Psych Congress Elevate | VIRTUAL EXPERIENCE

Awareness, Diagnosis, and Novel Treatment of Excessive Daytime Sleepiness in Patients with Psychiatric Disorders

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This activity has been supported through an independent educational grant from Jazz Pharmaceuticals, Inc.

Faculty Disclosure

- **Karl Doghramji, MD:** Consultant—Eisai Co., Ltd., Imbrium, Inspire, Harmony Biosciences, Jazz Pharmaceuticals, Purdue Pharma LP; Grant/Research Support—Inspire, Nyxoah; Major Share Stockholder—Merck & Co.

- **Saoirse Owens, CRNP** has no financial relationships to disclose relating to the subject matter of this presentation.

Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
  - Dr. Doghramji will be discussing off-label and investigational use of drugs in the presentation and will identify those issues.

- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

- This activity has been independently reviewed for balance.

Learning Objectives

- Outline the prevalence of excessive daytime sleepiness (EDS) in psychiatric populations, its various causes, and its implications for patient outcomes
- Apply EDS diagnostic tools and testing modalities appropriately for improved recognition in patients with psychiatric disorders
- Analyze available and emerging agents for the treatment of EDS and their optimal use in patients with psychiatric disorders

Excessive Daytime Sleepiness in Patients with Psychiatric Disorders

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Excessive Daytime Sleepiness

- ***Fatigue***: Sensation of weariness, tiredness, exhaustion, loss of energy; the desire to rest
- ***Sleepiness***: Increased likelihood of falling asleep
  - A normal biologic need or drive; sleep is to sleepiness as food is to hunger
- ***Hypersomnia***: Prolonged sleep times
- ***Excessive daytime sleepiness***: Sleepiness that occurs in a situation when an individual would usually be expected to be awake and alert

Impact of Excessive Daytime Sleepiness

- Slower response time
- Instability of attention
- Rapid deterioration of performance
- Cognitive slowing on subject-paced tasks
- Increased cognitive errors with increased time pressure
- Decline in both short-term recall and working memory performance
- Reduced learning (acquisition) of cognitive tasks
- Depression
- Diminished motivation
- Hypoxemia
- Insulin resistance
- Impaired immune function
- Elevated sympathetic activity

Lockley SW, et al. *N Engl J Med*. 2004;351(18):1829-1837. Zohar D, et al. *Sleep*. 2005;28(1):47-54. Philibert I. *Sleep*. 2005;28(11):1392-1402. Banks S, et al. *J Clin Sleep Med*. 2007;3(5):519-528. Hall MH, et al. *Sleep*. 2017;40(1):zsw003. Bhatia R, et al. Examining excessive daytime sleepiness in psychiatric patients. *Current Psychiatry*. 2017;16(7):27-32.

What Causes Excessive Daytime Sleepiness?

Sleep Disorders

- Insufficient sleep syndrome
- Circadian rhythm sleep disorders
- Sleep apnea syndrome, ie, OSA
- Narcolepsy

Neurological Disorders

- Epilepsy
- Dementia
- Parkinson's disease
- Multiple sclerosis
- Myotonic dystrophies
- Fibromyalgia

Psychiatric Disorders

- Depression
- Bipolar disorder
- Anxiety
- PTSD
- Schizophrenia
- Alcoholism

OSA = obstructive sleep apnea.

Doghramji K. In: Stoudemire A, ed. *Clinical Psychiatry for Medical Students*. Second Edition. Lippincott Williams & Wilkins; 1994:627-655. Krystal AD. *Neurol Clin*. 2012;30(4):1389-1413. Maestri M, et al. *Sleep Breath*. 2020;24(2):413-424.

Excessive Daytime Sleepiness and Psychiatric Disorders

Depression (MDD)	• Sleep difficulty occurs in up to 90% of those with MDD • Hypersomnia is seen in 30% of those with MDD and 50% of those with SAD
Bipolar Disorder	• Manic phase: Decreased need for sleep • Depressed phase: Hypersomnia
Anxiety (GAD)	• > 50% experience sleep difficulties and daytime fatigue
PTSD	• Difficulty initiating and maintaining sleep, nightmares, leading to daytime fatigue
Schizophrenia	• Shifts in circadian rhythm, 15% at risk for SDB
Alcoholism	• Poor sleep quality, EDS

GAD = generalized anxiety disorder; MDD = major depressive disorder; PTSD = posttraumatic stress disorder; SAD = seasonal affective disorder; SDB = sleep disordered breathing.

Krystal AD. *Neurol Clin*. 2012;30(4):1389-1413.

Hypersomnia Associated with a Psychiatric Disorder

ICSD-3 Criteria

1) Daytime sleepiness for at least 3 months

2) A concurrent psychiatric disorder

3) Sleepiness is not better explained by another untreated sleep, medical, or neurological disorder or from the effects of medication

HAPD accounts for 5%–7% of hypersomnia cases

Women > Men

Age of onset: 20–50 years

Those with insomnia and hypersomnia are 10× more likely to have MDD

Severe sleep disturbances often occur prior to episodes of acute psychotic decompensation in those with schizophrenia

ICSD-3 = *International Classification of Sleep Disorders, Third Edition*.

Berry RB, et al. *Sleep Medicine Pearls*. Third Edition. Saunders; 2015.

Key Learning Point

Sleep difficulties are encountered in up to 90% of patients with MDD and 30% of patients with MDD have hypersomnia.

Evaluation and Management of Excessive Daytime Sleepiness in the Psychiatric Setting

Systematically evaluate and screen for underlying conditions

- Sleep logs
- Epworth Sleepiness Scale, Stanford Sleepiness Scale
- STOP-BANG
- Comprehensive health history

Utilize good sleep hygiene measures

- Behavioral strategies

Treat the specific disorder whenever possible

- Pharmacologic agents

Consider direct management

Sleepiness Scales

Epworth Sleepiness Scale

Situation	Chance of Dozing			
Sitting and reading	0	1	2	3
Watching television	0	1	2	3
Sitting inactive in a public place (eg, a theater or a meeting)	0	1	2	3
As a passenger in a car for an hour without a break	0	1	2	3
Lying down to rest in the afternoon when circumstances permit	0	1	2	3
Sitting and talking to someone	0	1	2	3
Sitting quietly after a lunch without alcohol	0	1	2	3
In a car, while stopped for a few minutes in traffic	0	1	2	3

Stanford Sleepiness Scale

Degree of Sleepiness	Scale Rating
Feeling active, vital, alert, or wide awake	1
Functioning at high levels, but not fully alert	2
Awake, but relaxed; responsive but not fully alert	3
Somewhat foggy, let down	4
Foggy; losing interest in remaining awake; slowed down	5
Sleepy, woozy, fighting sleep; prefer to lie down	6
No longer fight sleep, sleep onset soon; having dream-like thoughts	7
Asleep	X

Johns MW. *Sleep*. 1991;14(6):540-545. Hoddes E, et al. The development and use of the Stanford Sleepiness Scale (SSS). *Psychophysiology*. 1972;9:150.

STOP-BANG

- Risk factors of OSA
  - **S**: Snoring?
  - **T**: Tired? (daytime fatigue, sleepiness)
  - **O**: Observed? (stopping breathing, choking, gasping)
  - **P**: Pressure? (high blood pressure)
  - **B**: BMI > 35?
  - **A**: Age > 50?
  - **N**: Neck size large? (Men > 16 inches; Women > 15 inches)
  - **G**: Gender = male?
- Scoring: Risk for OSA
  - **Low**: 0–2; **Intermediate**: 3–4; **High**: 5–8

BMI = body mass index.

Chung F, et al. *Anesthesiology*. 2008;108(5):812-821. Nagappa M, et al. *PLoS One*. 2015;10(12):e0143697.

Case #1: *Emily*

Emily

23-year-old female presents to psychiatrist/MHP with c/o excessive daytime sleepiness ongoing since high school. She is now in medical school and the sleepiness is becoming increasingly difficult to tolerate/accommodate, adding to her stress.

She is told she snores and is an active sleeper. She often wakes entangled in her sheets. Nighttime sleep is rarely, if ever, refreshing regardless of how many hours she sleeps (TST varies between 8–12 hours/day). She naps whenever she can, which does seem to help but her schedule does not always permit. Naps are refreshing and accompanied by vivid dreaming.

She falls asleep during sedentary activities such as lectures and even speaking with friends. Her struggle to stay awake during lectures and studying is not only upsetting but embarrassing. She drinks many cups of coffee or other energy beverages throughout the day but the effect of these seems to be waning over time.

Since high school, she has gradually gained weight, with her BMI now measured at 30. She reports decreased energy, decreased ability and desire to exercise and to socialize with friends, overwhelming feeling of fatigue, decreased concentration and memory for schoolwork, and inexplicable weight gain and increased appetite.

She denies h/o cataplexy, witnessed apneas, morning headaches, parasomnias (ie, sleep walking, RLS, etc.), anemia, thyroid d/o.

Her psychiatrist/MHP placed her on sertraline, but this does not seem to have adequately helped.

MHP = mental health professional; TST = total sleep time; RLS = restless legs syndrome.

Emily

Caffeine: 3–4 cups of coffee/day, 1–2 energy drinks/week, no soda
ETOH: 1–2 glasses of wine daily with dinner
Recreational drugs: Never
Tobacco: Never

Sleep Routine	
Bedtime	9 PM to 1 AM, reads and watches TV prior to bedtime
Sleep Latency	< 10 minutes
Awakenings	3–5 brief awakenings, lasting < 15 minutes
Awake and OOB	6 AM on school days, noon on weekends
Naps	1–2×/day (20–30 minutes each), accompanied by vivid dreaming

ESS: 18
SSS: 5
STOP-BANG score: 2

Labs including TSH: WNL
Medications: Sertraline 100 mg daily, Fexofenadine 180 mg as needed, Levonorgestrel-releasing IUD
Vital signs WNL
Mental status exam: WN WD in NAD. Poor eye contact. Psychomotor retardation, thought processes goal oriented, no HS ideation, sensorium clear. Affect appears despondent, mood “very tired”, “low all the time”

DDx: EDS associated with depression, OSA, narcolepsy, idiopathic hypersomnia, impaired sleep hygiene, hypersomnia r/t medication use

Assessment and Plan

- ✓ Continue sertraline (may need to adjust dosage/re-evaluate over time)
- ✓ Limit caffeine intake and avoid caffeine past 1 PM daily
- ✓ Encouraged to limit alcohol intake (eliminate if able)
- ✓ Advised to keep a strict sleep wake routine and allow for at least 8 hours of bedtime a night
- ✓ Avoid electronics in bed/bedroom
- ✓ May incorporate cat naps 20–30 minutes throughout the day as able. Avoid longer naps

Identification of Excessive Daytime Sleepiness in Patients with Narcolepsy and Psychiatric Disorders

DSM-5 Diagnostic Criteria for Narcolepsy

Recurrent, irrepressible sleep > 3×/week over 3 months

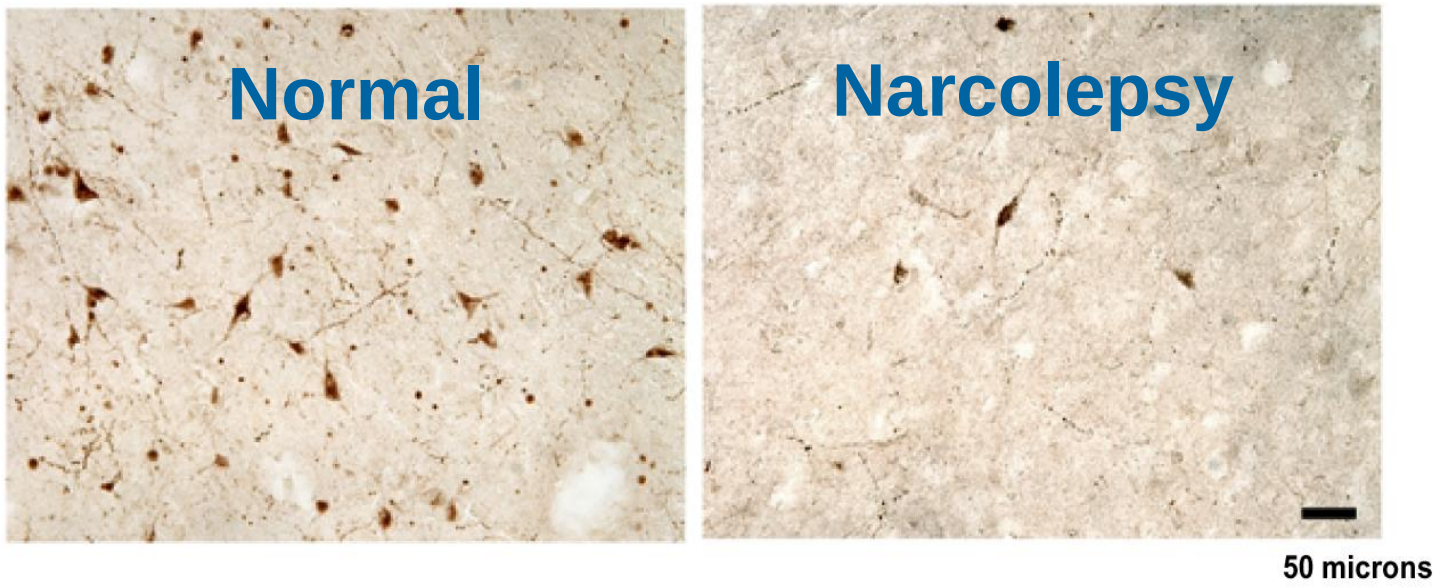
The presence of at least one:

- Cataplexy, a few times per month
- Hypocretin deficiency
- Nocturnal sleep polysomnography REM latency < 15 minutes or MSLT mean sleep latency < 8 minutes and two SOREMs

MSLT = Multiple Sleep Latency Test; SOREM = sleep onset rapid eye movement.

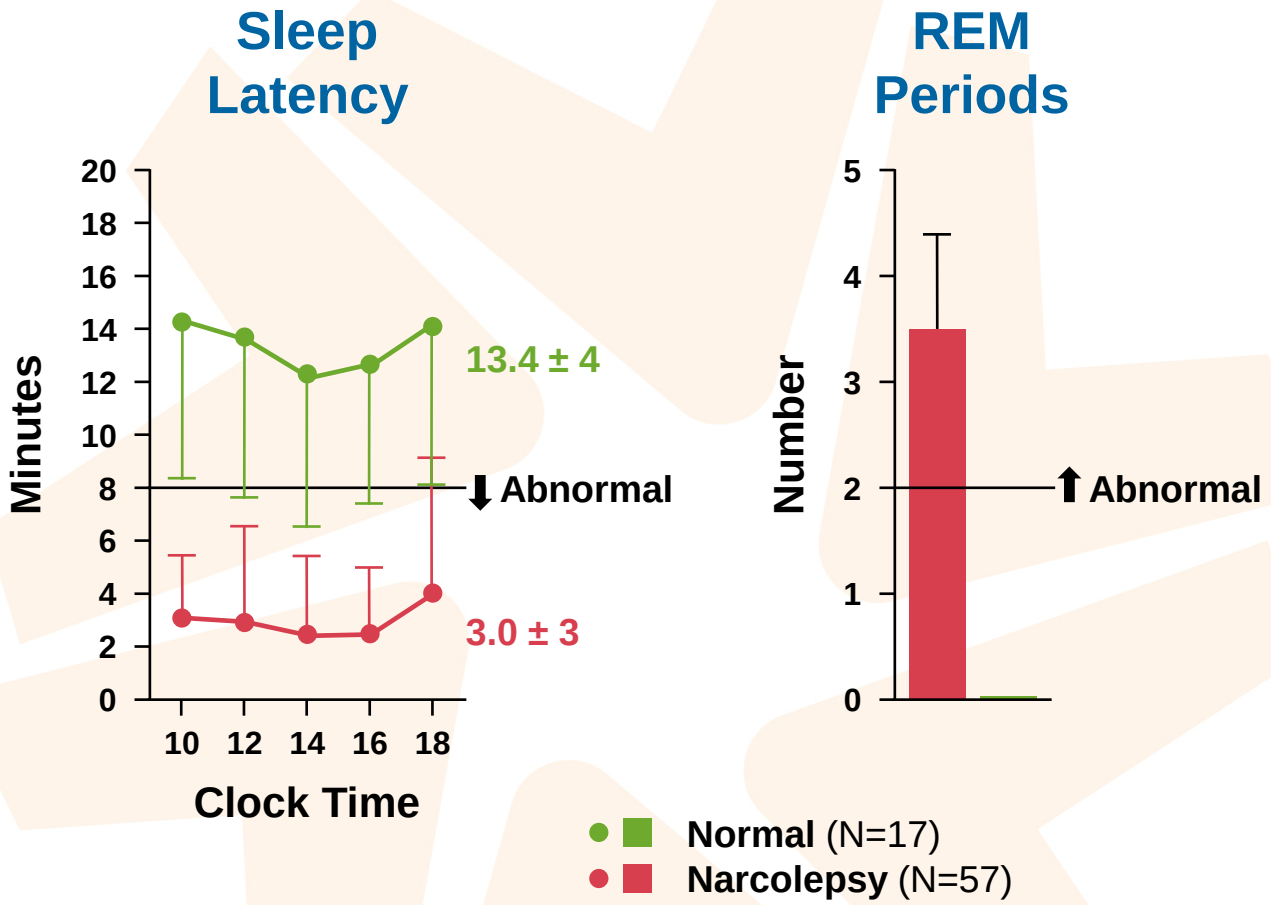
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. American Psychiatric Association Publishing; 2013.

Hypocretin/Orexin Cell Loss in Human Narcolepsy



Thannickal TC, et al. *Neuron*. 2000;27(3):469-474.

Diagnosis of Narcolepsy: Multiple Sleep Latency Test



Adapted from: Mitler MM, et al. *Psychiatr Clin North Am*. 1987;10(4):593-606.

Narcolepsy: Clinical Presentation

- **Excessive daytime sleepiness**
  - Prolonged daytime sleepiness
  - Voluntary naps
  - Involuntary sleep episodes (sleep attacks)
  - Automatic behavior, microsleep episodes

- **REM-related phenomena**
  - Cataplexy in 60%
  - Hypnagogic hallucinations in 67%
  - Sleep paralysis in 64%

- Disturbed nocturnal sleep

REM = rapid eye movement.

Moturi S, et al. *Psychiatry*. 2009;6(6):38-44.

Symptoms of Narcolepsy Can Be Confused with Other Disorders

Narcolepsy Symptom	Mimics
• Cataplexy	• TIA, syncope, akinetic seizure
• Hypnagogic hallucination	• Dreaming, nightmares, psychotic hallucinations
• Sleep paralysis	• Nocturnal panic, TIA, recurrent sleep paralysis
• Sleep disruption	• Insomnia

TIA = transient ischemic attack.

Psychiatric Comorbidity is Highly Prevalent in Narcolepsy

CCS Level 2 Category	Control (N=46,559) n (%)	Narcolepsy (N=9312) n (%)	*P*	OR (95% CI)
Anxiety disorders	5554 (11.9)	2333 (25.1)	<.0001	2.5 (2.4, 2.7)
Mood disorders	6407 (13.8)	3525 (37.9)	<.0001	4.0 (3.8, 4.2)

***P*: Conditional Chi-square test; accounts for matching.**
CCS = Clinical Classification System.
Ruoff CM, et al. *J Clin Psychiatry*. 2017;78(2):171-176.

Management of Excessive Daytime Sleepiness in Patients with Narcolepsy and Psychiatric Disorders

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Reduction of Excessive Daytime Sleepiness: *Alerting Medications*

Medication	Mechanism of Action	FDA Indication
Caffeine	Adenosine receptor antagonist	Not FDA-approved to treat EDS associated with narcolepsy
Methylphenidate, amphetamines	Sympathomimetic; enhance neurotransmission of dopamine, norepinephrine, serotonin	Narcolepsy
Modafinil, armodafinil	Dopamine reuptake inhibitor	Excessive sleepiness associated with narcolepsy, OSA, or SWD (adult patients)
Sodium oxybate Low-sodium oxybate (calcium, magnesium, potassium, and sodium oxybates)	$GABA_B$ agonist	Cataplexy or EDS in patients ≥ 7 years of age with narcolepsy
Solriamfetol	Dopamine–norepinephrine reuptake inhibitor	EDS associated with narcolepsy or OSA (adult patients)
Pitolisant	Histamine H_3 antagonist/inverse agonist	EDS or cataplexy in adult patients with narcolepsy
TAK-925	Hypocretin receptor agonist	Investigational; not FDA-approved for any indication

SWD = shift work disorder.

US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/.
Aldosari MS, et al. *Sleep Breath*. 2020;24(4):1675-1684. ClinicalTrials.gov Identifier: NCT03332784; NCT03748979.

Medications for Cataplexy

Sodium oxybate

Low-sodium oxybate (calcium, magnesium, potassium, and sodium oxybates)

Pitolisant

Antidepressants*

- TCAs: clomipramine, protriptyline
- SSRIs: fluoxetine, paroxetine
- NERIs: venlafaxine, atomoxetine, reboxetine

***FDA approved for other conditions; used off-label for cataplexy associated with narcolepsy.**
TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor; NERI = norepinephrine reuptake inhibitor.
PDR. 2021. Morgenthaler TI, et al. *Sleep*. 2007;30(12):1705-1711. Romigi A, et al. *Drug Des Devel Ther*. 2018;12:2665-2675.

Low-Sodium Oxybate

$GABA_B$ agonist—Schedule III

Approved for cataplexy or EDS in patients ≥ 7 years of age with narcolepsy

Dose

- Initiate dosage at 4.5 gm/night orally, divided into 2 doses
- Titrate to effect in increments of up to 1.5 gm/night/week
- Recommended dosage range: 6–9 gm/night orally

Adverse reactions in adults (≥ 5%): headache, nausea, dizziness, decreased appetite, parasomnia, diarrhea, hyperhidrosis, anxiety, and vomiting

At 6–9 gm/night, sodium oxybate contributes 1100–1640 mg to daily sodium intake

- 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

Novel oxybate product with a unique composition of cations resulting in 92% less sodium than sodium oxybate

- Low-sodium oxybate and sodium oxybate contain the same active moiety, ie, oxybate

US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/. American Heart Association. How much sodium should I eat per day? Accessed May 26, 2021. www.heart.org/en/healthy-living/healthy-eating/eat-smart/sodium/how-much-sodium-should-i-eat-per-day.

Pitolisant

H_3 antagonist/inverse agonist

Approved for adult patients with EDS or cataplexy

Dosage range 17.8–35.6 mg daily

- **Week 1**: 8.9 mg OD; **Week 2**: 17.8 mg OD; **Week 3**: May increase to 35.6 mg OD

Increases in QT interval. Avoid other drugs that increase the QT interval, monitor patients with hepatic or renal impairment for increased QTc

Adverse reactions (≥ 5% and 2× placebo): insomnia, nausea, anxiety

May reduce effectiveness of sensitive CYP3A4 substrates. Use an alternative non-hormonal contraceptive method during treatment

US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/.

Solriamfetol

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

Can be taken with/without food on awakening	Half-life 7 hours, T_{max} 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

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

Thorpy MJ, et al. *Ann Neurol*. 2019;85(3):359-370.

US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/.

Novel Treatments: *Clinical Data Review*

12-week randomized, double-blind, placebo-controlled, Phase 3 trial of solriamfetol for EDS in narcolepsy	• Solriamfetol was effective in treating EDS in participants with narcolepsy with or without cataplexy.
Open-label, single-arm, pragmatic study, recruited adult patients with narcolepsy and ESS score ≥12. After a titration period, patients were treated for up to 1 year with oral pitolisant once-a-day at up to 40 mg. Concomitant stimulants and anti-cataplectic agents were allowed.	• Two-thirds of patients completing the treatment were responders (ESS ≤ 10 or ESS decrease ≥ 3), and one-third had normalized ESS (≤ 10). Complete and partial cataplexy, hallucinations, sleep paralysis, and sleep attacks were reduced by 76%, 65%, 54%, 63%, and 27%, respectively.
≤ 30-day screening period; a 12-week, open-label, optimized treatment and titration period to transition to LXB from previous medications for the treatment of cataplexy; a 2-week SDP; a 2-week, DBRWP; and a 2-week safety follow-up. During DBRWP, participants were randomized 1:1 to placebo or to continue LXB treatment.	• Adults aged 18–70 years with narcolepsy with cataplexy were eligible. • Statistically significant worsening of symptoms was observed in participants randomized to placebo, with median change in weekly number of cataplexy attacks from SDP to DBRWP in the placebo group vs the LXB group (*P*<.0001), and median change in ESS score of 2.0 in the placebo group vs 0.0 in the LXB group.

DBRWP = double-blind, randomized withdrawal period; LXB = low-sodium oxybate; SDP = stable-dose period;

Dauvilliers Y, et al. *CNS Drugs*. 2020;34(7):773-784. Dauvilliers Y, et al. *Sleep*. 2019;42(11):zsz174. Bogan RK, et al. *Sleep*. 2021;44(3):zsaa206.

Key Learning Point

Novel wake-promoting agents available for the treatment of EDS include low-sodium oxybate ($GABA_B$ agonist), pitolisant (H_3 antagonist/inverse agonist), and solriamfetol (dopamine–norepinephrine reuptake inhibitor).

Emily
Follow-up 1

Returns after 4 weeks; has adhered to behavioral recommendations

Sleepiness has not improved; in fact, it has been steadily worsening and mood disturbance is worsening; reports feeling more depressed

She now reports episodes of sleep paralysis during vivid and frightening dreams while asleep

Referred for sleep testing

Undergoes nocturnal PSG and daytime MSLT:

PSG reveals no diagnostic abnormalities, but shows multiple awakenings and a reduced REM latency of 50 minutes

MSLT reveals a mean sleep latency of 4.5 minutes and 3 sleep onset REM episodes

Narcolepsy type 2 is diagnosed, and she is treated with a wake-promoting agent

MSLT = multiple sleep latency test; PSG = polysomnography.

Emily

Follow-up 2

Reports significant reduction in symptoms

- Focus and concentration have improved
- Able to stay awake all day long without impairment in daily activities
- Now napping only once per day, usually in afternoon, for 15 minutes
- MSE reveals that she is more animated, eye contact improved, affective modulation WNL

Case #2: *Charles*

Charles

56-year-old male presents with c/o of reduced motivation and energy gradually worsening over the past year, since he began working remotely from home as a result of the COVID-19 pandemic restrictions.

He spends most of his time either in bed or on the couch. He feels constantly sleepy but his ability to sleep seems to fluctuate, sleeping 10 or more hours some nights and 5 to 6 hours on other nights.

His focus and work performance have deteriorated, and he admits to calling out of work more often. His wife complains he is not helping around the house and berates him for being lazy, which makes him feel bad/guilty.

He no longer exercises and says he is ashamed of the weight he has put on. Some nights his wife sleeps in a different room as, she says, his snoring can disrupt her sleep.

Despite having received both COVID-19 vaccinations, he remains reluctant to leave his home for fear of contracting the virus. He has little interest in spending time with friends and often cancels when plans have been made.

A few months ago, his psychiatrist/MHP placed him on bupropion and suggested he try melatonin 3 mg on the nights he cannot sleep. Bupropion seems to have helped a little, but the melatonin is “useless.” He says he is “tired of feeling tired.”

Denies suicidal ideation or desire to self-harm. No h/o cataplexy or sleep paralysis. No witnessed apneas, morning headaches, or muscle aches. No h/o of parasomnias or RLS.

Charles

Caffeine: 1 cup in the morning, 2 cups when he has to work
ETOH: 2–6 beers a sitting, typically on weekends (Friday–Sunday)
Recreational drugs: Never
Tobacco: Never

Sleep Routine	
Bedtime	After dinner around 7–8 PM
Sleep Latency	Varies (watches TV) – 30 minutes to 2 hours
Awakenings	1–3 short awakenings
Awake and OOB	5–6 AM wakes, may linger in bed for about 1 hour
Naps	Dozes throughout the day (estimates 15–30 minutes 2–4×/day), couple of times a week he may nap as long as 2 hours

ESS:12
SSS: 4
STOP-BANG: 3

Labs including TSH: WNL
Medications: Bupropion, Amlodipine, Simvastatin, fish oil, coenzyme Q10, and melatonin as needed
Vital signs WNL
Mental status exam: Well nourished, but unkempt/disheveled appearance. NAD. Poor eye contact. Psychomotor retardation, thought processes goal oriented, no HS ideation, sensorium clear. Affect appears despondent, mood “very tired”, “low all the time”

DDx: Depression, anxiety, poor sleep hygiene, EDS, sleep-disordered breathing (snoring vs OSA)

Assessment and Plan

- ✓ Continue bupropion
- ✓ He is encouraged to exercise, preferably outside during daylight hours (Zeitgebers)
- ✓ Limit caffeine and ETOH intake, if not avoid
- ✓ Sleep hygiene
  - Advised to avoid daytime napping and keep a strict sleep wake routine. He should keep a consistent wake time of his choosing and allow for 7 to 8 hours of sleep opportunity. He should not get into bed prior to feeling tired and ready to sleep. He should avoid use of any and all electronics in the bedroom.
- ✓ HST to eval for OSA – if HST is positive for OSA – will treat with PAP therapy
- ✓ If EDS persists despite above measures, consider wake-promoting agent

HST = home sleep test; PAP = positive airway pressure therapy.

Clinical Profile of the Patient with OSA

Most Common Symptoms

- EDS, fatigue
- Restless sleep, insomnia
- Snoring

Additional Symptoms

- Memory impairment, altered attention
- Irritability, depression
- AM headache
- Decreased libido
- Obesity
- Refractory hypertension
- Gastroesophageal reflux
- Nocturia
- Cardiac dysrhythmias and nocturnal angina

Engleman HM, et al. *Thorax*. 2004;59(7):618-622. Gasa M, et al. *J Sleep Res*. 2013;22(4):389-397. Kryger MH, et al., eds. *Principles and Practice of Sleep Medicine*. Fifth Edition. Elsevier Saunders; 2011

Management of Residual EDS in OSA

Optimize PAP adherence

- Minimum adherence generally regarded as PAP use ≥ 4 hours/night for ≥ 70% of days over a 30-day period
- Greater adherence rates are related to lower residual EDS

Consider treatment alternatives for OSA

Ensure proper adherence to sleep hygiene habits

Treat comorbid causes of EDS

For residual sleepiness despite above

- Modafinil
- Armodafinil
- Solriamfetol

PAP = positive airway pressure.

Kribbs NB, et al. *Am Rev Respir Dis*. 1993;147(4):887-895. Gasa M, et al. *J Sleep Res*. 2013;22(4):389-397. Ballard RD. *J Fam Pract*. 2008;57(8 Suppl):S24-S30. Garnock-Jones KP, et al. *CNS Drugs*. 2009;23(9):793-803. Black JE, et al. *J Clin Sleep Med*. 2010;6(5):458-466.

OSA: *Clinical Data Review*

Meta-analysis of modafinil and armodafinil for residual EDS in OSA, 6 studies (N=1479 participants); 3 evaluated modafinil, and 3 armodafinil	• When compared with placebo, wakefulness promoting agents decreased ESS by 2.51 points (95% CI, 2.00–3.02), increased sleep latency in MWT by 2.73 minutes (95% CI, 2.12–3.34), increased the reporting of minimal improvement on the CGIC by 26% (RR 1.59; 95% CI, 1.36–1.86), and increased the risk of headaches by 8% (RR 1.98; 95% CI, 1.48–2.63).
Double-blind, randomized, placebo-controlled, parallel-group, 12-week trial comparing solriamfetol, 37.5, 75, 150, and 300 mg, with placebo; EDS in OSA (TONES 3)	• Co-primary endpoints (MWT sleep latency and ESS score) were met at all solriamfetol doses ($P<.05$), with dose-dependent effects observed at Week 1 maintained over the study duration. All doses except 37.5 mg resulted in higher percentages of participants reporting improvement on PGIC (key secondary endpoint; $P<.05$).
Meta-analysis of solriamfetol for EDS in OSA and narcolepsy; 8 articles reported from 6 clinical trials; pooled outcome measures from 5 trials	• The overall mean difference for MWT was 9.93 minutes (95% CI: 8.25–11.61), and the mean difference of ESS score was -4.44 (95% CI: -5.50 to -3.38), both in favor of solriamfetol over placebo. The overall risk ratio of adverse events with solriamfetol was 1.47 (95% CI: 1.28–1.69).

MWT = Maintenance of Wakefulness Test; CGIC = Clinical Global Impression of Change; PGIC = Patient Global Impression of Change.

Sukhal S, et al. *J Clin Sleep Med*. 2015;11(10):1179-1186. Schweitzer PK, et al. *Am J Respir Crit Care Med*. 2019;199(11):1421-1431. Subedi R, et al. *Sleep Med*. 2020;75:510-521.

Charles

Follow-up Appointments

- Returns after 4 weeks
- Has adhered to behavioral recommendations
- Feeling mildly more active during the day and sleep less interrupted at night. However, daytime sleepiness still interfering with ability to function during the day. Mood low
- HST reveals AHI of 23 and lowest SaO2 of 88%, confirming moderate OSA
- Psychiatrist/MHP, who is also a sleep specialist, starts management with CPAP
- Patient returns after 6 weeks. Interrogation of PAP machine reveals 90% compliance plus AHI of 2
- Wife reports snoring dissipated. However, patient remains sleepy
- Consider starting wake-promoting agent

AHI = apnea-hypopnea index; CPAP = continuous positive airway pressure.

Conclusion

- EDS, hypersomnia, and fatigue are commonly encountered in psychiatric disorders and are associated with significant impairment
- A systematic evaluation of EDS is important to uncover sleep disorders that may be treated directly
- Novel wake-promoting agents for the treatment of EDS in narcolepsy with or without cataplexy and OSA are available
- Mental health professionals have an opportunity to uncover and address EDS associated with narcolepsy and OSA in their patients

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Q&A