CMEO
BriefCase

Choosing and Optimizing Therapy in Narcolepsy

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Learning Objective

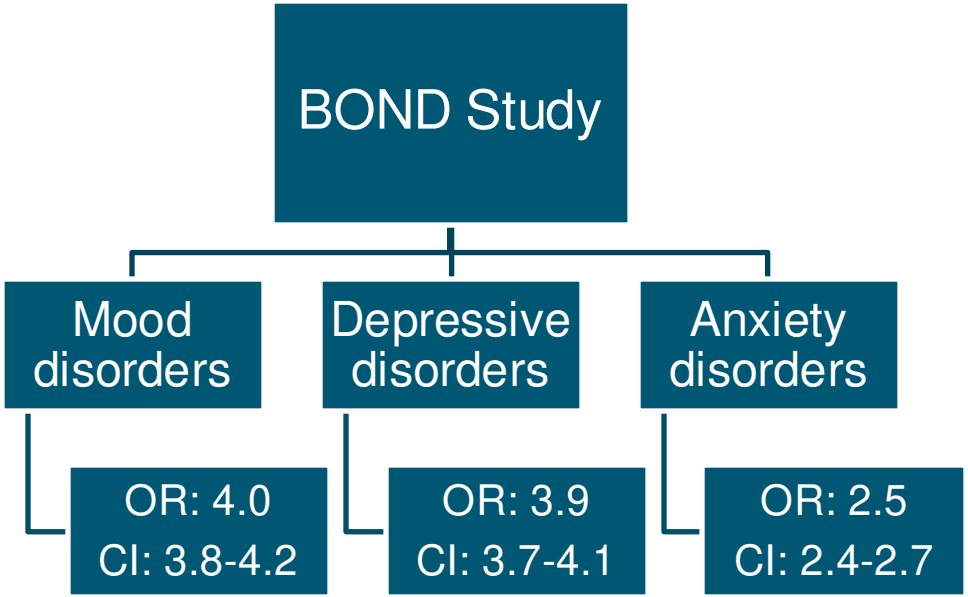
Initiate or, where appropriate, switch treatment plans for narcolepsy that consider CV comorbidities, dosing, and titration strategies.

Patient Case: Jennifer

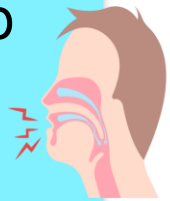
- 26-year-old Hispanic female presents for results of her sleep study; diagnosed with narcolepsy type 1 (NT1)
- Previous medical history: obesity, depression, hypertension
- Family history: obesity, CVD (father with HTN and MI)
- Social history: works as interior designer but struggles with deadlines due to complaints of tiredness; difficulty getting out of bed; has attempted to diet and exercise but frequently is too tired to make meals and go to the gym; she lives alone but has a boyfriend who helps her with these aspects when he can
- Findings: BMI = 33, BP = 136/89, PHQ-9 = 10
- Medications: venlafaxine HCL 75 mg daily, lisinopril 5 mg daily, hormonal birth control
- Treatment to be decided this visit

BMI = body mass index; BP = blood pressure; CVD = cardiovascular disease; HCL = hydrocholoride; PHQ = Patient Health Questionnaire

Comorbidities Associated with Narcolepsy



- Other comorbidities to consider
  - Sleep apnea (hazard ratio: 19.2; CI: 7.7-48.3)
  - Obesity (hazard ratio: 13.4; CI: 3.1-57.6)



CI = confidence interval; OR = odds ratio

Black J, et al. *Sleep Med.* 2017;33:13-18. Ohayon MM. *Sleep Med.* 2013;14(6):488-492.

Comorbidities Associated with Narcolepsy

CV Burden of Narcolepsy Disease (CV-BOND): A Real-World Evidence Study

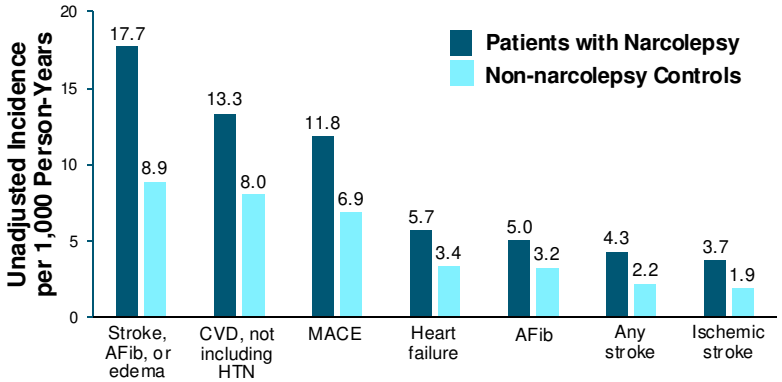
Key Findings:

Individuals with narcolepsy are at increased risk of developing new-onset CV events compared with individuals without narcolepsy

Physicians should consider future CV risk in patients with narcolepsy when weighing treatment options

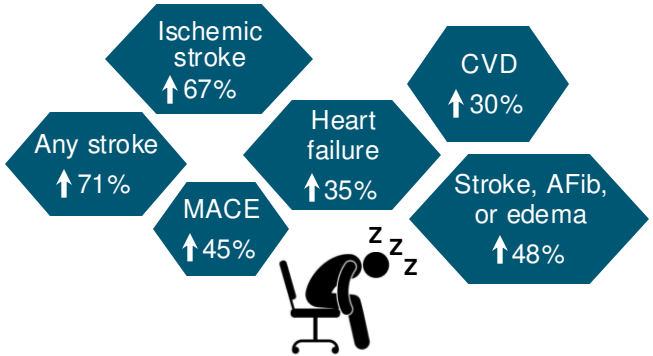
Using an administrative claims database, adults age ≥ 18 with a narcolepsy diagnosis were matched 1:3 with a non-narcolepsy control cohort

New-Onset Outcome of Interest



Unadjusted incidence rates for outcomes were higher in patients with narcolepsy than in matched controls

Increased Risk of Developing New-Onset CV Events



Adjusted hazard ratios demonstrated increased risk of new-onset CV events in the narcolepsy cohort compared with matched non-narcolepsy controls; statistical significance was achieved for all CV outcomes of interest

Other CVD-Related Risks:

- Hypertension 1.3x
- Diabetes 1.8x
- Hyper-cholesterolemia 1.5x

AFib = atrial fibrillation; MACE = major adverse cardiac event

Ben-Joseph RH, et al. *Sleep.* 2023 Jun 12:zsad161. [Epub ahead of print]. Black J, et al. *Sleep Med.* 2017;33:13-18. Ohayon MM. *Sleep Med.* 2013;14(6):488-492.

Audience Response

Which of the following can be considered in our patient with hypertension to avoid an increase in blood pressure and heart rate?

A. Sodium oxybate and lower-sodium oxybate
B. Sodium oxybate and pitolisant
C. Lower-sodium oxybate and pitolisant
D. Lower-sodium oxybate and solriamfetol
E. I don’t know

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Treatments with CV Impact: Stimulants

FDA-approved for narcolepsy: EDS	• Only approved agents are amphetamine/dextroamphetamine, methylphenidate
Mechanism of action	• Enhances neurotransmission of dopamine, norepinephrine, serotonin
Efficacy	• Data limited • Meta-analysis: ESS reduction = 3.1 (methylphenidate) and 3.3 (amphetamine)
Safety	• Increased BP/heart rate • Black box warning for sudden cardiac death • Risk of abuse

Dextroamphetamine

- Age 6-12: 5-mg dose, raised in increments of 5 mg weekly
- Age ≥ 12: 10-mg dose, raised in increments of 10 mg weekly

Methylphenidate

- Age ≥ 6: 5-mg dose twice daily, increase 5-10 mg weekly
- Adults: Divide 2-3 times daily, average 20-30 mg but can go up to 60 mg

CV = cardiovascular; EDS = excessive daytime sleepiness; ESS = Epworth Sleepiness Scale; FDA = U.S. Food and Drug Administration

Thakrar C, et al. *J Sleep Res*. 2018;27(4):e12627. Ritalin® (methylphenidate hydrochloride) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; Revised 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/010187s071s082,018029s041s051lbl.pdf.
Dexedrine® (dextroamphetamine sulfate) [package insert]: Research Triangle Park, NC: GlaxoSmithKline; Published 2007. https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/017078s042lbl.pdf.

Treatments with CV Impact: Venlafaxine

Not FDA-approved for narcolepsy	• Used for cataplexy in patients with narcolepsy, not EDS
Mechanism of Action	• Serotonin and norepinephrine reuptake inhibitor (SNRI)
Efficacy	• Data limited • Second-line treatment for cataplexy
Safety	• Dose-dependent increases in BP • Does not worsen pre-existing hypertension

Venlafaxine

Dosing: 37.5-225 mg

Abrupt discontinuation can produce severe rebound effect

Calvi A, et al. *Front Cardiovasc Med.* 2021;8:704281. Franceschini C, et al. *Neurotherapeutics.* 2021;18:6-19.

Treatments with CV Impact: Modafinil/Armodafinil

FDA-approved for narcolepsy	• EDS • Indicated for adults, not pediatric patients
Mechanism of Action	• Unknown; theorized to inhibit dopamine reuptake
Efficacy	• Meta-analysis: ESS reduction = 2.73
Safety	• Increased BP/heart rate • Should be avoided in patients with unstable CVD • Reduces oral contraception effectiveness

Modafinil
- 200-400 mg once daily in the morning
- Split-dosing studies have shown better efficacy

Armodafinil
- 150-250 mg once daily in the morning

Schwartz JR, et al. *J Neuropsychiatry Clin Neurosci*. 2005;17(3):405-412. Golicki D, et al. *Med Sci Monit*. 2010;16:RA177-RA186.
Provigil® (modafinil) [package insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; Revised 2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020717s037s038lbl.pdf.
Nuvigil® (armodafinil) [package insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; Revised 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021875s023lbl.pdf.

Treatments with CV Impact: Solriamfetol

FDA-approved for narcolepsy	• EDS • Indicated for adults, not pediatric patients
Mechanism of Action	• Dopamine and norepinephrine reuptake inhibitor (DNRI)
Efficacy	• Meta-analysis: ESS reduction = 4.79
Safety	• Increased BP/heart rate • Should not be started in patients with uncontrolled HTN; avoid use in unstable CVD, arrhythmias, other serious heart disease • Dose adjustments for renal impairment

Solriamfetol

- Start dose: 75 mg once daily
- Dose increase at intervals of at least 3 days
- Maximum dose: 150 mg once daily

Renal Adjustments

- Moderate impairment: 37.5 mg once daily
  - May increase to 75 mg once daily after at least 7 days
- Severe impairment: 37.5 mg once daily
- ESRD: not recommended

ESRD = end-stage renal disease; HTN = hypertension

Zhan S, et al. *Nat Sci Sleep.* 2023;15:217-230. Sunosi® (solriamfetol) [package insert]. New York, NY: Axsome Therapeutics; Revised 2023. https://www.sunosihcp.com/assets/files/sunosi.en.uspi.pdf.

Treatments with Potential CV Impact: Sodium Oxybate (SXB)

FDA-approved for narcolepsy	• EDS and cataplexy in patients age ≥ 7 • Two formulations: once and twice nightly
Mechanism of Action	• Sodium of gamma-hydroxybutyrate (GHB); mechanism unknown
Efficacy	• Meta-analysis: ESS reduction = 3.19
Safety	• High sodium content (9-mg dose = 1,640 mg sodium) • Use with caution in patient with CVD/CKD • CNS depressant

Sodium Oxybate

- Twice-nightly formulation
  - Initiate 4.5 g nightly, divided into two doses
  - Take first at bedtime, second 2.5-4 hours later
  - Titrate to effect by 1.5 g nightly at weekly intervals
  - Target dose: 6-9 g nightly
- Once nightly formulation
  - Initiate 4.5 g nightly
  - Titrate to effect by 1.5 g nightly at weekly intervals
  - Target dose: 6-9 g nightly

CKD = chronic kidney disease; CNS = central nervous system

Zhan S, et al. *Nat Sci Sleep*. 2023;15:217-230. Xyrem® (sodium oxybate) [package insert].Palo Alto, CA: Jazz Pharmaceuticals, Inc.; Revised 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021196s030lbl.pdf.
Lumryz™ (sodium oxybate) [package insert]. Chesterfield, MO: Avadel CNS Pharmaceuticals, LLC; Published 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214755Orig1s000lbl.pdf.

Treatments with Less CV Impact: Pitolisant

FDA-approved for narcolepsy	• EDS and cataplexy in adults
Mechanism of Action	• Histamine-3 receptor antagonist/inverse agonist
Efficacy	• Meta-analysis: ESS reduction = 2.13
Safety	• No increases in BP/heart rate like traditional narcolepsy medications • Prolongs QT interval • Reduces oral contraceptive effectiveness

Pitolisant

- Week 1: start 8.9 mg once daily
- Week 2: increase to 17.8 mg once daily
- Week 3: may increase to maximum dose of 35.6 mg once daily
- Moderate hepatic impairment: 8.9 mg, titrate to maximum dose 17.8 mg after 14 days
- Moderate and severe renal impairment: 8.9 mg, titrate to maximum dose 17.8 after 7 days
- Not recommended in ESRD

Zhan S, et al. *Nat Sci Sleep*. 2023;15:217-230. Wakix® (pitolisant) [package insert]. Plymouth Meeting, PA: Harmony Biosciences, LLC; Published 2019. https://wakixhcp.com/pdf/wakix-tablets-pi.pdf.

Treatments with Less CV Impact: Lower-Sodium Oxybate (LXB)

FDA-approved for narcolepsy	• EDS and cataplexy in patients age ≥ 7
Mechanism of Action	• Calcium, magnesium, potassium, sodium salts of gamma-hydroxybutyrate (GHB), mechanism unknown
Efficacy	• Meta-analysis: ESS reduction = 3
Safety	• No increases in BP/heart rate • 92% sodium reduction vs. SXB • Neutral cardiovascular profile

Lower-Sodium Oxybate

Adult Dosing

- Initiate 4.5 g nightly, divided into two doses
- Take first at bedtime, second 2.5-4 hours later
- Titrate to effect by 1.5 g nightly at weekly intervals
- Target dose: 6-9 g nightly

Pediatric Dosing

- Pediatric dosing is weight-based
- Transition from SXB to LXB is dose for dose

Zhan S, et al. *Nat Sci Sleep*. 2023;15:217-230. Xywav® (calcium, magnesium, potassium, and sodium oxybates) [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; Revised 2023. https://pp.jazzpharma.com/pi/xywav.en.USPI.pdf.

Audience Response

Which of the following risk factors for CVD can be modified in this patient?

A. Physical activity and sodium intake
B. Smoking and sodium intake
C. Physical activity and family history
D. Physical activity and aging
E. I don’t know

Audience Response

Which of the following risk factors for CVD can be modified in this patient?

A. Physical activity and sodium intake
B. Smoking and sodium intake
C. Physical activity and family history
D. Physical activity and aging
E. I don’t know

Modifiable CV Risk Factors

American Heart Association: Essential Eight program can mitigate CV risk factors

- Smoking cessation, physical activity, manage weight, eat better, control cholesterol, manage blood sugar, manage blood pressure, get healthy sleep

Jackson SL, et al. *MMWR Morb Mortal Wkly Rep*. 2016;64(52):1393-1397. Tsao CW, et al. *Circulation*. 2022;145(8):e153-e639. Magkos F, et al. *Cell Metab*. 2016;23(4):591-601. American Heart Association Website. 2023. https://www.heart.org/en/healthy-living/healthy-lifestyle/lifes-essential-8.

Patient Case: Discussion

- 26-year-old Hispanic female presents for results of her sleep study; diagnosed with narcolepsy type 1 (NT1)
- Previous medical history: obesity, depression, hypertension
- Family history: obesity, CVD
- Social history: works as interior designer but struggles with deadlines due to complaints of tiredness; difficulty getting out of bed; has attempted to diet and exercise but frequently is too tired to make meals and go to the gym; she lives alone but has a boyfriend who helps her with these aspects when he can

How can we help the patient make lifestyle changes that can improve her overall health and well-being?

Data on CV Impact in Patients with Narcolepsy: A Quick Glance

Modafinil/Armodafinil

- 40-week trial (n = 478)
- Most common CV events
  - Palpitations (1.5%)
  - HTN (1%)
  - Tachycardia (1%)
- 12-week trial (n = 328)
  - 43% had prevalent CVD (mostly HTN)
  - 6% developed HTN, three serious CV adverse effects
  - Pulmonary embolism, MI, chest pain
  - Two had long QT syndrome/QRS prolongation
  - Three had QTc > 60 msec

Solriamfetol

- 12-week trials
  - Mean systolic BP increase from baseline: 3.1 and 6.8 mmHg for 75-mg and 300-mg doses, respectively
  - Mean HR increase from baseline: 3.7 and 6.5 bpm for 75-mg and 300-mg doses, respectively
- No increase in non-dipping HTN
  - Minimal risk of QTc prolongation

Pitolisant

- Analysis of 7-, 8-, and 12-week trials (n = 166)
  - No significant changes in BP/heart rate
  - In 12-week trial, mean change in QTc interval from baseline was 3.1 msec at 6 months, 6.1 msec at 12 months
  - Three patients had postbaseline increase > 60 msec and none had > 500 msec
  - Cardiac adverse events:
    Heart rate increase (n = 4)
    Right bundle branch block (n = 1)
    Sinus tachycardia (n = 1)
    Palpitations (n = 1)

bpm = beats per minute; MI = myocardial infarction; msec = millisecond; QTc = corrected QT

Mitler M, et al. *Sleep Med*. 2000;1(3):231-243. Schwartz JR, et al. *J Clin Sleep Med*. 2010;6:450-457. Abad VC. *Nat Sci Sleep*. 2021;13:75-91. Winter W, et al. *Neurology*. 2021;96(15 Suppl):1472.

Data on CV Impact: Sodium Oxybate

Increased Risk of Hypertension Onset Among Patients with Narcolepsy Newly Treated with High-Sodium Oxybate

- Claims data (2014-2020)
- 954 SXB/1,906 controls
- Transition gram for gram
- Risk per 100 patients

Endpoints

1. Composite of new-onset HTN diagnosis or initiation of antihypertensive medication
2. New-onset HTN diagnosis alone

	Endpoint 1	Endpoint 2
Findings (SXB vs. Controls)	6.6 vs. 4.2 (OR: 1.61; 95% CI; 1.15-2.27)	0.94 vs. 0.52 (OR: 1.81; 95% CI: 0.73-4.46)
Sensitivity Analysis Findings (SXB vs. Controls)	6.22 vs. 4.06 (OR: 1.57; 95% CI: 1.10-2.24)	0.89 vs. 0.44 (OR: 2.01; 95% CI: 0.75-5.36)

Macfadden W, et al. American Academy of Neurology Website. 2023. https://www.aan.com/MSA/Public/Events/AbstractDetails/55168.

Data on CV Impact: Sodium Oxybate

- Transition Experience of persons with Narcolepsy taking Oxybate in the Real-world (TENOR)
  - Real-world data investigating patients' transition from SXB to LXB

Patient Characteristics

- 85 patients
  - 45 NT1
  - 40 NT2
- Median age: 40.3
- 73% female
- Mean time on SXB: 57.8 months

Findings

- 84% noted switching from SXB to LXB was "extremely easy," "not difficult at all," or "easy"
- 95% stated lower-sodium content as a reason for switching
- 46% stated lower CV risk as a reason for switching
- Minimal mean changes in TSQM version II scores for global satisfaction, satisfaction with effectiveness, side effects, or convenience after transition

NT2 = narcolepsy type 2; TSQM = Treatment Satisfaction Questionnaire for Medication

Bae C, et al. *Sleep.* 2023;46(Suppl_1):A268. National Academies of Sciences, Engineering, and Medicine National Academies Press; 2019.

Patient Case Recap: Jennifer

- 26-year-old Hispanic female presents for results of her sleep study and treatment initiation for narcolepsy type 1 (NT1)

Which of these patient characteristics should guide us in our treatment decisions?

What should go into our conversations with our patients regarding comorbidities?

How can we support patients when they are starting new treatments?

How do we approach treatment in patients who have CV risk or CVD?

How do we manage patients who develop CVD while on treatment for narcolepsy?

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Consider the cardiovascular risk associated with narcolepsy when initiating a treatment plan for patients with narcolepsy
- Recognize the potential cardiovascular impacts specific to each treatment for narcolepsy during the shared decision-making process
- Optimize patient treatment by considering the whole patient with narcolepsy and factors that can support the patient during their treatment initiation

CMEO BriefCase 1

Recognition of Narcolepsy in Your Patients

CMEO BriefCase 2

Differential Diagnosis for Narcolepsy

www.cmeoutfitters.com/sleep-disorders-hub/

Sleep Disorders Hub

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https://www.cmeoutfitters.com/sleep-disorders-hub/

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