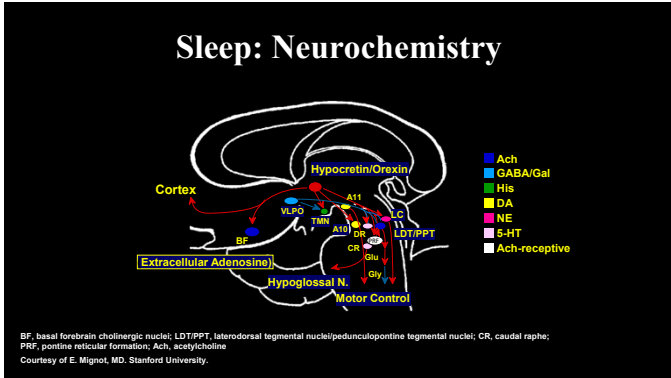
Hypothalamus Sleep/Wake Switch

SCN Circadian Clock

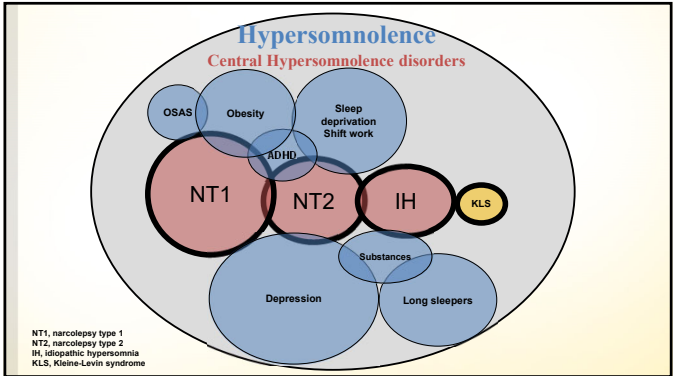
Brainstem Ascending Cortical Activation REM/SWS Switch

Thalamus Cortical Activation Sleep Spindle EEG Synchronization

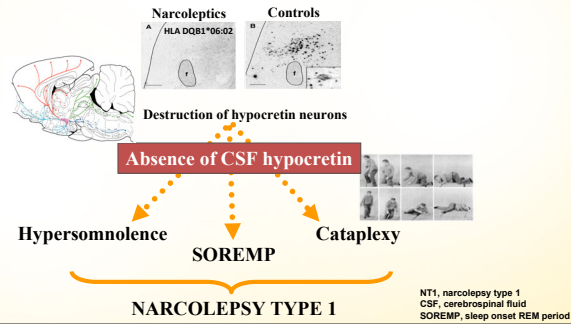
Courtesy of E. Mignot, MD, Stanford University.



- ### Sleep Disorders: Causes of Excessive Sleepiness Pathologic Mechanisms?
- Circadian
 - Homeostatic
 - Sleep Mechanisms
 - Arousal Mechanisms



Neurobiology of NT1: Loss of orexin/hypocretin neurons



Narcolepsy: Differential Diagnosis

- Cataplexy is pathognomonic of narcolepsy
- Daytime sleepiness and SOREMs can be seen with many conditions that disrupt sleep, especially REM sleep
 - SOREMs and EDS very common with shift work
 - Can also occur with insufficient sleep, sleep apnea, periodic limb movements of sleep, etc.

What Causes the Loss of Hypocretin Neurons in Narcolepsy?

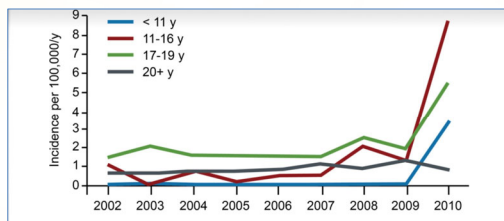
- 90% of patients with narcolepsy and cataplexy have HLA-DQB1*0602 allele compared to only 12–25% of the general population
- This may confer a susceptibility for some individuals to develop an autoimmune attack against the hypocretin neurons
- While this gene is generally necessary for developing narcolepsy, the genetic risk is still low:
 - If a parent has narcolepsy, the risk of an affected child is only ~1%
 - Among monozygotic twins in which one has narcolepsy, the risk to the other twin is only 30%

Mignot E. *Sleep*. 1997;20:1012-1020.
Mignot E. *Am J Hum Genet*. 1997;60:1289-1302.
Chabas D, et al. *Annu Rev Genomics Hum Genet*. 2003;4:459-483.

Triggers of Narcolepsy

- Usually begins in teen years, so some developmental or environmental factor may contribute
- *Streptococcal* infection may be a trigger as strep often precedes narcolepsy
- Onset of narcolepsy most common March – July

Narcolepsy After H1N1 Vaccine



- 8- to 12-fold increase in narcolepsy in children in Finland and Sweden given Pandemrix (vaccine with potent AsO₃ adjuvant)
- All children are 0602-positive, and narcolepsy began ~40 days after vaccine
- No clear increase with vaccines used in the United States

Partinen M, et al. *PLoS One*. 2012;7:e33723.
Heier MS, et al. *Sleep Med*. 2013;14:967-971.

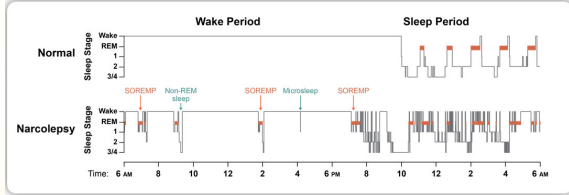
Secondary Narcolepsy

- Can occur with lesions of the posterior and lateral hypothalamus or midbrain; may injure the hypocretin neurons or their connections to REM- and wake-regulatory regions
- Lesions are usually caused by tumors, strokes, demyelination, or inflammation
- Patients always have excessive amounts of sleep and overt neurologic deficits (e.g., abnormal eye movements, focal weakness, pituitary dysfunction, obesity)
- No need for MRI if bedside neurological exam is normal

Kanbayashi T, et al. *Curr Neurol Neurosci Rep*. 2011;11:235-241.
Scammell T. *Sleep Disorders and Neurologic Diseases*. 2007:117-134

Narcolepsy is a Chronic Neurologic Disorder Characterized by Sleep-Wake State Instability

Patients with narcolepsy have frequent, unpredictable transitions between sleep-wake states



van der Heide A, Lammers GJ. Sleepiness: Causes, Consequences and Treatment; 2011:111-125.
 España RA, Scammell TE. Sleep. 2011;34(7):845-858.
 Rogers AE, et al. Sleep. 1994;17(7):295-297.
 Pizze F, et al. Sleep. 2015;38(8):1277-1284.

Clinical Presentation

- Excessive daytime sleepiness (EDS)
 - Cataplexy
 - Hypnagogic hallucinations (vivid dreams)
 - Sleep paralysis
- Tetrad**
- Fragmented nocturnal sleep
- Pentad**

How do these present in pediatric patients?

Scammell TE. *N Engl J Med.* 2016;373:2654.

Measuring the Severity of EDS Epworth Sleepiness Scale (ESS)

SITUATION	CHANCE OF DOZING
Sitting and reading	
Watching television	
Sitting inactive in a public place (eg, a theater or meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	
TOTAL SCORE:	

0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing

ESS ≥ 16 = High level of EDS¹
 ESS > 10 = EDS²

The Epworth Sleepiness Scale assesses the propensity to doze or fall asleep in 8 common daily activities^{1,2}

Mean ESS scores lower in OSA (9 \pm 5) than narcolepsy (17 \pm 4)^{3,4}

OSA, obstructive sleep apnea
¹Johns MW. Sleep. 1991;14:540. ²Johns MW. Sleep. 1991;20:844-8. ³Lipford MC. *J Clin Sleep Med.* 2015;15:33-8. ⁴Luca G. *J Sleep Res.* 2013;22:462-85.

The Two Variants of Narcolepsy: ICSD-3 Criteria

Narcolepsy Type 1 (Narcolepsy with Cataplexy). A and B must be met.

- A. EDS for at least 3 months
- Use validated questionnaires such as ESS
- B. At least one of the following:
- Cataplexy and a positive MSLT* or short REM latency on PSG
 - Low CSF hypocretin-1 concentrations (≤ 110 pg/mL or $< 1/3$ of normal)

Narcolepsy Type 2 (Narcolepsy without Cataplexy). A and B must be met.

- A. EDS for at least 3 months
- B. Positive MSLT*

*Positive MSLT: mean sleep latency of < 8 minutes and 22 sleep-onset rapid eye movement periods (SOREMPs)
 Sateia MJ. *Chest.* 2014;146(5):1387-1394.

DSM-5 Criteria for Narcolepsy

- Recurrent periods of irrepresible need to sleep, lapsing into sleep, or napping occurring within the same day, at least 3 times per week over the past 3 months
- The presence of at least one of the following:
 - Episodes of cataplexy, occurring at least a few times per month, and as defined by either:
 - In individuals with long-standing disease, brief (sec to min) episodes of sudden, bilateral loss of muscle tone with maintained consciousness that are precipitated by laughter or joking
 - In children or individuals within 6 months of onset, spontaneous grimaces or jaw-opening episodes with tongue thrusting or global hypotonia, without any obvious emotional triggers
 - Low CSF hypocretin-1 concentrations (≤ 110 pg/mL or $< 1/3$ of normal)
 - Nocturnal sleep polysomnography (PSG) showing rapid eye movement (REM) sleep latency of 15 minutes or less, or a positive MSLT*

*Positive MSLT: mean sleep latency of < 8 minutes and 22 sleep-onset rapid eye movement periods (SOREMPs)
 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. 2013.

Differential Diagnosis

- EDS**
 - Idiopathic hypersomnia
 - Kleine-Levin syndrome
 - Poor sleep hygiene
 - Periodic limb movement disorder
 - Circadian rhythm abnormality
 - Behavioral symptoms of EDS (irritability, poor attentiveness, aggression, hallucinations) can be misinterpreted as:
 - Conduct or oppositional defiant disorder
 - Depression, ADHD
 - Conversion disorder
 - Substance abuse
- Cataplexy**
 - Seizure
 - Myasthenia gravis
 - Prader-Willi syndrome
 - Hypotension
 - Postural orthostatic hypotension
 - Syndrome of autosomal dominant cerebellar ataxia, deafness, and narcolepsy
- Hallucinations**
 - Schizophrenia
 - Night terrors
 - Panic attacks

Nevsimalova S. *Curr Neurol Neurosci Rep.* 2014;14(8):469.
 Dauvillier Y, et al. *Neurologus Psychiatry.* 2003;74(12):1667-1673.

Waman J, et al. *Neurology.* 2013;80(7 Suppl):S43-003.
 Zhou J, et al. *Shanghai Arch Psychiatry.* 2014; 26(4):232-235.

Diagnostic Process

- Detailed sleep history
- Medical, psychiatric, social, family history
- Physical examination
- Sleep questionnaires
 - Epworth Sleepiness Scale
 - Functional Outcomes of Sleep Questionnaire
 - Fatigue Severity Scale
 - Idiopathic Hypersomnia Severity Scale
- Laboratory testing as appropriate

- Sleep study/polysomnography
- Multiple Sleep Latency Test
- Maintenance of Wakefulness Test
- Performance Testing
 - Psychomotor Vigilance Test
 - Oxford Sleepiness Resistance Test

Diagnosis

- Clinical Story
- Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD)
- PSG/MSLT
 - Limitations, pitfalls in testing children
- CSF hypocretin
- Diagnostic criteria:
 - ICSD-3
 - DSM-5

CSF, cerebrospinal fluid; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICSD, International Classification of Sleep Disorders; MSLT, Multiple Sleep Latency Test; PSG, polysomnography; Janssen KC, et al. *Sleep Med.* 2017;33:30-35.

Goals of Narcolepsy Treatment

- Reduce daytime sleepiness
- Control ancillary symptoms
 - Cataplexy
 - Nightmares and hallucinations
 - Sleep paralysis
 - Disturbed nocturnal sleep
- Improve psychosocial and work functioning
- Improve safety of patient and public
- Prevent adverse medication effects

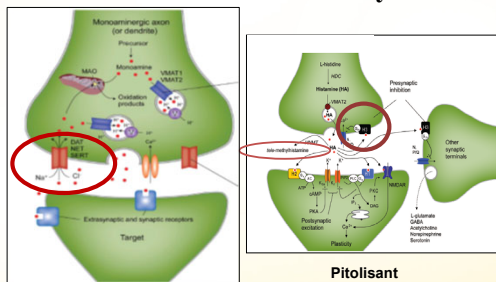
Thorpy MJ, Dauvilliers Y. *Sleep Med.* 2015;16:9-16.

Treatment of Narcolepsy: Nonpharmacologic Approaches

- One or two 15- to 20-minute naps are often helpful (sometimes during school or work)
- Avoid sleep deprivation, sedating medications, heavy meals
- Patients often do best with work that keeps them active (e.g., schoolteacher) as they can have difficulty with sedentary jobs, especially those requiring sustained vigilance
 - Avoid shift work

Morgenstern TL, et al. *Sleep.* 2007;30:1765-1771; Mignot EJ. *Neurotherapeutics.* 2012;9:739-752.

Mechanisms of Action of Most Psychostimulants



Modafinil, Methylphenidate, Solriamfetol...

Pitolisant

FDA-Approved Treatments for Narcolepsy

Drug	MOA	Dose	EDS	Cataplexy	Adults	Children
Modafinil	Dopamine (DA) reuptake inhibitor	100-400 mg	X		X	
Armodafinil	DA reuptake inhibitor	50-250 mg	X		X	
Solriamfetol	DA-norepinephrine (NE) reuptake inhibitor	75-150 mg	X		X	
Pitolisant	Histamine H3 antagonist/inverse agonist	8.9-35.6 mg	X	X	X	
Sodium oxybate (SXB) / lower sodium oxybate (LXB) ER SXB (once-nightly)	GABA _B agonist	4.5-9.0 g (twice-nightly dosing)	X	X	X	X
Amphetamines / Methylphenidate	Sympathomimetic; enhance DA, NE, serotonin	Varies			X	X

Amphetamines and methylphenidate are approved for narcolepsy but not specifically cataplexy or EDS. ER, extended-release; Barateau L, et al. *Ther Adv Neurol Disord.* 2019;12:1756286419875622.

Safety Considerations for FDA-Approved Treatments for EDS and Cataplexy in Narcolepsy

Drug	Schedule	Common AEs (≥5%)
Modafinil / Armodafinil	IV	Anxiety, back pain, diarrhea, dizziness, dyspepsia, headache, insomnia, and nausea
Solriamfetol	IV	Anxiety, decreased appetite, headache, insomnia, and nausea
Pitolisant	–	Anxiety, insomnia, and nausea
SXB / LXB	III	Anxiety (adults), decreased appetite, diarrhea (adults), dizziness, enuresis (peds), headache, hyperhidrosis (adults), parasomnia (adults), vomiting, and weight decrease (peds)
Amphetamines / Methylphenidate	II	Dry mouth, upset stomach, loss of appetite, weight loss, headache, dizziness, tremors, tachycardia, elevated blood pressure, insomnia, mood changes

AEs, adverse events; SXB, sodium oxybate; LXB, lower sodium oxybate
US FDA. Drugs. www.fda.gov/drugs.

Safety: Other Considerations

Agent	Additional Considerations
Modafinil/ Armodafinil ^{1,2,3}	<ul style="list-style-type: none"> May reduce effectiveness of hormonal contraceptive agents May increase heart rate and diastolic and systolic blood pressure Allergic reactions and rashes
Solriamfetol ^{4,5,6}	<ul style="list-style-type: none"> Precautions regarding blood pressure and heart rate increases No effect on birth control
Pitolisant ^{7,8}	<ul style="list-style-type: none"> May reduce effectiveness of hormonal contraceptives No clinically relevant effects on vital signs, laboratory findings May increase QTc intervals Not a controlled substance
SXB / LXB ^{9,10}	<ul style="list-style-type: none"> High sodium formulation may be contraindicated in patients at risk for CVD events May decrease body mass index Common, early-onset AEs are generally of short duration and decrease over time LXB formulation may be ideal in those with CVD risks
Amphetamines / Methylphenidate ³	<ul style="list-style-type: none"> Schedule II controlled substance High potential for abuse Serious cardiovascular events (such as sudden deaths, stroke, myocardial infarction)

1. Volkow ND, et al. *JAMA*. 2009;301(11):1148-1154. 2. Black JE, et al. *J Clin Sleep Med*. 2010;6(5):458-466. 3. US FDA. Drugs. www.fda.gov/drugs.
4. Meskill GJ, et al. *Sleep*. 2020;43(Suppl 1):A291. 5. Zomorodi K, et al. *J Clin Pharmacol*. 2019;59(8):1120-1129. 6. Carier LP, et al. *J Psychopharmacol*. 2018;32(12):1351-1361. 7. Scart-Gres C, et al. *Sleep*. 2019;42(Suppl 1):A244-245. 8. Setnik B, et al. *Sleep*. 2020;43(4):za262.
9. Hussain AM, et al. *J Clin Sleep Med*. 2020;16(9):1469-1474. 10. Dauvilliers Y, et al. *Sleep*. 2020;43:A296.

AASM Practice Parameters for Narcolepsy: Excessive Sleepiness (Recommendations 2007)

Agent	Indication	Recommendation Level	Based on
Modafinil	Narcolepsy: EDS	Standard	<ul style="list-style-type: none"> 4 level 1 studies 2 level 2 studies
Sodium oxybate	Narcolepsy: EDS	Standard	<ul style="list-style-type: none"> 3 level 1 studies 2 level 4 studies
Amphetamine Methamphetamine d-amphetamine Methylphenidate	Narcolepsy: EDS	Guideline	<ul style="list-style-type: none"> 3 level 2B studies 4 level 5C studies
Selegiline	Narcolepsy: EDS, cataplexy	Option	<ul style="list-style-type: none"> 2 level 2B studies 1 level 4C studies
Ritanserlin	Narcolepsy: EDS	Option	<ul style="list-style-type: none"> 2 level 2B studies

AASM, American Academy of Sleep Medicine.
Morgenthaler TI, et al. *Sleep*. 2007;30:1705-1711.

Therapeutic Interventions for Narcolepsy: Cataplexy Medications

Medication	Mechanism of action
Sodium oxybate ^{1*} Lower-sodium oxybate ^{2*}	GABA _B agonist
Pitolisant ^{3*}	Histamine H ₃ antagonist/inverse agonist
Antidepressants	Monoamine reuptake inhibitors
OREXIN Agonists: TAK-925/TAK-994 ^{4†}	Hypocretin receptor agonist

*FDA approved to treat excessive sleepiness associated with narcolepsy.
†Investigational, not FDA-approved for any indication.

1. Xyrem[®] (sodium oxybate) prescribing information. Jazz Pharmaceuticals, Palo Alto, CA, 2023.
2. Xyrem[®] (calcium, magnesium, potassium, and sodium oxybates) prescribing information. Jazz Pharmaceuticals, Palo Alto, CA, 2023.
3. Wakix[®] (pitolisant) prescribing information. Harmony Biosciences, LLC, Plymouth Meeting, PA, 2022.
4. Kimura H et al. *Sleep*. 2019;42(suppl 1):A23.

AASM Practice Parameters for Narcolepsy: Ancillary Symptoms (Recommendations 2007)

Agent	Indication	Recommendation Level	Based on
Sodium oxybate	Cataplexy, disrupted sleep, hypnagogic hallucinations, sleep paralysis	Standard Option	<ul style="list-style-type: none"> 3 level 1 study 2 level 2 studies
Tricyclic antidepressants (TCAs), SSRIs, venlafaxine, and reboxetine	Cataplexy	Guideline	<ul style="list-style-type: none"> 1 level 2 study 1 level 4 study 1 level 5 study
TCAs, SSRIs, venlafaxine, and reboxetine	Sleep paralysis, hypnagogic hallucinations	Option	—

Morgenthaler TI, et al. *Sleep*. 2007;30:1705-1711.

Traditional Stimulants

- Methylphenidate**
 - Methylphenidate hydrochloride—Concerta[®], Ritalin[®], Daytrana[®], Metadate CD[®], Methylin[®]; IR and ER: 5–60 mg/day
 - Dexmethylphenidate—Focalin[®]; IR and XR: 5–20 mg/day
- Amphetamines**
 - Dextroamphetamine—Dexedrine[®], Dextrostat[®]; 5–60 mg
 - Methamphetamine—Desoxy[®]; 10–60 mg/day
 - Lisdexamfetamine—Vyvanse[®]
 - Mixed amphetamine salts—Adderall[®]; IR* and XR; 5–40 mg

*FDA indicated for narcolepsy
IR, immediate release; ER and XR, extended release.

Psychostimulant Adverse Effects

- 58 patients who were taking high-dose stimulants for narcolepsy or idiopathic hypersomnia were compared with 58 control patients
 - High-dose stimulants were taken at $\geq 120\%$ of the recommended maximal doses
 - The prevalence of psychosis, psychiatric hospitalizations, tachyarrhythmias, polysubstance abuse, anorexia, and weight loss were significantly increased in the stimulant group
- Greater risk of new-onset psychosis with therapeutic amphetamines
- In 2014, approximately 1000 deaths involved prescription stimulants
- Abuse-deterrent formulations (ADFs)

Auger RR, et al. *Sleep*. 2005;28:667-672.
Moran LV et al. *N Engl J Med*. 2019;380:1128-1138.

Effect of Psychostimulants on BP Profile

- Patients treated for NT1 showed higher 24-hour, daytime, and nighttime diastolic BP and HR values compared with an untreated group
- Combination of stimulant and anti-cataplectic drugs showed a synergistic effect on BP
- Based on 24-hour BP monitoring, hypertension diagnosed in 58% of psychostimulant-treated patients and in 40.6% of untreated patients

BP, blood pressure; HR, heart rate
Bosco A, et al. *Neurology*. 2018;90:e479-e481.

Modafinil/Armodafinil

- Predominantly dopaminergic
- Retrospective analysis (n=1,529) of the use of antihypertensive medications
 - Patients taking modafinil required new or increased use of antihypertensive medications (2.4%) vs patients taking placebo (0.7%)
- Increased monitoring of BP may be appropriate
- Decreases ethinyl estradiol, therefore an alternative non-hormonal contraceptive method advised
- Potential for serious allergic reactions

Provigil® (modafinil) prescribing information. Teva Pharmaceuticals USA, Inc.; North Wales, PA, 2015.
Nuvigil® (armodafinil) prescribing information. Teva Pharmaceuticals, Parsippany, NJ, 2022.
Roth T, et al. *J Clin Sleep Med*. 2007;3(6):595-602.

Sodium Oxybate (SXB)

- Improves nocturnal sleep
 - Increases slow-wave sleep
 - Reduces arousals and awakenings
- Can eliminate cataplexy
- Reduces vivid dreams, nightmares, and hallucinations
- Reduces sleep paralysis
- Only medication that can treat all symptoms of narcolepsy
- Improves overall cognitive functioning

Sodium Oxybate (SXB)

- First-line drug for treatment of narcolepsy
- Split dosing according to clinical situation
 - 2 doses per night
 - Varying initial and subsequent dose amounts depending on clinical situation
- At 6–9 g/night, sodium oxybate contributes 1100–1640 mg to daily sodium intake

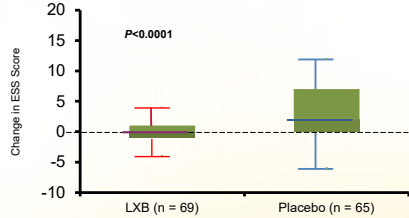
Lopez R, Dauvilliers Y. *Expert Opin Pharmacother*. 2013;14:895-903.
Pineau-Carboneau L. *Curr Treat Options Neurol*. 2019;21:57.
Barateau L, Dauvilliers Y. *Ther Adv Neurol Disord*. 2019;12:1-12.
Xyrem® (sodium oxybate) prescribing information. Jazz Pharmaceuticals; Palo Alto, CA, 2023.

Lower-Sodium Oxybate [LXB]

- Calcium, magnesium, potassium, and sodium oxybates
- Previously known as JZP-258
- A novel oxybate formulation with the same active moiety as SXB but a unique composition of cations, resulting in 92% less sodium
 - A reduction of 1013–1509 mg at a dose range of 6–9 g/night
- Lower-sodium oxybate (LXB) approved 7/21/20; available Q4 2020.
- Approved for same indication as SXB

Change in Epworth Sleepiness Scale with Lower-Sodium Oxybate (LXB)

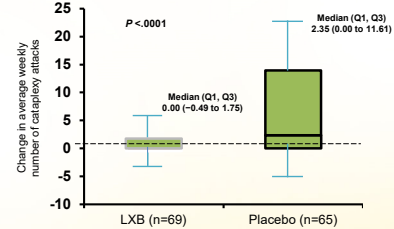
From stable-dose period to double-blind randomized withdrawal period



Bogan RK, et al. *Sleep Med.* 2019;64(Suppl 1):S43.
Thorpy MJ. *CNS Drugs.* 2020;34:9-27.

Change in Weekly Number of Cataplexy Attacks With Lower-Sodium Oxybate (LXB)

From stable-dose period to double-blind randomized withdrawal period



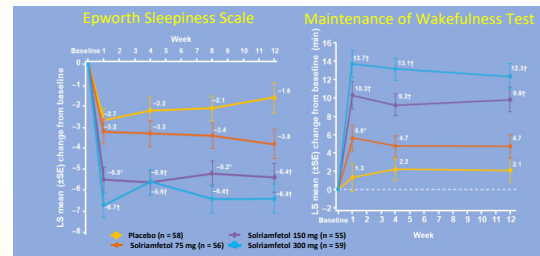
Bogan RK, et al. *Sleep Med.* 2019;64(Suppl 1):S43.
Thorpy MJ. *CNS Drugs.* 2020;34:9-27.

Solriamfetol

- FDA Approved 3/21/19
- Dopamine norepinephrine reuptake inhibitor (DNRI)—Schedule IV
- Half-life 7 hours, T_{max} 2 hours
- Contraindicated with MAOIs
- Renal excretion (95%): reduced dose in renal disease
- Can cause increased BP and HR, no effect on QTc
- Avoid use in unstable cardiovascular disease
- No effect on cataplexy
- No effect on oral contraceptives

MAOI, monoamine oxidase inhibitor; BP, blood pressure; HR, heart rate
Sunovion® (solriamfetol) prescribing information. Axsome Therapeutics, Inc.; New York, NY, 2023.
Thorpy MJ, et al. *Ann Neurol.* 2019;85:369-370.

Solriamfetol in Narcolepsy



*P < .05, †P < .0001 vs placebo
Thorpy MJ, et al. *Ann Neurol.* 2019;85:369-370.

300 mg dose not approved for use

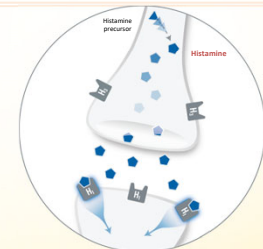
Pitolisant

- **Dosing**
 - Recommended dosage range: 17.8–35.6 mg once daily
 - Adjustments in patients with hepatic or renal impairment or poor metabolizers of CYP2D6
- **Contraindications**
 - Patients with severe hepatic impairment
- FDA approved for treatment of EDS in adults with narcolepsy
- Not controlled, not scheduled
- **Warning and precautions**
 - Increases QTc interval; avoid use in patients who:
 - Are taking other drugs that prolong QTc interval
 - Have risk factors for prolonged QTc interval
- **Pregnancy and lactation**
 - Unknown (present in rat milk)
 - Alternative non-hormonal contraceptive method during and for at least 21 days after discontinuation of treatment

Romigi A, et al. *Drug Des Devel Ther.* 2016;12:2665-2675.
Wakix® (pitolisant) prescribing information. Harmony Biosciences, LLC, Plymouth Meeting, PA, 2022.
FDA drug approvals (www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/new-drug-approvals-2019).
NCT03431311 (https://clinicaltrials.gov/ct2/show/NCT03431311?term=NCT03431311&rank=1).

In the Brain, Histamine is an Important Neurotransmitter¹⁻³

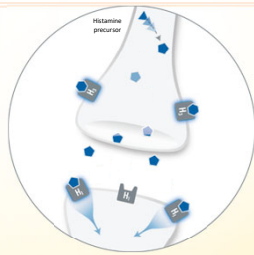
- Histamine is synthesized in the presynaptic neuron¹
- When released into the synapse, histamine binds to postsynaptic H₁ receptors¹
 - Allows for communication with brain regions important for sleep and wakefulness^{1,2,4}



H₁ histamine 1.
1. Scammell TE, et al. *Sleep.* 2019;42(1). doi: 10.1093/sleep/zsy163.
2. Scammell TE, et al. *Neuron.* 2017;93(4):747-765.
3. España RA, Scammell TE. *Sleep.* 2011;34(7):845-858.
4. Haas HL, et al. *Physiol Rev.* 2008;88(3):1183-1241.

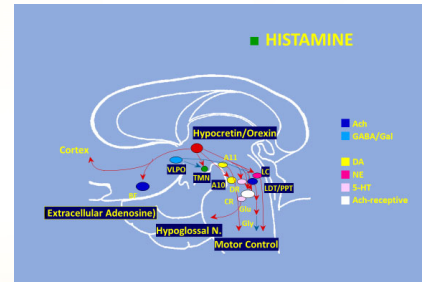
H₃ Receptors Help Regulate Histamine Synthesis and Release in the Brain^{1,2}

- H₃ receptors are found primarily in the brain^{3,4}
- Normally, when histamine levels in the brain are high, histamine binds to presynaptic H₃ autoreceptors to inhibit further synthesis and release of histamine in the brain^{1,2}



H₃, histamine 3.
 1. Scammell TE, et al. *Sleep*. 2019;42(1). doi: 10.1093/sleep/zay183.
 2. Nieto-Alamilla G, et al. *Mol Pharmacol*. 2016;90(5):849-873.
 3. Panula P, et al. *Pharmacol Rev*. 2015;67(3):601-655.
 4. Schlicker E, et al. *Handb Exp Pharmacol*. 2017;241:277-299.

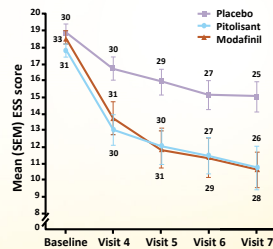
Sleep: Neurochemistry



BF, basal forebrain cholinergic nuclei; LDT/PPT, laterodorsal tegment nuclei/pedunculopontine tegment nuclei; CR, caudal raphe; PRF, pontine reticular formation; Ach, acetylcholine.
 Courtesy of E. Mignot, MD, Stanford University.

Pitolisant: Epworth Sleepiness Scale

- Histamine H₃ receptor inverse agonist/antagonist
- Selective for the H₃ subtype

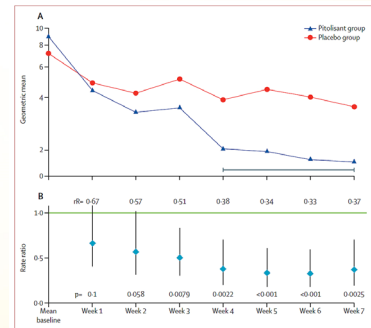


SEM, standard error of the mean.
 Dauvilliers Y, et al. *Lancet Neurol*. 2013;12:1068-1075.
 FDA drug approvals (www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/ novel-drug-approvals-2019).

Pitolisant – Cataplexy

Weekly Cataplexy Rate (WCR)

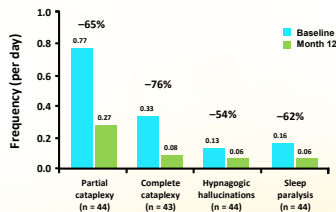
Approved for cataplexy, December 2021



Dauvilliers Y, et al. *Lancet Neurol*. 2013;12:1068-75.

Pitolisant: Symptoms After 12 Months of Treatment

Improvement in cataplexy and other symptoms in patients who completed 12 months of treatment



Dauvilliers Y, et al. *Sleep*. 2019;42(11):zaz174. doi: 10.1093/sleep/zaz174.
 FDA drug approvals (www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/ novel-drug-approvals-2019).

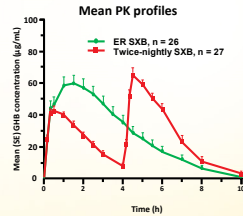
Extended-Release (ER) Sodium Oxybate: Once-Nightly Dosing

- The approved effective doses of SXB are 6, 7.5, and 9 g per night, divided into 2 doses
 - The first is taken at bedtime and the second is taken 2.5–4 hours later
- ER SXB is a controlled-release formulation of sodium oxybate intended for once-nightly dosing, using proprietary Micropump[®] technology
- Same amount of sodium as sodium oxybate

Xyrem[®] (sodium oxybate) prescribing information. Jazz Pharmaceuticals; Palo Alto, CA, 2023.
 Lumryx (sodium oxybate) for extended-release oral suspension. Avadel CNS Pharmaceuticals, LLC, Chesterfield, MO, 2023.
 Avadel Pharmaceuticals press release, January 10, 2018 (www.globenewswire.com/news-release/2018/01/10/1286550/0/en/Avadel-Pharmaceuticals-Receives-Orphan-Drug-Designation-from-FDA-for-FT-218-for-the-Treatment-of-Narcolepsy.html).

Pharmacokinetic Study Comparing ER SXB (6 g) with Twice-Nightly Sodium Oxybate IR (3+3 g)

- Main analysis
 - AUC of ER SXB bioequivalent with twice-nightly sodium oxybate IR
 - C_{max} of ER SXB is lower than twice-nightly sodium oxybate IR
- Post-hoc analysis
 - Morning plasma levels (C_{8h}) of ER SXB similar to twice-nightly sodium oxybate IR



AUC, area under the curve; C_{max}, maximum concentration; C_{8h}, concentration 8 hours; PK, pharmacokinetic; IR, immediate release
 Thorpy MJ, et al. World Sleep meeting, Vancouver 2019.

Antidepressants for Cataplexy

- Can be effective for cataplexy
- Norepinephrine reuptake inhibitors most effective (e.g., venlafaxine, atomoxetine)
- Can cause sexual side effects
- Can disturb nocturnal sleep
- Not effective for other REM phenomena (e.g., sleep paralysis, hypnagogic hallucinations)
- Not effective for sleepiness
- Cardiovascular effects: bradycardia, tachycardia, hypertension, hypotension, orthostatic hypotension, electrocardiogram (ECG) changes, electrolyte abnormalities, reduced cardiac conduction and output, arrhythmias, and sudden cardiac death¹

1. Marano G, et al. J Geriatr Cardiol. 2011;8:243-253.

Potential Agents Under Investigation

Modafinil augmentation

- Modafinil/fecainide (THN102)

GABA-A antagonists

- Clarithromycin
- Flumazenil
- Pentetrazol (BTD-001)

Norepinephrine reuptake inhibitor (NRI)

- Reboxetine

H3R inverse agonist

- SUVN-G3031

Orexin agonists

- TAK-925/994/Others

Sympathomimetic amine/Hypocretin agonist

- Mazindol

Narcolepsy Treatment: Cardiovascular Risks and Risk Reduction Strategies

Alerting medications

- Traditional Stimulants
 - Cardiostimulation: HTN, cardiac arrhythmias
- Modafinil /Armodafinil
 - Cardiostimulation: HTN, arrhythmias (less than traditional stimulants)
 - Avoid in: left ventricular failure and in some patients with mitral valve prolapse
- Solriamfetol
 - Can cause increased BP and HR
- Pitolisant
 - Increases QTc interval
- Anti-cataplectic drugs
 - Cardiostimulation: HTN, cardiac arrhythmias
- Sodium oxybate
 - Sodium load

Lower-sodium oxybate has potential for reducing risk of adverse cardiovascular effects

- Current nonpharmacologic options:
 - Weight reduction, exercise, dietary measures

Summary

- Excessive sleepiness is prevalent.
- Excessive sleepiness has a major impact on alertness, executive function, mood and therefore quality of life.
- Narcolepsy is a window into understanding sleep/wake processes, diagnosis and treatment.
- Early recognition and treatment of narcolepsy has a major impact on quality of life, school or workplace performance and social interaction.