CMEO
BriefCase

Treatment Factors: What Should Be Driving My Treatment Decisions?

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CME OUTFITTERS

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Learning Objective

Evaluate the constellation of patient symptoms (e.g., EDS, cognitive impairment, functioning) that influence treatment selection for EDS associated with OSA.

Virtual Visit

Meet Donovan

Patient Case: Donovan

- 45-year-old Black male with severe OSA initiated on CPAP 3 months ago
- Complains of “being tired all of the time” and “like my sleep switch is never turned off”
- Complaints about his work performance at call center; sleepiness and lack of attention have caused him to miss calls
- Tolerating CPAP; 100% adherence but still has sleepiness and cognitive dysfunction
- Past medical history: obesity, GERD, depression
- Baseline AHI = 31 episodes/hour, current AHI = 2 episodes/hour, BMI = 33, ESS = 13, BP = 132/84
- Medications: omeprazole 20 mg daily, citalopram 40 mg daily

AHI = Apnea-Hypopnea Index; BMI = body mass index; BP = blood pressure; CPAP = continuous positive airway pressure; ESS = Epworth Sleepiness Scale; GERD = gastroesophageal reflux disease; OSA = obstructive sleep apnea; PSG = polysomnography

Excessive Daytime Sleepiness (EDS) and OSA

Prevalence of EDS in OSA

- 41%-58% of patients with OSA have EDS at time of initial diagnosis

CPAP Unmet Needs

- One-third to one-half of patients fail CPAP, continue struggle with OSA and EDS

CPAP Success

- Over one-fourth of patients succeeding on CPAP by 5-month follow-up have residual EDS

Heidi AH, et al. *Respir Care*. 2020;65(10):1541-1546. Bonsignore MR, et al. *Front Neurol*. 2021;12:690008. Marklund M, et al. *JAMA Intern Med.* 2015;175(8):1278-1285. Bjorvatn B, et al. *Sleep Breath.* 2015;19:1387-1393.

Personal Impact of EDS

- Depression and anxiety

- Increased motor vehicle and occupational accidents

- Attention and memory impairments

- Impaired higher-order executive functioning

Lal C, et al. *Ann Am Thorac Soc*. 2021;18(5):757-768.

Common Comorbidities to Consider

Multimorbidity and overall comorbidity of sleep apnea: a Finnish nationwide study (n = 3,223,399)

- 63% of patients with OSA multimorbid vs. 38% of general population
- 34% of patients with OSA had 4 or more comorbidities vs. 14% of general population

HTN = hypertension; T2DM = type 2 diabetes mellitus

Palomäki M, et al. *ERJ Open Res*. 2022;8(2):00646-2021.

Treatments: Modafinil and Armodafinil

Modafinil

Indication for OSA-associated EDS in Adults

Mechanism of Action

- Inhibitor of dopamine reuptake
- **Mixture of R- and S-enantiomers**

Dosing

- 200-400 mg/day

Adverse Effects

- Headache, nausea (> 10%)
- Anxiety, insomnia, dizziness, diarrhea, rhinitis (5%-10%)
- Warning: monitor patients with known CVD
- Warning: use caution in patients with history of psychosis, depression, or mania

Armodafinil

Indication for OSA-associated EDS in Adults

Mechanism of Action

- Inhibitor of dopamine reuptake
- **R-modafinil**

Dosing

- 150-250 mg/day

Adverse Effects

- Headache, nausea (> 10%)
- Insomnia, dizziness (5%-10%)
- Warning: monitor patients with known CVD
- Warning: use caution in patients with history of psychosis, depression, or mania

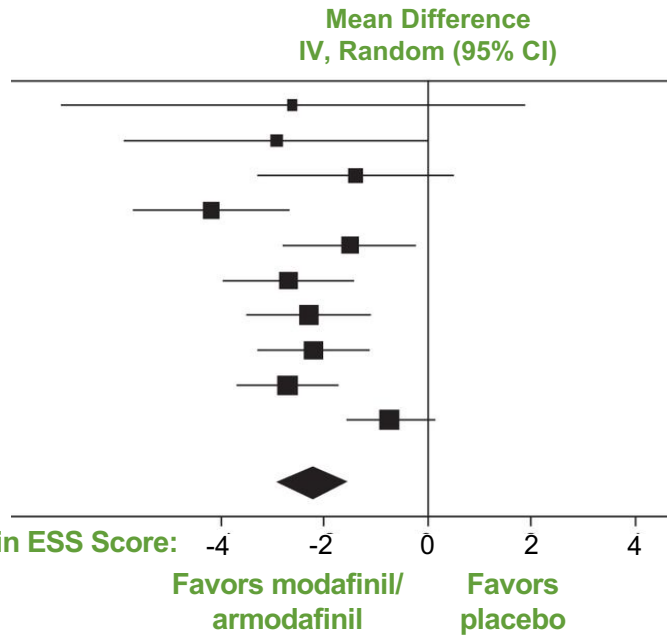
CVD = cardiovascular disease

Provigil® (modafinil) [package insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc. Revised 2005. 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.

Treatment Considerations: Efficacy

Epworth Sleepiness Scale (ESS) Outcomes

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)

Modafinil/armodafinil in OSA: a systematic review and meta-analysis

- 10 studies included
- N = 1,466
- ESS reduction: 2.21 (95% CI: -2.88 to -1.54)

CI = confidence interval

Julia L, et al. *Eur Respir J*. 2016;47(5):1420-1428.

Audience Response

Which of the following is accurate regarding treatment considerations for modafinil and armodafinil?

A. Modafinil, armodafinil, and solriamfetol all have significant enzymatic interactions with other drugs
B. Modafinil and armodafinil have drug interactions that can affect contraceptives and other medications
C. Modafinil has significantly less drug interactions compared to armodafinil
D. There are no considerations for giving selective serotonin reuptake inhibitors (SSRIs) for comorbid depression when taking modafinil
E. I don’t know

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Treatment Considerations: Drug Interactions and Comorbidities

Enzymatic Interactions

- Metabolized partially by CYP3A4
- CYP2C19 inhibitor
- Suppresses CYP2C9
- Induces CYP3A4, CYP2B6, CYP1A2

Steroidal Contraceptives

- Clearance of steroidal contraceptives increased
- Must consider barrier methods if sexually active

Depression

- Certain selective serotonin reuptake inhibitors interact with modafinil/armodafinil
- SSRIs are first-line treatment for depression

GERD

- Proton pump inhibitors (PPIs) interact with modafinil/armodafinil
- PPIs are first-line treatment for GERD
- Clearance of drug reduced

CVD

- Potential interactions with clopidogrel and warfarin
- Associated with blood pressure, heart rate increases

SSRI = selective serotonin reuptake inhibitors

Provigil® (modafinil) [package insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc. Revised 2005. 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.

Treatment: Solriamfetol

Indication for OSA-associated EDS in Adults

Mechanism of Action

- Dopamine and norepinephrine reuptake inhibitor

Dosing

- Starting dose: 37.5 mg once daily
- May increase at intervals of at least 3 days
- Maximum dose: 150 mg once daily

Adverse Effects

- Headache, nausea, decreased appetite, insomnia, anxiety (≥ 5%)
- Warning: measure heart rate and blood pressure prior to initiating and throughout treatment
- Warning: use caution in treating patients with history of psychosis or bipolar disorders

Sunosi® (solriamfetol) [package insert]. New York, NY: Axsome Therapeutics, Inc. Revised 2023. https://www.sunosihcp.com/assets/files/sunosi.en.uspi.pdf.

Audience Response

Which of the following is true regarding solriamfetol treatment for OSA-related EDS?

A. EDS improvement can be variable in patients who are non-adherent to OSA therapy
B. EDS improvement is comparable to modafinil/armodafinil in patients who are non-adherent to OSA therapy
C. Improvement in EDS was seen regardless of adherence to OSA therapy
D. ESS scores improved significantly in all patients, but not MWT sleep latency
E. I don’t know

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E. I don't know

Effects of Solriamfetol on EDS Based on OSA Therapy Adherence

Study Design

- Randomized, placebo-controlled study (N = 459)
- Efficacy of solriamfetol (37.5, 75, 150, or 300 mg daily)*

Results

- 70.6% adherent vs. 29.4% nonadherent
- Compared to baseline, adherent and nonadherent subgroups on solriamfetol demonstrated mean increases in MWT sleep latency, mean decreases in ESS score, and mean increases in FOSQ-10 total score
  - MWT sleep latency increased 3.2 minutes to 13.4 minutes
  - ESS reductions ranging from 4.3 to 8.9 points
  - FOSQ-10 total score ranging from 1.5 to 3.5 points
- PGI-C: Improvements with solriamfetol vs. placebo regardless of adherence (except nonadherent subgroup taking the 37.5-mg dose)
- Improvement in EDS from solriamfetol not impacted by OSA therapy adherence

*Solriamfetol treats EDS associated with OSA but is not a substitute for primary therapy for OSA

FOSQ = Functional Outcomes of Sleep Questionnaire; MWT = Maintenance of Wakefulness Test; PGI-C = Patient Global Impression of Change

Schweitzer PK, et al. *Chest*. 2021;160(1):307-318.

Treatment Considerations: Cognitive Improvement

Solriamfetol Demonstrates Durable Cognitive Improvement in Adults with OSA and EDS

Study Design

- Randomized, double-blind, placebo-controlled, crossover trial
- Patients with OSA-associated EDS and concurrent cognitive impairment (n = 59)
- 75 mg/day for 3 days, 150 mg/day thereafter dosing
- 2-week treatment period → 1-week washout → 2-week placebo

Results

- **Primary endpoint:** change from baseline on the coding subtest of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), which is equivalent to the Digit Symbol Substitution Test (DSST)
- **Secondary endpoint:** Patient Global Impression of Severity (PGI-S)
- DSST-RBANS solriamfetol vs. placebo: **6.49 vs. 4.75 (*p* = .009)**
- PGI-S solriamfetol vs. placebo: **-0.90 vs. -0.61 (*p* = .034)**

Van Dongen H, et al. *Sleep*. 2023;46(Suppl 1):A246.

Treatment Considerations: Drug Interactions and Comorbidities

BP, Heart Rate Increases

- Includes interactions with other dopaminergic drugs

Obesity

- In clinical trials up to 52 weeks, 22% of patients receiving solriamfetol 75 mg or 150 mg experienced weight loss ≥ 5% relative to baseline

No CYP Involvement

- No enzymatic interactions with other treatments

CYP = cytochrome P450

Malhotra A, et al. *Sleep Med*. 2022;100:165-173.

Personalizing Treatment Selection for Patients with OSA

- Patient's needs and preferences
- Severity of EDS
- Comorbidities, including substance use disorder
- Polypharmacy
- Monitoring treatment effectiveness
- Assessment of EDS:
  - Interviews, questionnaires
    - ESS, FOSQ, PHQ-9
  - Objective data: MSLT, MWT, etc.

MSLT = Multiple Sleep Latency Test; PHQ-9 = Patient Health Questionnaire-9

Rosenburg R, et al. *Postgrad Med*. 2021;133(7):772-783.

Patient Case: Donovan

- 45-year-old Black male with severe OSA initiated on CPAP 3 months ago

What factors of Donovan's case are pertinent to our treatment decision?

When might we consider certain treatments over others?

How can we practice shared decision-making with our patients with OSA?

Are there nonpharmacological methods we can use?

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Identify the prevalence and personal impact of EDS in patients with OSA
- Develop personalized treatment plans that fit patient characteristics, comorbidities, and current medications
- Recognize multifactorial considerations that are necessary to treat the whole patient with EDS caused by OSA

CMEO BriefCase 1

More Than Just Sleepiness: Impact of EDS in Patients with OSA

CMEO BriefCase 3

Tailoring Therapy to Fit the Whole Patient with OSA-Associated EDS

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