A 3D PERSPECTIVE - SLEEP-RELATED PATIENT SYMPTOMS:

Evaluation and Treatment of Excessive Daytime Sleepiness Secondary to OSA or Narcolepsy

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).
Supported by an educational grant from Jazz Pharmaceuticals, Inc.

A 3D Perspective - Sleep-Related Patient Symptoms: Evaluation and Treatment of Excessive Daytime Sleepiness Secondary to OSA or Narcolepsy

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PROGRAM OVERVIEW
This live activity will cover treating and managing patients with sleep-related disorders.

TARGET AUDIENCE
This initiative is designed to meet the educational needs of U.S.-based neurologists, internists, pulmonologists, psychiatrists, and sleep specialists who treat patients who have or are at risk for sleep-related disorders.

LEARNING OBJECTIVES
On completing the program, attendees should be able to:

- Discuss the recognition of impaired daytime wakefulness and Excessive Daytime Sleepiness (EDS) due to either narcolepsy or OSA
- Describe patients at risk for EDS and impaired wakefulness, resulting in prompt referral and diagnosis
- Review the uses and limitations of currently available pharmacologic options for people with EDS due to either OSA or narcolepsy
- Evaluate clinical trial data for agents to treat impaired wakefulness and EDS in patients with either OSA or narcolepsy

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NURSING CREDIT INFORMATION
Purpose: This program would be beneficial for nurses involved in treating and managing patients with sleep-related disorders.
Credits: 1.0 ANCC Contact Hour

CNE Accreditation Statement: Ultimate Medical Academy/CCM is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Awarded 1.0 contact hour of continuing nursing education of RNs and APNs.

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Phyllis C Zee, MD, PhD	**Consultant**	Eisai, Jazz, Philips, Takeda, Sanofi-Aventis, Merck, Pear
	Research	Philips Respironics; Apnimed (Research Grant to Northwestern University
	Ownership Interest	Teva
Clete A. Kushida, MD, PhD	**Consultant**	Avadel CNS Pharmaceutical
	Research	Avadel CNS Pharmaceutical
Russell P. Rosenberg, PhD	**Speakers Bureau**	Jazz Pharmaceuticals, Harmony Bioscience, Eisai,
	Consultant	Harmony Biosciences, Eisai, & Jazz Pharmaceuticals
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2. Participate in the live activity.
3. Submit the pre- and post-test and evaluation form to Med Learning Group.

You will receive your certificate as a downloadable file.

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A 3D Perspective
Sleep-Related Patient Symptoms: Evaluation and Treatment of Excessive Daytime Sleepiness Secondary to OSA or Narcolepsy

PROPOSED AGENDA

I. Excessive Daytime Sleepiness: An Overview (10 MIN)

a) Definition and prevalence
b) Subjective vs. objective sleepiness
c) Burden (physical, societal, emotional, occupational)
d) Associations with narcolepsy and obstructive sleep apnea

II. Challenges in the Diagnosis and Management of EDS Secondary to Narcolepsy or OSA (25 MIN)

a) The importance of early diagnosis and intervention **(5-10 min)**
    1. Challenges in diagnosis
    2. Age of onset and diagnostic criteria
    3. Differential diagnosis (i.e., identifying the cause of EDS as narcolepsy or OSA, and ruling out others such as insomnia, restless legs syndrome, idiopathic hypersomnia, circadian rhythm disorder)
    4. Causes of residual sleepiness and pathophysiology
b) Traditional standard of care therapies **(~20 min)**
    1. OSA: CPAP; lifestyle measures; surgical interventions; hypoglossal nerve stimulation; oral appliance therapy
        a. Efficacy and adherence
        b. Cardiovascular impact of these interventions
    2. Narcolepsy: stimulants (e.g., dextroamphetamine, methylphenidate); wake promoting agents (e.g., modafinil, armodafinil, sodium oxybate); others (off-label – e.g., antidepressants)
        a. Goals of treatment
        b. Strengths and limitations of current therapy (response, tolerability, potential for abuse)
    3. 3D Video 1: Excessive vs. normal sleepiness; traditional standard of care therapies: MOAs, how they are effective, and ways in which they may be suboptimal in treating EDS associated with narcolepsy, e.g., abuse potential, side effects, response and tolerability

III. Novel Approaches to the Treatment of EDS Associated with Narcolepsy or OSA (15 MIN)

a) Solriamfetol (March, 2019)
    1. Mechanism of Action: Dual-acting dopamine and norepinephrine reuptake inhibitor
    2. Clinical data
b) Pitolisant (August, 2019)
    1. Mechanism of Action: Selective histamine 3 receptor antagonist/inverse agonist
    2. Clinical data
c) Medications for cataplexy
d) Other options on the horizon
    1. Sodium oxybate formulations: low sodium with CV implications, and once-a-night
    2. Reboxetine, antidepressants, and others
e) 3D Video 2: MOA and pharmacology of new/novel agents: solriamfetol and pitolisant; future pharmacotherapy directions (new sodium oxybate formulations, reboxetine, etc)

IV. Conclusions and Q/A (10 MIN)

A 3D Perspective

Sleep-Related Patient Symptoms: Evaluation and Treatment of Excessive Daytime Sleepiness Secondary to OSA or Narcolepsy

Disclosures

- In this presentation, the faculty will be discussing both FDA-approved and investigational agents.

This program is supported by an educational grant from Jazz Pharmaceuticals, Inc.

Learning Objectives

- Discuss the recognition of impaired daytime wakefulness and excessive daytime sleepiness (EDS) due to either narcolepsy or obstructive sleep apnea (OSA)
- Describe those individuals at risk for EDS and impaired wakefulness to assist with prompt diagnosis and referral
- Review the uses and limitations of currently available pharmacologic options for individuals with EDS due to either narcolepsy or OSA
- Evaluate clinical trial data for agents to treat impaired wakefulness and EDS in patients with either OSA or narcolepsy

Normal vs Excessive Sleepiness Definitions and Terminology

- Normal sleepiness
  - A biological drive state of decreased ability to maintain wakefulness or an increased propensity to fall asleep
- Excessive sleepiness
  - A symptom of difficulty in maintaining wakefulness and an increased propensity to fall asleep, even in inappropriate circumstances and in situations that interfere with activities of daily living

Challenges in the Diagnosis and Management of EDS Due to Narcolepsy and OSA

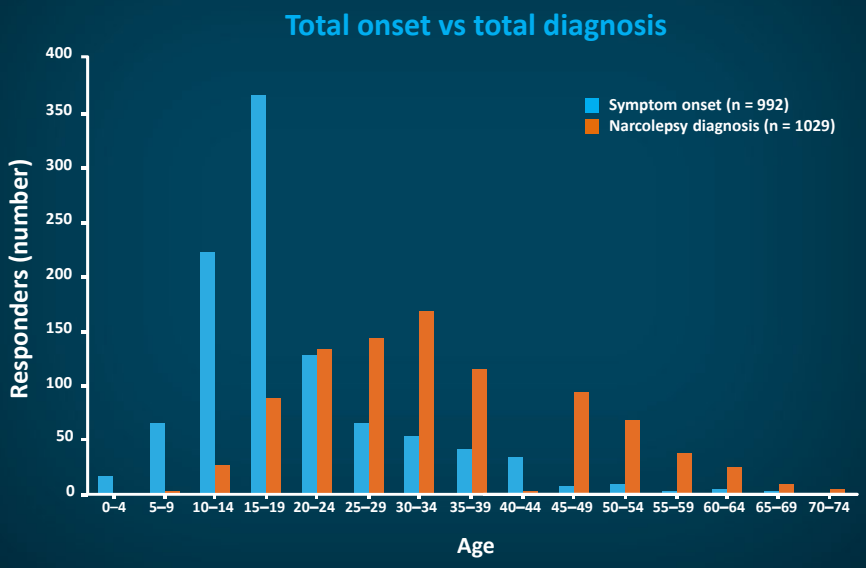
Narcolepsy

- Narcolepsy is a neurologic disorder characterized by:
- Excessive daytime sleepiness
  - Continual sleepiness (background)
  - Voluntary sleep episodes (naps)
  - Involuntary sleep episodes (sleep attacks)
  - Wakeful sleepiness (automatic behavior, microsleeps)
- REM-related phenomena
  - Cataplexy = ~60%
  - Hypnagogic hallucinations = ~67%
  - Sleep paralysis = ~64%
- Disturbed nocturnal sleep

REM = rapid eye movement (sleep).

Moturi S, Ivanenko A. *Psychiatry* (Edgmont). 2009;6:38-44.

Narcolepsy Onset and Age at time of Diagnosis



Thorpy MJ, Krieger AC. *Sleep Med*. 2014;15:502-507.

Narcolepsy Diagnosis Criteria

ICSD-3 and DSM-5

Narcolepsy type 1 (narcolepsy with cataplexy)

- Chronic EDS (daily for at least 3 months) **and**
- Presence of 1 or both of the following:
  - Cataplexy + mean sleep latency ≤8 minutes and ≥2 SOREMPs on MSLT*
  - CSF hypocretin-1 level is either ≤110 pg/mL or <1/3 of mean values

Narcolepsy type 2 (narcolepsy without cataplexy)

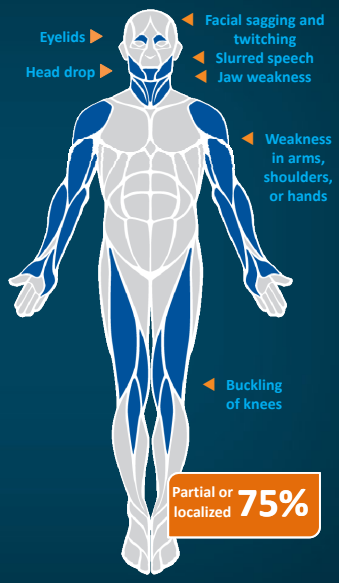
- Chronic EDS (daily for at least 3 months)
- Mean sleep latency ≤8 minutes and ≥2 SOREMPs on MSLT*
- Cataplexy absent
- CSF hypocretin-1 concentration not measured **or** CSF hypocretin-1 level is >110 pg/mL or >1/3 of mean values
- Hypersomnolence and/or MSLT findings not explained by other causes

***A SOREMP on the preceding night's polysomnogram may substitute for 1 of the SOREMPs on MSLT.**
SOREMP = sleep-onset REM period; MSLT = multiple sleep latency test; CSF = cerebrospinal fluid.

AASM. *The International Classification of Sleep Disorders, 3rd ed* (ICSD-3). 2014. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 5th ed* (DSM-5), 2015.

Difficulties in Diagnosis of Cataplexy

- Pathognomonic for narcolepsy
- Sudden and transient loss or reduction of muscle tone
- Triggered by strong emotions
  - Laughter, elation, surprise, anger
- Typically partial or localized—~75%
- Usually of short duration, ie, seconds to minutes
- Frequency varies widely, ie, yearly to daily
- Narcolepsy with cataplexy can be socially disabling and isolating.



AASM. *The International Classification of Sleep Disorders, 3rd ed* (ICSD-2), 2005. Overeem S, et al. *Sleep Med*. 2011;12:12-18. Ahmed I, Thorpy M. *Clin Chest Med*. 2010;31:371-381.

Limitations of The MSLT

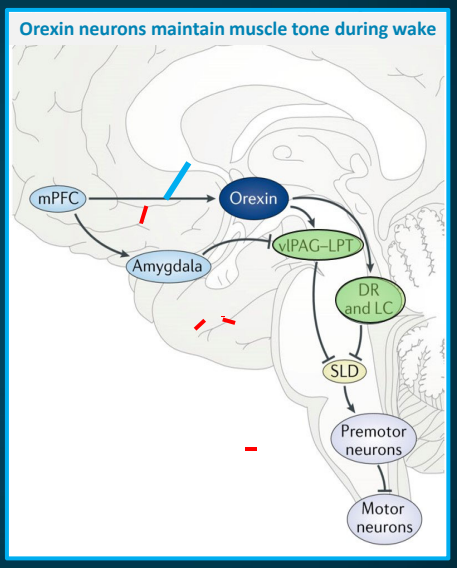
- False-positive MSLT
  - ≥2 SOREMS occur in 13% of men and 6% of women
  - ≥2 SOREMs and MSLT latency <8 min occur in 6% of men and 1% of women
  - Can be caused by shift work, OSA, insufficient sleep, etc.
- False-negative MSLT (~20%)
  - Anxiety, psych medications, noise in lab, etc.
- MSLT often not performed per guidelines
  - Actigraphy and sleep logs not done routinely
  - Patients not routinely sleep satiated
  - PSG sleep time of 6–7 hours may not be enough.
- Poor test/re-test reproducibility in NT2 and IH
  - Diagnosis changes in ~50%

PSG = polysomnography; NT2 = narcolepsy type 2; IH = idiopathic hypersomnia.

Okun ML, et al. *Sleep*. 2002;25:27-35. Mignot E, et al. *Brain*. 2006;129:1609-1623. Dauvilliers Y, et al. *Neurology*. 2001;57:2029-2033. Furuta H, et al. *Psychiatry Clin Neurosci*. 2001;55:241-242. Andlauer O, et al. *Sleep*. 2012;35:1247-1255F. Trotti LM, et al. *J Clin Sleep Med*. 2013;9:789-795. Ruoff C, et al. *J Clin Sleep Med*. 2018;14:65-74.

Pathophysiology of Narcolepsy

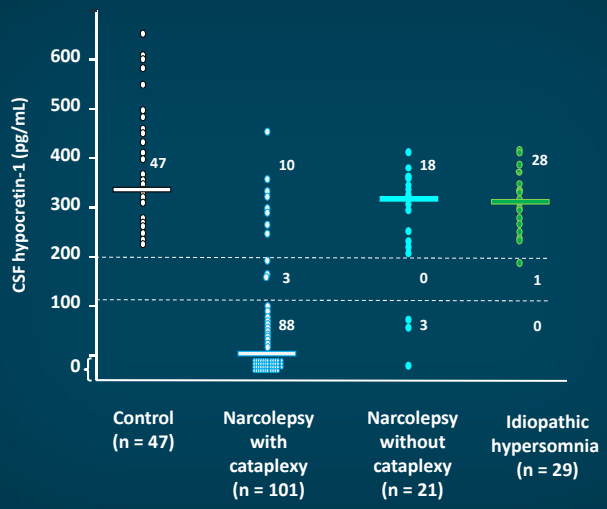
- Lack of orexin neurons reduces activity of vlPAG/LPT and DR/LC (green)
- Emotions via the amygdala strongly inhibit the vlPAG-LPT; in narcolepsy, excitatory drive from orexin neurons is absent, enabling the SLD, thereby resulting in cataplexy



vlPAG/LPT = ventrolateral periaqueductal grey and lateral pontine tegmentum; DR = dorsal raphe; SLD = sublaterodorsal nucleus; mPFC = medial prefrontal cortex.

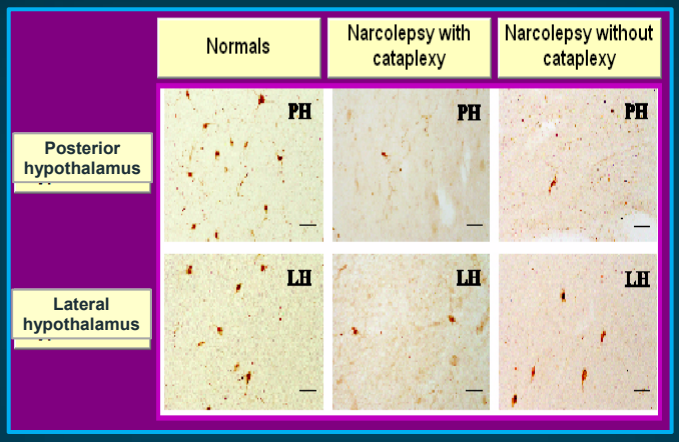
Modified from Mahoney CE, et al. *Nat Rev Neurosci*. 2019;20:83-93.

Hypocretin/Orexin Levels



Modified from Mignot E, et al. *Arch Neurol*. 2002;59:1553-1562.

Hypocretin in Narcolepsy without Cataplexy



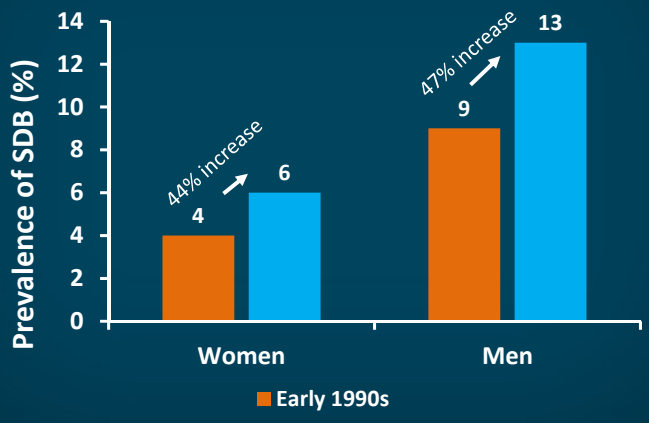
- Hypocretin cells in hypothalami of normals, narcolepsy with cataplexy, and narcolepsy without cataplexy
- Cell loss in patients with narcolepsy without cataplexy found in PH and LH

PH = posterior hypothalamus; LH = lateral hypothalamus.

Thannickal TC, et al. *Sleep.* 2009;32:993-998.

Increased Prevalence of SDB in US Adults Over ~20-Year Span

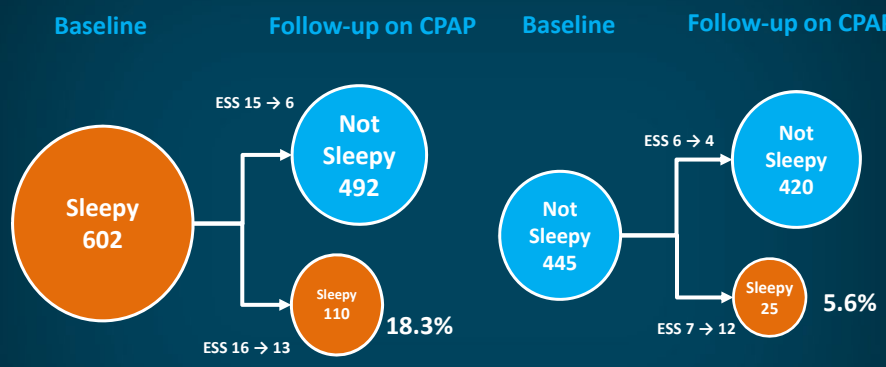
SDB in adults aged 30–70 years of age (AHI ≥15 events/h)



SDB = sleep-disordered breathing; AHI = apnea-hypopnea index.

Peppard PE, et al. *Am J Epidemiol.* 2013;177:1006-1014.

Prevalence of Sleepiness in 1047 Patients With OSA
French National Sleep Registry



- 58% were sleepy at baseline
- 13% were sleepy at follow-up

CPAP = continuous positive airway pressure; ESS = Epworth Sleepiness Scale.

Gasa M, et al. *J Sleep Res*. 2013;22:389-397.

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Causes of Residual Sleepiness in OSA

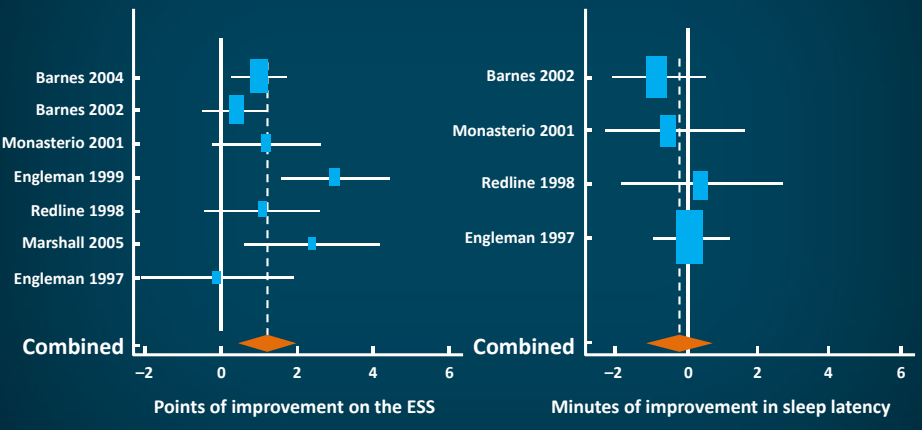
- Poor adherence with therapy
- Residual or complex sleep apnea
- Chronic partial sleep deprivation
- Disorders of sleep fragmentation, eg, PLMs
- Comorbidities or medications (even SSRIs)

PLM = periodic limb movement (during sleep); SSRI = selective serotonin reuptake inhibitor.

The Management of EDS in OSA and Narcolepsy

CPAP Reduces Subjective but Not Objective Sleepiness: Meta-analysis

Results of CPAP treatment

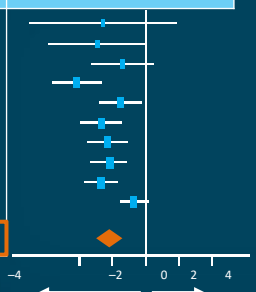


Marshall NS, et al. *Thorax*. 2006;61:430-434. (Complete references for the studies cited are available in Marshall et al.)

Meta-Analysis of 10 RPC Trials of Modafinil and Armodafinil in Treatment of Residual Sleepiness in OSA

Epworth Sleepiness Scale Scores

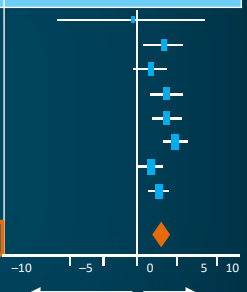
First author	Mean difference IV, random (95% CI)
Bittencourt	−2.60 (−7.07 to 1.87]
Greve	−2.90 (−5.83 to 0.03)
Kingshott	−1.39 (−3.25 to 0.47)
Inoue	−4.17 (−5.66 to −2.68]
Krystal	−1.50 (−2.77 to −0.23)
Pack, Dinges	−2.70 (−3.94 to −1.46)
Hirschkowitz	−2.28 (−3.46 to −1.10)
Roth	−2.20 (−3.27 to −1.13)
Black	−2.70 (−3.69 to −1.71)
Herring	−0.74 (−1.60 to 0.12)
Total	−2.21 (−2.88 to −1.54)



Heterogeneity: τ^2=0.60; χ^2=21.21, df=9 (*P*= .001); I^2=58%
Test for overall effect: Z=6.48 (*P* <.00001)

Maintenance of Wakefulness Test Sleep-Onset Latencies

First author	Mean difference IV, random (95% CI)
Bittencourt	−0.51 (−9.29 to 8.27)
Inoue	3.20 (0.80 to 5.60)
Krystal	1.60 (−0.37 to 3.57)
Hirschkowitz	3.60 (1.70 to 5.50)
Roth	3.65 (1.88 to 5.42)
Herring	4.65 (3.21 to 6.09)
Kingshott	1.69 (0.26 to 3.12)
Black	2.65 (1.46 to 3.84)
Total	2.29 (2.12 to 3.82]



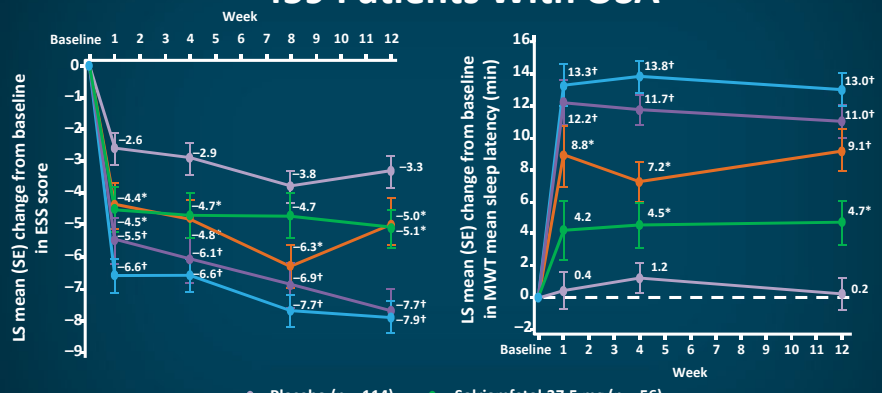
Heterogeneity: τ^2=0.58; χ^2=12.06, df=7 (*P*= .010); I^2=42%
Test for overall effect: Z=6.88 (*P* <.00001)

FOSQ total score improved by 1 point over placebo in 3 studies

RPC = randomized, placebo-controlled; FOSQ = Functional Outcomes of Sleep Questionnaire; IV = inverse variance (in this context).

Chapman JL, et al. *Eur Respir J.* 2016;47:1420-1428. (Complete references for the studies cited are available in Chapman et al.)

Effect of Solriamfetol on Subjective and Objective Measures of Excessive Sleepiness in 459 Patients With OSA



Placebo (n = 114)
Solriamfetol 37.5 mg (n = 56)
Solriamfetol 75 mg (n = 58)
Solriamfetol 150 mg (n = 116)
Solriamfetol 300 mg (n = 115)

**P* <.05; †*P* <.0001 versus placebo.
LS = least squares; SE = standard error; MWT = Maintenance of Wakefulness Test.

Schweitzer PK, et al. *Am J Respir Crit Care Med.* 2019;199:1421-1431.

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

Thorpy MJ, Dauvilliers Y. *Sleep Med*. 2015;16:9-18.

Therapeutic Interventions for Narcolepsy: Alerting Medications

Medication	Mechanism of action
Caffeine[1]	Adenosine receptor antagonist
Methylphenidate[2]*, **amphetamines**[3]*	Sympathomimetic; enhance neurotransmission of dopamine, norepinephrine, serotonin
Modafinil[4]*, **armodafinil**[5]*	Dopamine reuptake inhibitor
Sodium oxybate[6]*	$GABA_B$ agonist
Solriamfetol[7]*	Dopamine-norepinephrine reuptake inhibitor
Pitolisant[8]*	Histamine H_3 antagonist/inverse agonist
Reboxetine[9]†	Selective norepinephrine reuptake inhibitor
TAK-944/925[10]†	Orexin 2 receptor agonist

*FDA approved to treat excessive sleepiness associated with narcolepsy; †Investigational; not FDA-approved for any indication.
GABA = gamma-aminobutyric acid

1. Okuro M, et al. *Sleep*. 2010;33:930-942. 2. Methylphenidate (Ritalin®) prescribing information (PI) 2019 (www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/ritalin_ritalin-sr.pdf). 3. Amphetamine+dextroamphetamine (Adderall®) PI 2007 (www.accessdata.fda.gov/drugsatfda_docs/label/2007/011522s040lbl.pdf). 4. Modafinil (Provigil®) PI 2018 (http://provigil.com/provigil.pdf). 5. Armodafinil (Nuvigil®) PI 2018 (www.nuvigil.com/globalassets/nuvigil-consumer/prescribinginformation.pdf). 6. Sodium oxybate (Xyrem®) PI 2018 (http://pp.jazzpharma.com/pi/xyrem.en.USPI.pdf). 7. Solriamfetol (Sunosi™) PI 2019 (http://pp.jazzpharma.com/pi/sunosi.en.USPI.pdf). 8. Pitolisant (Wakix®) PI 2019 (www.accessdata.fda.gov/drugsatfda_docs/ label/2019/0211150s000lbl.pdf). 9. Larrosa O, et al. *Sleep*. 2001;24:282-285. 10. Centerwatch (www.centerwatch.com/clinical-trials/listings/158528/healthy-participants-and-patients-with-narcolepsy-phase-1-tak-925-study/). All PIs and other URLs accessed on 5/29/2020.

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

Agent	Indication	Recommendation Level	Based on
Modafinil	Narcolepsy: EDS	**Standard**	• 4 level 1 studies • 2 Level 2 studies
Sodium oxybate	Narcolepsy: EDS	**Standard**	• 3 level 1 studies • 2 Level 4 studies
Amphetamine Methamphetamine d-amphetamine Methylphenidate	Narcolepsy: EDS	**Guideline**	• 3 level 2B studies • 4 level 5C studies
Selegiline	Narcolepsy: EDS, cataplexy	**Option**	• 2 level 2B studies • 1 level 4C studies
Ritanserin	Narcolepsy: EDS	**Option**	• 2 level 2B studies

AASM = American Academy of Sleep Medicine.
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—Desoxyn®; 10–60 mg/day
  - Lisdexamfetamine—Vyvanse®
  - Mixed amphetamine salts—Adderall®; IR* and XR; 5–40 mg

***Indicated for narcolepsy**

IR = immediate release; ER and XR = extended release.

Mixed Amphetamine Salts: Adderall®

- Four amphetamine salts
  - racemic amphetamine aspartate monohydrate
  - racemic amphetamine sulfate
  - dextroamphetamine saccharide
  - dextroamphetamine sulfate
- Dopamine- and norepinephrine-releasing agent; mildly serotonergic
- Available in two formulations: IR and XR
- IR is indicated for narcolepsy
  - XR formulation is not indicated for narcolepsy.
- Dosage = 5–60 mg

Stimulant 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 ≥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.

Armodafinil

- Longer-acting isomer of modafinil (R-(-)-modafinil)
- Metabolized in the liver
- Half-life approximately 3 x S-(-)-modafinil (approximately 15 hours)
- Once-per-day formulation
- Dose = 50–250 mg (equivalent to 400 mg of modafinil)
- No effect on cataplexy
- Reduces efficacy of oral contraceptives
  - Increases metabolism of ethinylestradiol
- Can cause serious rashes and allergic reactions

Sodium Oxybate

- 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: Clinical Use

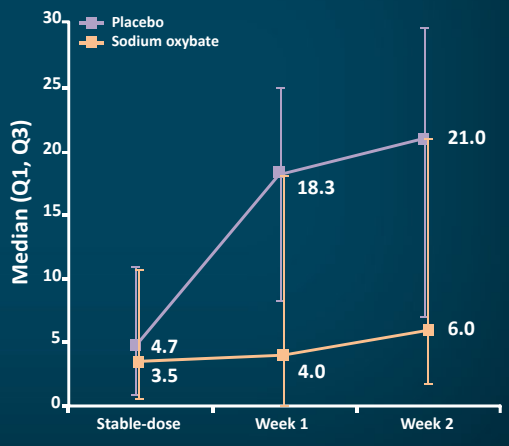
- First-line drug for treatment of narcolepsy
- Most effective drug for treatment of cataplexy
- Most effective for sleepiness, in combination with armodafinil
- Split dosing according to clinical situation
  - 2 doses per night
  - Varying initial and subsequent dose amounts depending on clinical situation
- Side effects can be reduced by either:
  - More rapid increase in dose
  - Reduction of initial dose

Lopez R, Dauvilliers Y. *Expert Opin Pharmacother*. 2013;14:895-903. Pérez-Carbonell L. *Curr Treat Options Neurol.* 2019;21:57. Barateau L, Dauvielliers Y. *Ther Adv Neurol Disord.* 2019;12:1-12. Sodium oxybate (Xyrem®) PI 2018 (http://pp.jazzpharma.com/pi/xyrem.en.USPI.pdf).

SXB in Children

- Open-label study with 63 participants aged 7–16 years of age at screening
- Primary diagnosis of narcolepsy with cataplexy

Median number of weekly cataplexy attacks in weeks 1 and 2 of the double-blind treatment period



Q = quartile.

Plazzi G, et al. *Lancet Child Adolesc Health*. 2018;2:483-494.

Novel Approaches to the Treatment of EDS Associated with Narcolepsy and OSA

Solriamfetol: FDA Approved 3/21/19

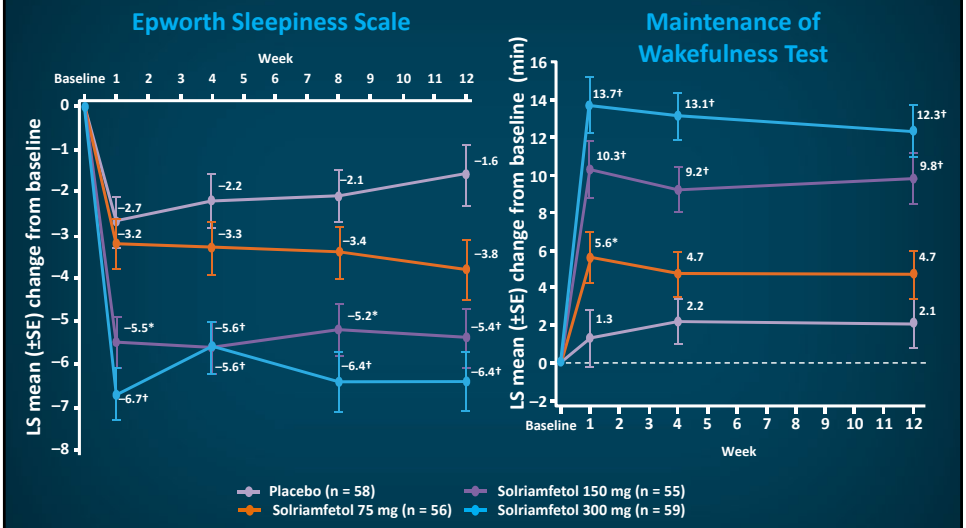
- Dopamine norepinephrine reuptake inhibitor (DNRI)—Schedule IV
- Available in 75 mg scored or 150 mg tablets
- Approved for adults: narcolepsy (75–150 mg) and OSA (37.5–150 mg)

Can be taken with/without food on awakening	Half-life 7 hours, Tmax 2 hours
Contraindicated with MAOIs	Drug-liking score similar to or lower than for phentermine
Renal excretion (95%): reduced dose in renal disease	No effect on oral contraceptives
Can cause increased BP and HR, no effect on QTc	No evidence of increase pregnancy risk
Avoid use in unstable cardiovascular disease	No data on breast milk (present in rat milk)
Can cause anxiety, insomnia, and irritability	No effect on cataplexy
No evidence of dependence or withdrawal	Caution in geriatric population d/t renal excretion

MAOI = monoamine oxidase inhibitor; BP = blood pressure; HR = heart rate; d/t = due to.

Solriamfetol (Sunosi™) PI 2019 (http://pp.jazzpharma.com/pi/sunosi.en.USPI.pdf). Accessed 5/29/2020.
Thorpy MJ, et al. *Ann Neurol*. 2019;85:359-370.

Solriamfetol in Narcolepsy

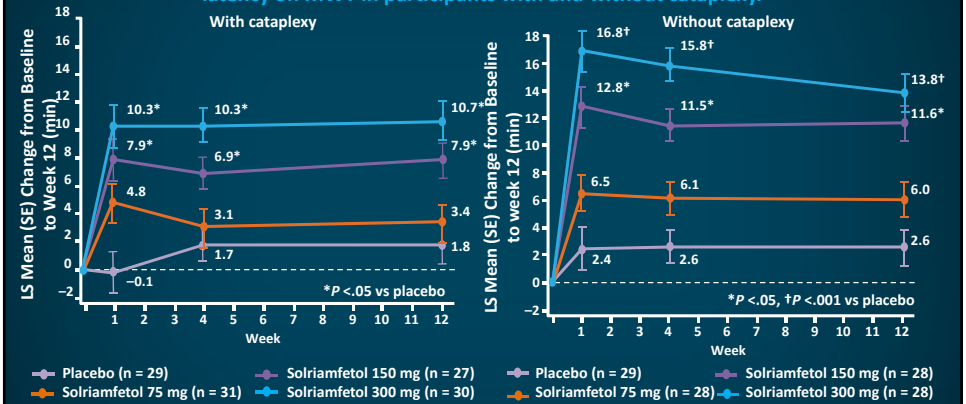


*P <.05, †P <.0001 vs placebo

Thorpy MJ, et al. *Ann Neurol*. 2019;85:359-370.

Solriamfetol in Maintenance of Wakefulness of NT1 vs NT2

Solriamfetol 150 mg and 300 mg significantly increased sleep latency on MWT in participants with and without cataplexy.



Improvements in wakefulness were observed with solriamfetol 150 mg and 300 mg at week 1 (first evaluated time point)

Dauvilliers Y, et al. Presented at the 32nd Annual Meeting of the Associated Professional Sleep Societies , 2018.

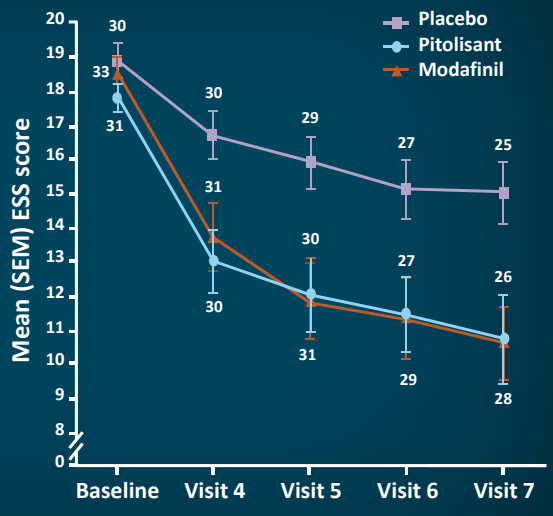
Pitolisant: FDA-Approved 8/14/19, Became Available 11/4/19

- **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.* 2018;12:2665-2675. Pitolisant (Wakix®) PI 2019 (www.accessdata.fda.gov/drugsatfda_docs/label/2019/0211150s000lbl.pdf). FDA drug approvals (www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2019). NCT03433131 (https://clinicaltrials.gov/ct2/show/NCT03433131?term=NCT03433131&draw= 2&rank=1). Accessed 5/29/2020.

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; Harmony I study group. *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). Accessed 5/29/2020.

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**	• 3 level 1 study • 2 level 2 studies
Tricyclic antidepressants (TCAs), SSRIs, venlafaxine, and reboxetine	Cataplexy	**Guideline**	• 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.

Medications for Cataplexy

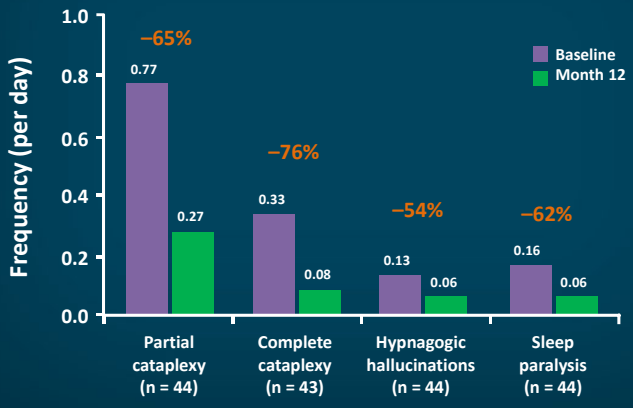
- Sodium oxybate
- Histamine H3 receptor antagonist/agonist
  - Pitolisant
- Antidepressants
  - TCAs: clomipramine hydrochloride, protriptyline
  - SSRIs: fluoxetine, paroxetine
  - NRI/NERIs: atomoxetine, reboxetine
  - SSNRI: venlafaxine

NRI/NERI = norepinephrine reuptake inhibitor; SSNRI = selective serotonin and norepinephrine reuptake inhibitor.

Pitolisant: Symptoms After 12 Months of Treatment

Pitolisant is a highly potent, selective histamine H3-receptor antagonist/inverse agonist

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



Dauvilliers Y, et al; HARMONY III study group. *Sleep*. 2019;42:Epub ahead of print. FDA drug approvals (www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/ novel-drug-approvals-2019). Accessed 5/29/2020.

Agents Under Investigation

New forms of sodium oxybate
- Once-a-night formulation
- Low-sodium formulation

Modafinil augmentation
- Modafinil/flecainide (THN102)

GABA-A antagonists
- Clarithromycin
- Flumazenil
- Pentetrazol (BTD-001)

Norepinephrine reuptake inhibitor (NRI)
- Reboxetine

H3R inverse agonist
- SUVN-G3031

Orexin agonists
- TAK-925/944
- Mazindol

JZP-258: Low-Sodium Oxybate*

- At 6–9 g/night, sodium oxybate contributes 1100–1640 mg to daily sodium intake[1]
  - The American Heart Association recommends total daily sodium intake of <1500 mg as ideal and 2300 mg as the upper limit to maintain blood pressure and heart health[2]
- JZP-258 is a novel oxybate product with a unique composition of cations resulting in 92% less sodium than SXB[3]
  - JZP-258 and sodium oxybate contain the same active moiety, ie, oxybate
- NDA is currently with FDA undergoing priority review

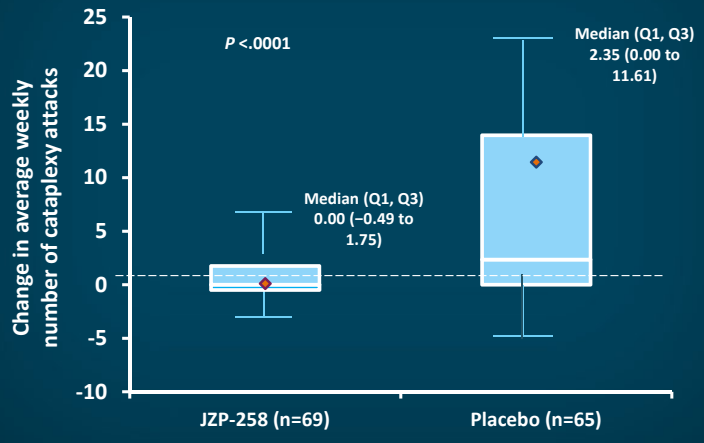
*This formulation is not currently approved by the FDA.

NDA = New Drug Application

Sodium oxybate (Xyrem®) PI 2018 (http://pp.jazzpharma.com/pi/xyrem.en.USPI.pdf). American Heart Association (www.heart.org/en/healthy-living/healthy-eating/eat-smart/sodium/how-much-sodium-should-i-eat-per-day). Jazz Pharmaceuticals press release, September 25, 2019 (www.prnewswire.com/news-releases/jazz-pharmaceuticals-presents-positive-jzp-258-phase-3-study-data-at-world-sleep-2019-300925650. html). Jazz Pharmaceuticals press release, March 25, 2020 (https://investor.jazzpharma.com/news-releases/news-release-details/jazz-pharmaceuticals-announces-fda-acceptance-new-drug). Accessed 5/29/2020.

Change in Weekly Number of Cataplexy Attacks With JZP-258*

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



*This formulation is not currently approved by the FDA.

Bogan RK, et al. World Sleep Meeting, Vancouver, September 2019. Unpublished data. Thorpy MJ. *CNS Drugs.* 2020;34:9-27.

Treatment-Emergent Adverse Events (TEAEs) With JZP-258*

TEAEs, n (%)	SXB Only (n = 52)	SXB + Other Anticataplectics (n = 23)	Other Anticataplectics (n = 36)	Anticataplectic Naïve (n = 90)	Total (N = 201)
Patients with ≥1 TEAE	31 (59.6)	20 (87.0)	30 (83.3)	72 (80.0)	153 (76.1)
Preferred term in ≥5% of total participants					
Headache	7 (13.5)	3 (13.0)	7 (19.4)	24 (26.7)	41 (20.4)
Nausea	2 (3.8)	1 (4.3)	7 (19.4)	16 (17.8)	26 (12.9)
Dizziness	1 (1.9)	1 (4.3)	6 (16.7)	13 (14.4)	21 (10.4)
Cataplexy†	0	11 (47.8)	6 (16.7)	3 (3.3)	20 (10.0)
Decreased appetite	0	1 (4.3)	2 (5.6)	12 (13.3)	15 (7.5)
Nasopharyngitis	2 (3.8)	1 (4.3)	5 (13.9)	7 (7.8)	15 (7.5)
Influenza	5 (9.6)	3 (13.0)	3 (8.3)	3 (3.3)	14 (7.0)
Diarrhea	4 (7.7)	0	0	7 (7.8)	11 (5.5)
Vomiting	1 (1.9)	0	4 (11.1)	5 (5.6)	10 (5.0)

Incidences of enuresis and somnambulism were low, ie, 3.5% and 2.0% of total participants, respectively.

During main study (OLOTTP, SDP, and DBRWP), excluding placebo data (main study safety population).
*This formulation is not currently approved by the FDA; † Worsening from baseline.
DBRWP = double-blind randomized withdrawal period; OLOTTP = open-label optimized treatment and titration period; SDP = stable-dose period.
Bogan RK, et al. World Sleep Meeting, Vancouver, September 2019.

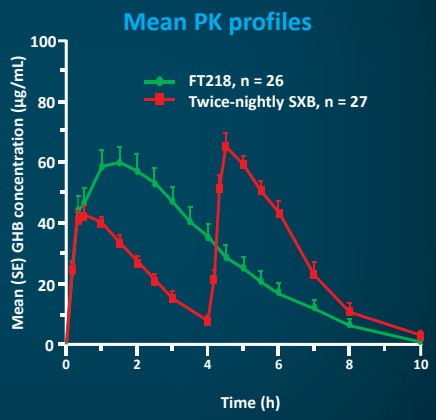
FT218: Once-Nightly Sodium Oxybate

- 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
- FT218 is an investigational controlled-release formulation of sodium oxybate intended for once-nightly dosing, using proprietary Micropump® technology

Sodium oxybate (Xyrem®) PI 2018 (http://pp.jazzpharma.com/pi/xyrem.en.USPI.pdf). Avadel Pharmaceuticals press release, January 10, 2018 (www.globenewswire.com/news-release/2018/01/10/1286580/0/en/ Avadel-Pharmaceuticals-Receives-Orphan-Drug-Designation-from-FDA-for-FT-218-for-the-Treatment-of-Narcolepsy.html. Accessed 5/30/2020.

Randomized, Cross-Over, 2-Period, 2-Sequence Study Comparing FT218* (6 gm) with Twice-Nightly Sodium Oxybate IR (3+3 gm)

- Main analysis
  - AUC of FT218 meets bioequivalence criteria compared with twice-nightly sodium oxybate IR
  - Cmax of FT218 is lower than overall Cmax of Twice-nightly sodium oxybate IR
- Post-hoc analysis
  - Morning plasma levels (C8h) of FT218 are similar to C8h of twice-nightly sodium oxybate IR.



*This formulation is not currently approved by the FDA

AUC = area under the curve; C_{max} = maximum concentration; C_{8h} = concentration 8 hours; PK = pharmacokinetic; GHB = gamma-hydroxybutyrate.

Thorpy MJ et al. *World Sleep* meeting, Vancouver 2019.

Antidepressants for Cataplexy

- Can be effective for cataplexy
- Norepinephrine reuptake inhibitors most effective, eg, venlafaxine, atomoxetine
- Can cause sexual side effects
- Can disturb nocturnal sleep
- Not effective for other REM phenomena, eg, SP, HH
- Not effective for sleepiness

SP = sleep paralysis; HH = hypnagogic hallucinations.

Reboxetine*

- A norepinephrine reuptake inhibitor
- In a phase 2 study was shown to be effective in reducing cataplexy and improving the ESS, as well as sleep quality
- The most commonly reported adverse events with reboxetine treatment were anxiety, constipation, and insomnia

*Not currently approved by the FDA.

Axsome Therapeutics press release, 12/3/19 (www.globenewswire.com/news-release/2019/12/03/1955366/0/en/Axsome-Therapeutics-Announces-AXS-12-Achieves-Primary-Endpoint-in-CONCERT-Phase-2-Trial-in-Narcolepsy.html). NCT03881852 (https://clinicaltrials.gov/ct2/show/NCT03881852?term=NCT03881852&draw=2&rank=1). Accessed 5/30/2020.

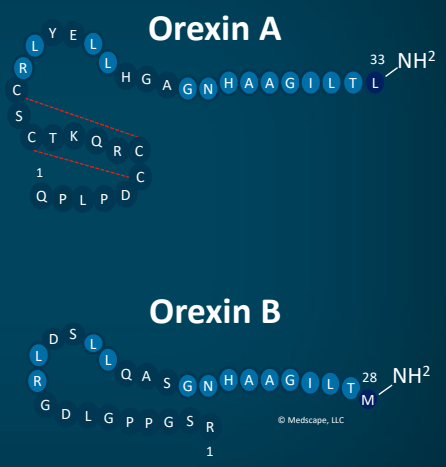
Orexin Treatment in Narcolepsy

- Orexin replacement
- Orexin gene therapy
- Orexin cell transplantation
- Orexin agonists

Nepovimova E, et al. *Med Res Rev*. 2019;39:961-975.

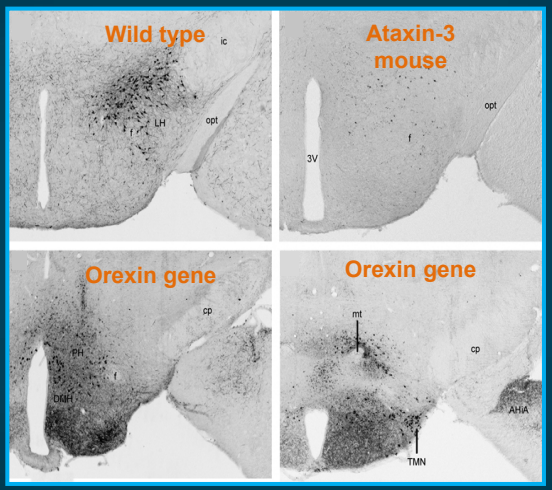
Orexin Replacement

- Orexin-A: low permeability to the blood-brain barrier
- Orexin-B: does not cross the blood-brain barrier
- Orexin-A more stable in the blood and CSF than orexin-B
- Orexin-A binds with 2 to 3 times affinity to OX_1R than to OX_2R
- Orexin-B binds with 10 times affinity to OX_2R than to OX_1R



Nepovimova E, et al. *Med Res Rev.* 2019;39:961-975. Scammell TE, et al. *Annu Rev Pharmacol Toxicol*. 2011;51:243-66.

Orexin Gene Therapy Restores Timing and Maintenance of Wakefulness in Narcoleptic Mice



ic = internal capsule; opt = optic tract; 3V = third ventricle; f = fornix; DMH = dorsomedial nucleus of hypothalamus; TMN = tuberomammillary nucleus; mt = mammillothalamic tract; cp = cerebral peduncle; AHiA = amygdalohippocampal area.

Kantor S, et al. *Sleep*. 2013;36:1129-1138.

TAK-925/TAK-994

TAK-925 (investigational)[1,2]

- Hypocretin/orexin 2 receptor-selective agonist
- Demonstrated improved wakefulness, reduced cataplexy-like episodes, and ameliorated weight gain in orexin/ataxin-3 transgenic mice model of narcolepsy
- The wake-promoting effect of TAK-925 was not diminished after 14 days sub-chronic administration
- Shown to be effective for EDS and cataplexy in a phase 1 study from Japan

TAK-994 (investigational)[3,4]

- Hypocretin/orexin 2 receptor-selective agonist (OX2R)
- Phase 2, double-blind RCT in USA of oral TAK-994 in patients with narcolepsy type 1 (NT1) and type 2 (NT2)

1. Kimura H, et al. *Sleep.* 2019;42(suppl 1):A23 (abstract 0055). 2. NCT03332784. https://clinicaltrials.gov/ct2/show/NCT033327843. 3. NCT04096560 (https://clinicaltrials.gov/ct2/show/NCT04096560). 4. Ishikawa T, et al. Biennial World Sleep Congress; 20–25 Sep 2019; Vancouver.

Case

- 21 year old single female clerk who presents with tiredness, fatigue and lethargy for the last 6 years getting more severe with time
- Bedtime: 11pm; out of bed: 7am; one nap after work for 30 mins
- Falls asleep rapidly but awakens after 2 hours for 10 minutes then several additional times during the night. She thinks she awakens to dreams which are frequent, vivid and sometimes frightening.
- She rarely has sleep paralysis on falling asleep, during the night and on awakening
- No cataplexy

Case (continued)

- She has mild anxiety and feels a little depressed because her social life is limited due to the fatigue and tiredness
- Sexually active and on oral contraceptives
- Was put on methylphenidate 20mg ER by her PCP but it makes her irritable and anxious, with mild tachycardia and headaches
- Her ESS was 16/24
- PSG: SL - 12 mins; RL - 15 mins; AHI 1.0/hr; Lo2 Sat 91%
- MSLT: 2.3 mins, 2 SOREMPs

Case: Discussion

- What is your diagnosis?

- Was is your treatment plan?

Conclusion

- EDS is present in all patients with narcolepsy and most patients with OSA
- Despite adequate treatment of OSA, residual sleepiness is common
- According to AASM guidelines released in 2007:
  - Modafinil, armodafinil and sodium oxybate are considered standard treatment for EDS associated with narcolepsy
  - Stimulants, methylphenidate, and amphetamines are alternatives
- Solriamfetol was recently approved for treating excessive sleepiness in narcolepsy and OSA
- Pitolisant has been approved for the treatment of excessive sleepiness in narcolepsy
- New low-sodium and once-nightly formulations of sodium oxybate may be approved for narcolepsy in the near future
- Reboxetine (NERI) and TAK-994 (hypocretin/orexin 2 receptor-selective agonist) are being studied for the treatment of EDS and cataplexy in patients with narcolepsy

Thank You!

Excessive Daytime Sleepiness in Narcolepsy and Obstructive Sleep Apnea: Diagnosis and Management Resources

Resource	Address
Barateau L, et al. Recent Advances in Treatment for Narcolepsy. *Ther Adv Neurol Disord*. 2019;12:1756286419875622.	https://pubmed.ncbi.nlm.nih.gov/31632459/
Berger M, et al. Risk Factors of Excessive Daytime Sleepiness in a Prospective Population-Based Cohort. *J Sleep Res*. 2020 May 15;e13069.	https://pubmed.ncbi.nlm.nih.gov/32412149/
Berkowski J, et al. Disorders of Excessive Daytime Sleepiness Including Narcolepsy and Idiopathic Hypersomnia. *Sleep Med Clin* 2016;11(3):365-78.	https://pubmed.ncbi.nlm.nih.gov/27542882/
Bhattarai J, et al. Current and Future Treatment Options for Narcolepsy: A Review. *Sleep Sci*. 2017;10(1): 19–27.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5611768/
Dauvilliers Y, et al. Long-term Use of Pitolisant to Treat Patients With Narcolepsy: Harmony III Study. *Sleep*. 2019;42(11):174.	https://pubmed.ncbi.nlm.nih.gov/31529094/
Dauvilliers Y, et al. Pitolisant for Daytime Sleepiness in Patients With Obstructive Sleep Apnea Who Refuse Continuous Positive Airway Pressure Treatment. A Randomized Trial. *Am J Respir Crit Care Med*. 2020;201(9):1135-45.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7193861/
Leger D, et al. The Economic and Societal Burden of Excessive Daytime Sleepiness in Patients With Obstructive Sleep Apnea. *Sleep Med Rev.* 2020;51:101275.	https://pubmed.ncbi.nlm.nih.gov/32169792/
Mahoney C, et al. The Neurobiological Basis of Narcolepsy. *Nat Rev Neurosci*. 2019;20(2):83-93.	https://pubmed.ncbi.nlm.nih.gov/30546103/
Roth T. Effects of Excessive Daytime Sleepiness and Fatigue on Overall Health and Cognitive Function. *J Clin Psychiatry*. 2015;76(9):e1145.	https://pubmed.ncbi.nlm.nih.gov/26455683/
Schweitzer P, et al. Solriamfetol for Excessive Sleepiness in Obstructive Sleep Apnea (TONES 3). A Randomized Controlled Trial.	https://pubmed.ncbi.nlm.nih.gov/30521757/

Am J Respir Crit Care Med. 2019;199(11):1421-31.	
Smith S, et al. Multiple Dimensions of Excessive Daytime Sleepiness. *J Thorac Dis*. 2018;10(Suppl 1):S170-S176.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5803055/
Thorarinsdottir E, et al. Definition of Excessive Daytime Sleepiness in the General Population: Feeling Sleepy Relates Better to Sleep-Related Symptoms and Quality of Life Than the Epworth Sleepiness Scale Score. Results From an Epidemiological Study. *J Sleep Res*. 2019;28(6):e12852.	https://pubmed.ncbi.nlm.nih.gov/30968492/
Thorpy M, et al. A Randomized Study of Solriamfetol for Excessive Sleepiness in Narcolepsy. *Ann Neurol*. 2019;85(3):359-70.	https://pubmed.ncbi.nlm.nih.gov/30694576/
Thorpy M, et al. Clinical and Practical Considerations in the Pharmacologic Management of Narcolepsy. *Sleep Med.* 2015;16(1):9-18.	https://pubmed.ncbi.nlm.nih.gov/25458251/
Thorpy M, et al. Delayed Diagnosis of Narcolepsy: Characterization and Impact *Sleep Med*. 2014;15(5):502-7.	https://pubmed.ncbi.nlm.nih.gov/24780133/

Resources and Societies

Resource	Address
American Academy of Neurology	https://www.aan.com/
American Academy of Sleep Medicine	https://aasm.org/
American Sleep Association	https://www.sleepassociation.org/
National Center on Sleep Disorders Research	https://www.nhlbi.nih.gov/about/divisions/division-lung-diseases/national-center-sleep-disorders-research
Sleep Foundation	https://www.sleepfoundation.org/
Sleep Research Society	https://www.sleepresearchsociety.org/
World Sleep Society	https://worldsleepsociety.org/