CMEO
BriefCase

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

Supported by an educational grant from Axsome

CME OUTFITTERS

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Learning Objective

Develop real-world dosing and titration strategies that personalize treatment for optimal outcomes in patients with EDS associated with OSA.

Virtual Visit

Meet Alvin

Patient Case: Alvin

- 40-year-old Black male with severe OSA initiated on CPAP 8 months ago
- Has received some relief of symptoms since start of therapy; starting to have more energy; has more quality time with family
- Still experiences EDS during the day; tends to drift off while at work as a computer programmer; work performance has improved somewhat but still complains of cognitive impairment
- Drinks several cups of coffee a day with limited effect; started on modafinil but no significant improvement in sleepiness
- Baseline AHI = 34 episodes/hour, current AHI = 3 episodes/hour, ESS = 13, BMI = 31 kg/m^2, 100% adherence to CPAP
- Medications: modafinil 200 mg orally every morning

AHI = Apnea-Hypopnea Index; BMI = body mass index; CPAP = continuous positive airway pressure; EDS = excessive daytime sleepiness; ESS = Epworth Sleepiness Scale; OSA = obstructive sleep apnea

Impact of EDS in Patients with OSA

EDS and OSA

- EDS reported to affect 41%-58% of individuals with OSA

EDS and CPAP Therapy

- Over 25% of patients succeeding on CPAP by 5-month follow-up still have residual EDS; those sleeping < 6 hours have worse EDS

EDS and QoL

- Patients with OSA and EDS are at higher risk for mental/physical deficits, work and daily activity impairment, and lower QoL

QoL = quality of life

Lal C et al. *Ann Am Thorac Soc*. 2021;18(5):757-768. Heidi AH, et al. *Respir Care*. 2020;65(10):1541-1546.
Bonsignore MR, et al. *Front Neurol*. 2021;12:690008.

FDA-Approved Medications

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; FDA = U.S. Food and Drug Administration

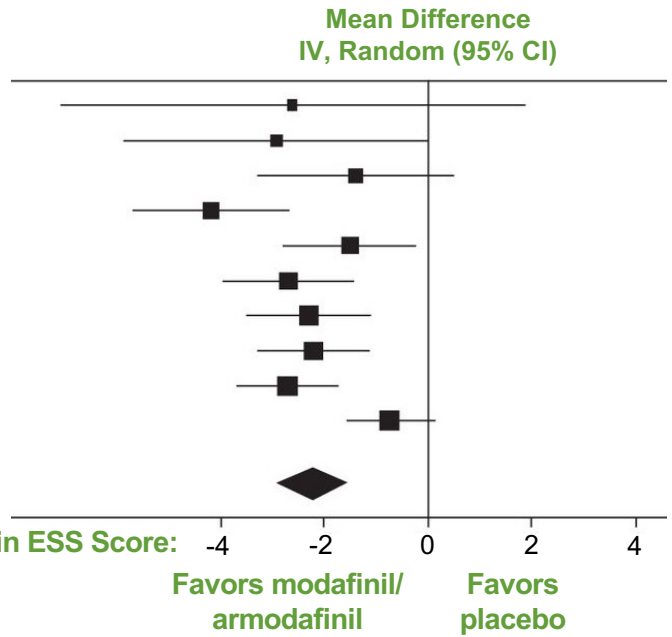
Provigil® (modafinil) [package insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc. Revised 2005. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020717s037s038lbl.pdf.
Nuvigil® (armodafinil) [package insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc. Revised 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021875s023lbl.pdf

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)



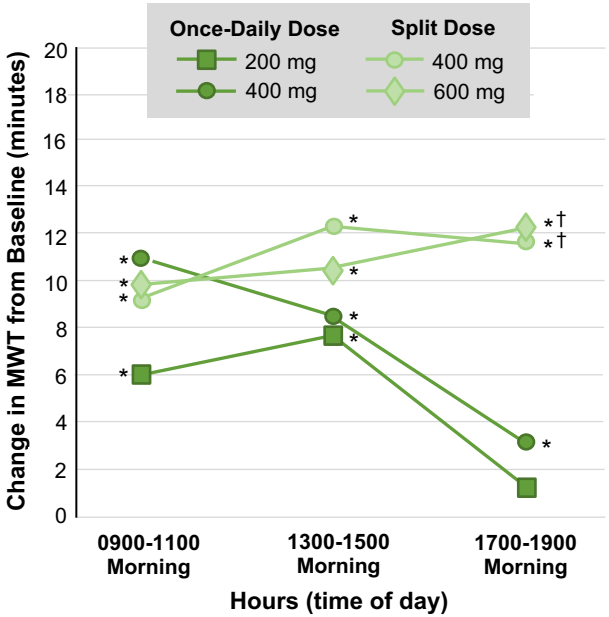
Modafinil/armodafinil in OSA: a systematic review and meta-analysis

- 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.

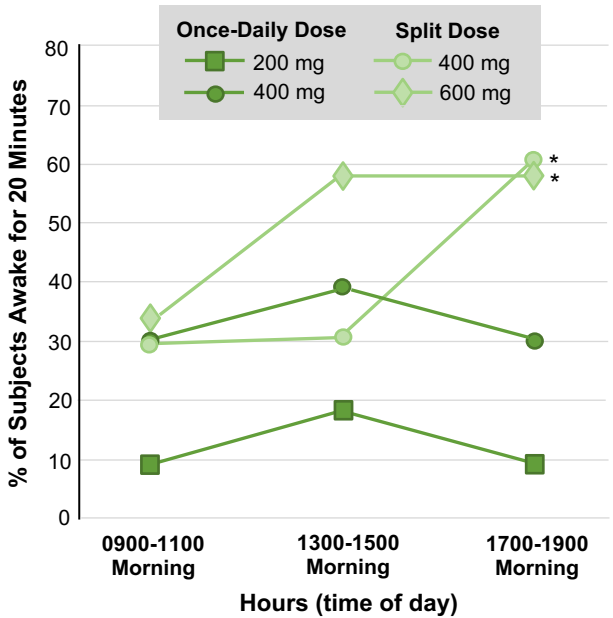
Modafinil Dosing Strategy: Split Dosing

Mean Change from Baseline in MWT Sleep Latency Times



*p < .01 for change from baseline for each group
†p < .05 for modafinil 400 mg split dose (0700 and 1200 hour) and modafinil 600 mg split dose vs. modafinil 200 mg once daily (at 0700 hour)

% of Patients Remaining Awake for First 20 Minutes of Both MWT Sessions



*p < .05 for modafinil 400 mg split dose and modafinil 600 mg split dose vs. modafinil 200 mg once daily

- 3-week randomized, double-blind, parallel study design
- N = 56
- Once-daily dose: 0700 hour
- Split dose: 0700, 1200 hour

MWT = Maintenance of Wakefulness Test

Schwartz JR, et al. *J Neuropsychiatry Clin Neurosci*. 2005;17(3):405-412.

Treatment: Solriamfetol

Indication for OSA-Associated EDS in Adults

Mechanism of Action

- Dopamine and norepinephrine reuptake inhibitor

Dosing

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

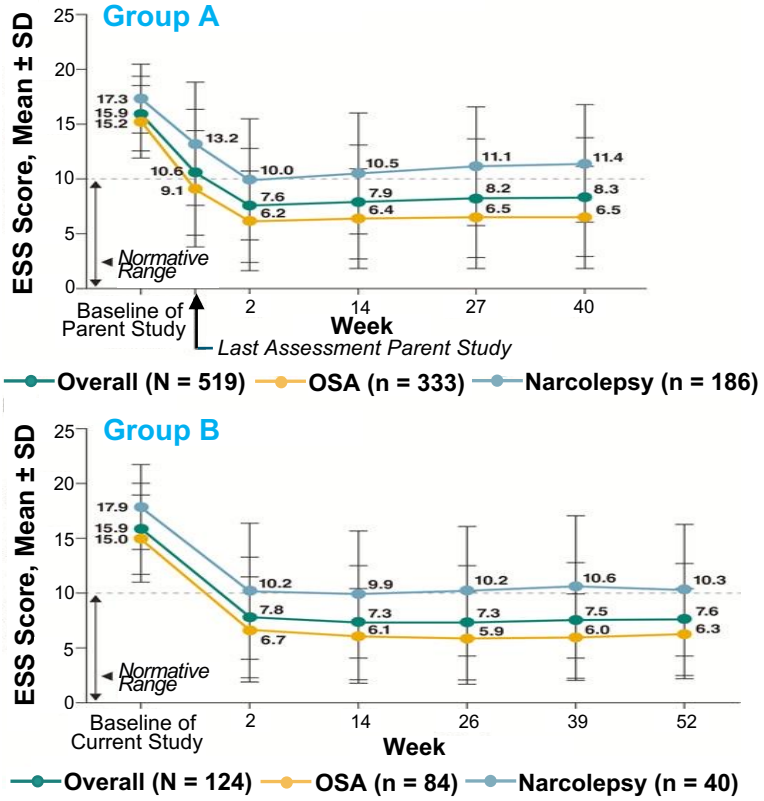
Adverse Effects

- 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.

Treatment Considerations: Long-Term Efficacy

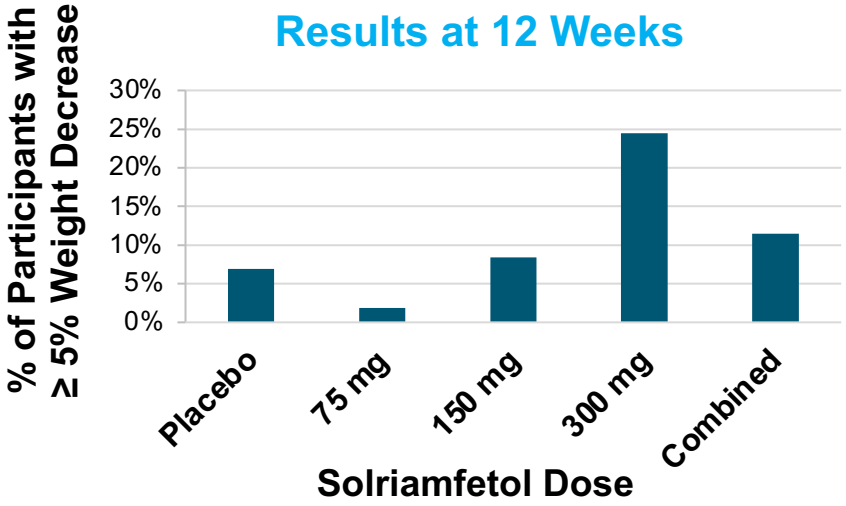
- Study design
  - Group A (40 weeks)
    (n = 333 patients with OSA)
  - Group B (52 weeks)
    (n = 84 patients with OSA)
  - Randomized withdrawal period at 6 months
  - 2-week titration period
- Results
  - Group A (OSA); ESS mean reduction: 9
  - Group B (OSA); ESS mean reduction: 8.3
  - ESS improvement maintained for study duration

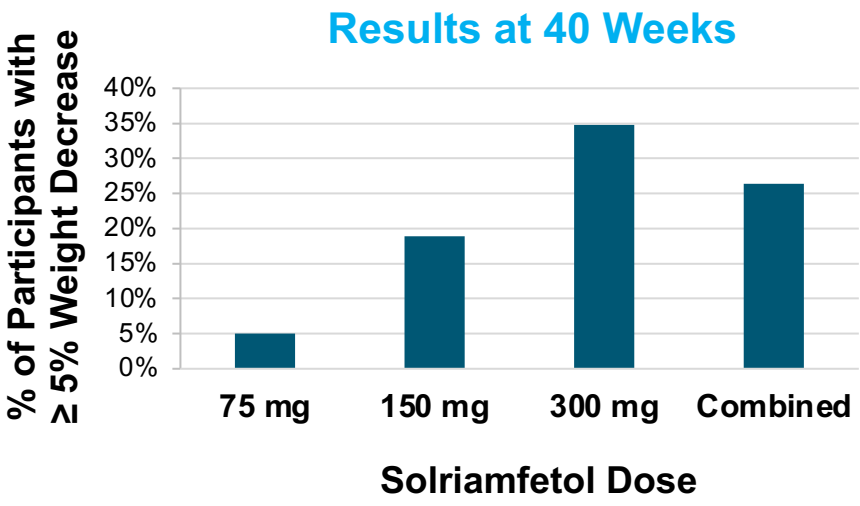


SD = standard deviation

Malhotra A, et al. *Sleep*. 2020;43(2):zsz220.

Effects of Solriamfetol on Body Weight in Patients with OSA





- Two 12-week randomized, controlled trials + 1-year open-label extension study
- Evaluated changes in weight of patients with OSA and narcolepsy on treatment
- 333 patients with OSA out of 474
- Average patient with OSA was obese (BMI: 33.1-33.3)

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

Audience Response

Which of the following regarding the Solriamfetol Titration and AdministRaTion (START) study is true?

A. Dosing and titration strategies for solriamfetol did not differ in OSA vs. narcolepsy patient groups

B. Severity of EDS, but not comorbidities, were considerations for switching patients to solriamfetol

C. The majority of patients from the OSA and narcolepsy groups required two or more dose adjustments when titrating solriamfetol

D. For both OSA and narcolepsy groups, no patients were kept on 37.5mg as a stable dose

E. I don’t know

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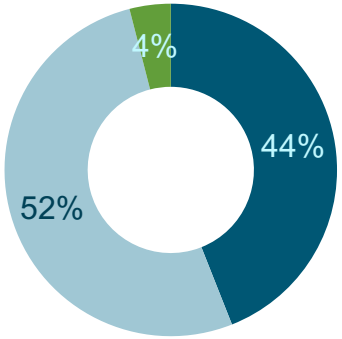
E. I don't know

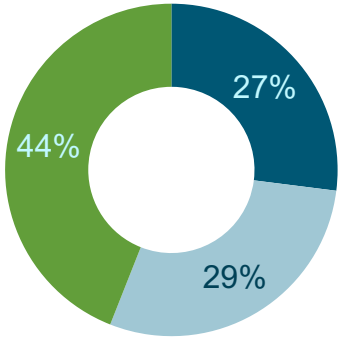
Solriamfetol Titration and AdministRaTion (START): Dosing and Titration Strategies

Solriamfetol Initiation (OSA)



De Novo Transition Add-On

Solriamfetol Initiation (Narcolepsy)



De Novo Transition Add-On

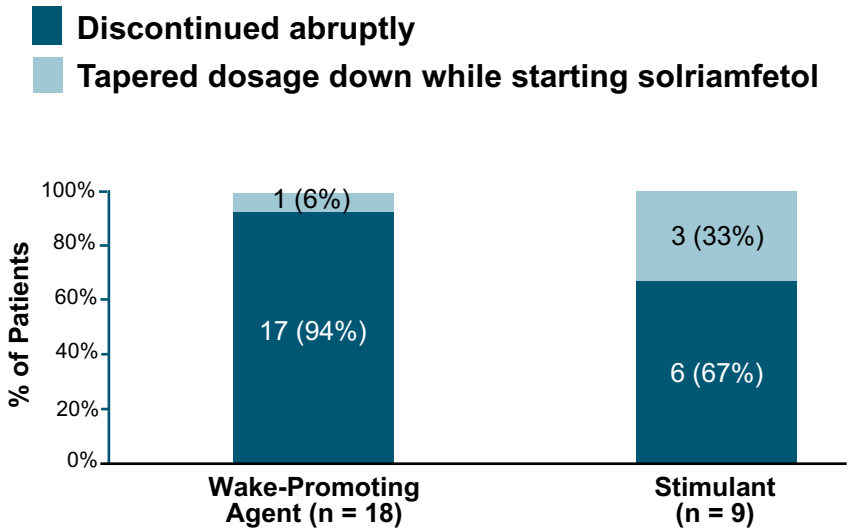
- Guidance on titrating solriamfetol and transitioning to solriamfetol is limited
- Retrospective medical record review and qualitative survey
- Titration strategies classified as de novo (EDS medication-naïve), transition (switched or switching from existing EDS medication), or add-on (to current EDS medications)
- OSA (n = 50), narcolepsy (n = 70)

Thorpy MJ, et al. *Clin Ther*. 2022;44(10):1356-1369. Singh H, et al. *Adv Ther*. 2022;39(9):4359-4373.

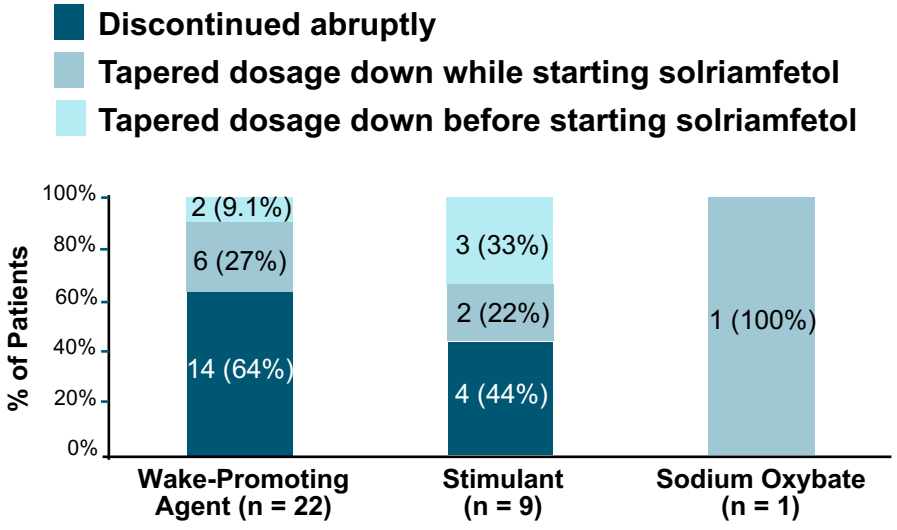
Solriamfetol Titration and AdministRaTion (START): Dosing and Titration Strategies

Discontinuation approach differed between OSA and narcolepsy groups

OSA



Narcolepsy



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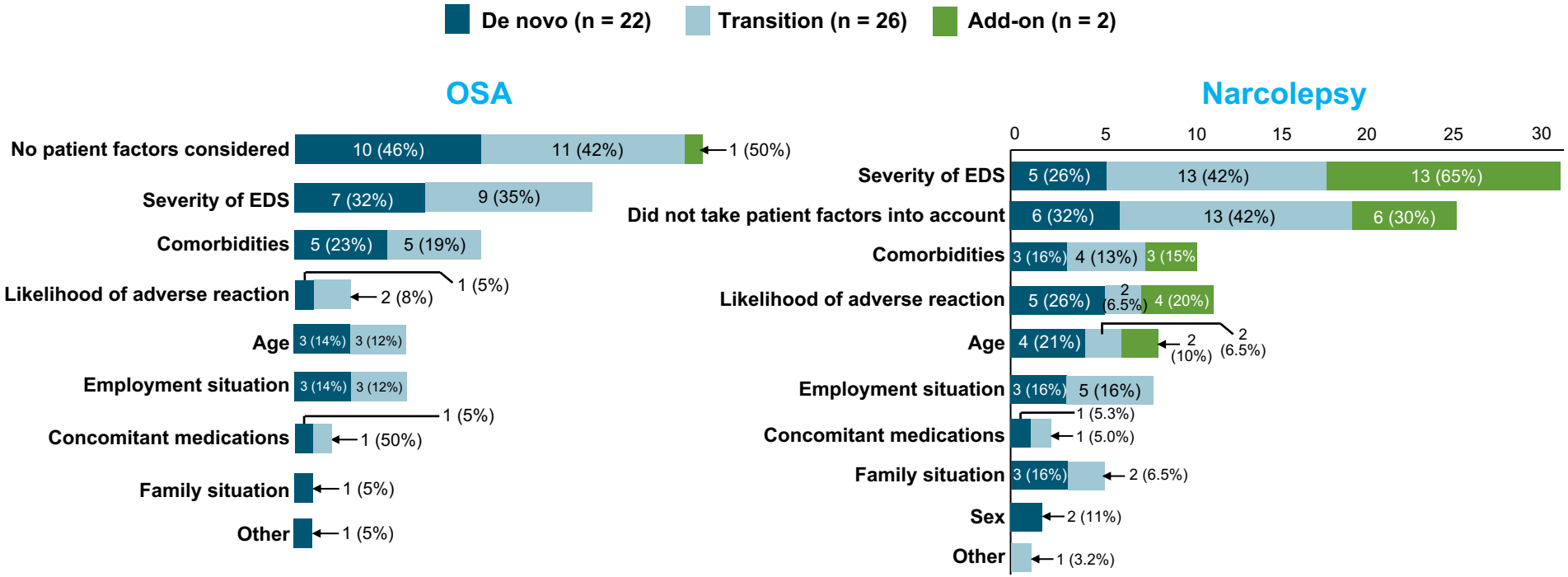
Solriamfetol Titration and AdministRaTion (START): Dosing and Titration Strategies

Number (%) of patients for whom physician considered each characteristic



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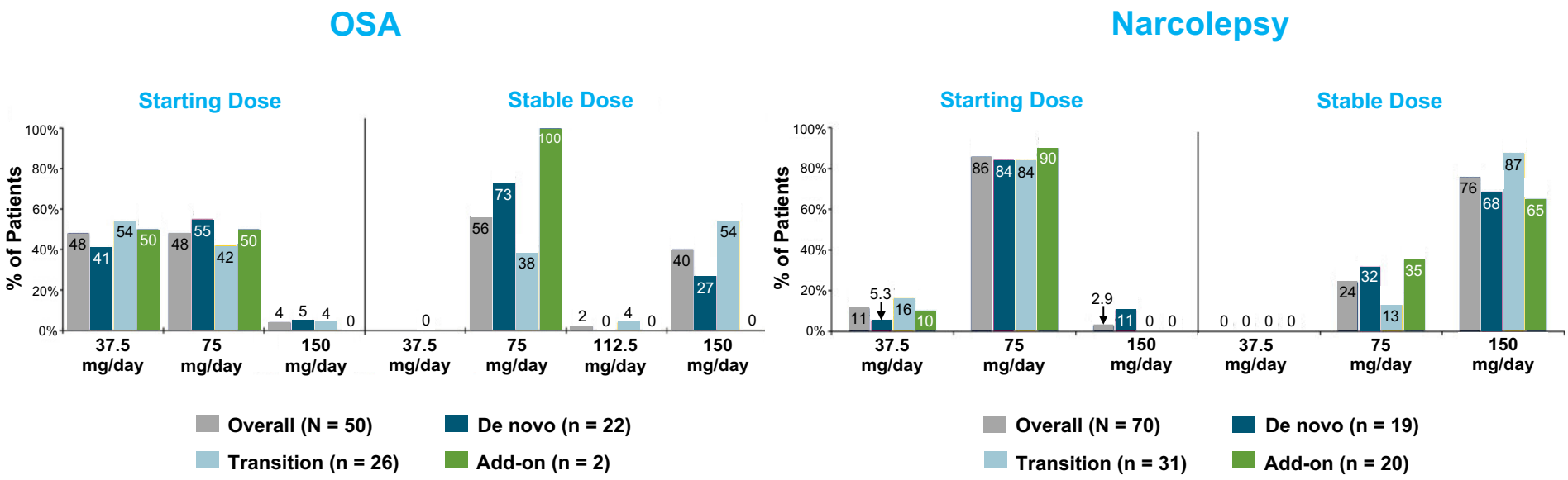
Dosing and titration strategies differed between OSA and narcolepsy groups



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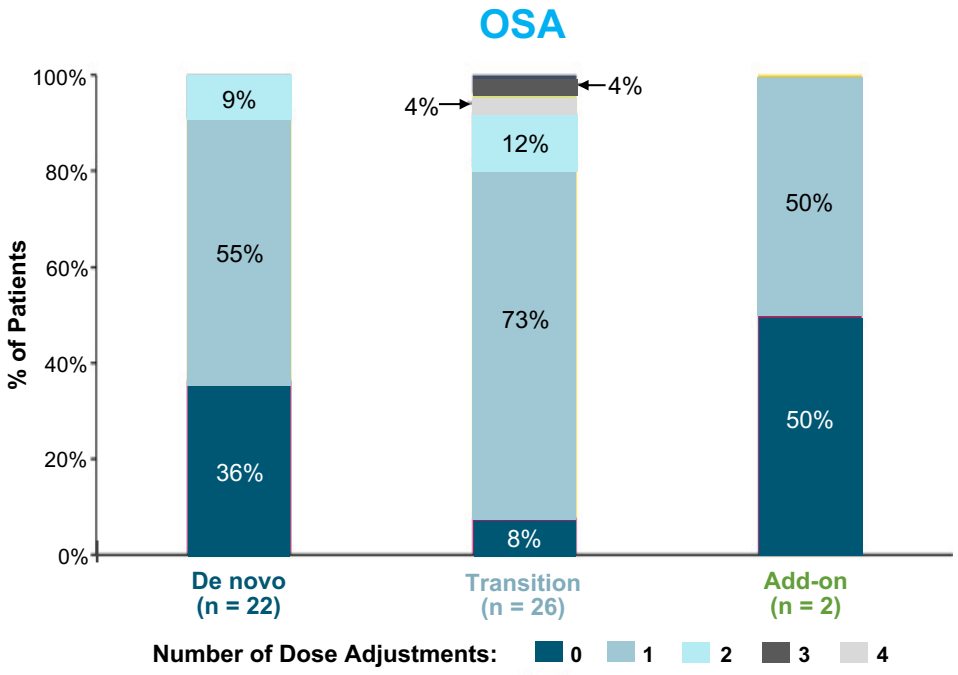

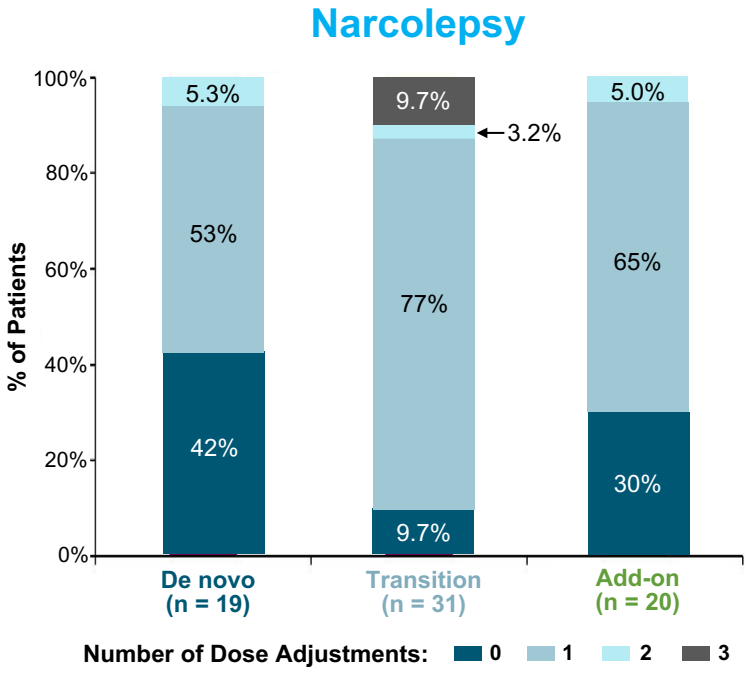

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Patient Case: Alvin

- 40-year-old Black male with severe OSA initiated on CPAP 8 months prior

What aspects of Alvin's presentation do we need to consider?

What should we consider regarding Alvin's modafinil?

What dosing, titration, and/or transitioning strategies should we use moving forward?

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Utilize efficacy data from FDA-approved treatments in developing treatment plans for patients with OSA-related EDS
- Develop personalized treatment plans that address needs specific to patients with OSA, such as cognitive impairment and obesity
- Initiate dosing and titration strategies that optimize outcomes for patients with OSA-related EDS

CMEO BriefCase 1

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

CMEO BriefCase 2

Treatment Factors: What Should Be Driving My Treatment Decisions?

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