Laying to Rest Challenges in Managing Excessive Daytime Sleepiness in Patients with Obstructive Sleep Apnea or Narcolepsy – An Augmented Reality Experience

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#SleepAR

FACULTY
Richard K. Bogan, MD, FCCP, FAASM
Michael J. Thorpy, MD

Recorded on Monday, June 15, 2020
Credit Expiration Date: Tuesday, June 15, 2021

This continuing education activity is provided by
INFORMATION FOR PARTICIPANTS

Statement of Need
Excessive daytime sleepiness (EDS) is a common symptom of obstructive sleep apnea (OSA) and narcolepsy. EDS is often associated with traffic accidents and occupational incidents, cognitive impairments, and increased risk of medical and psychiatric comorbidities, resulting in poorer quality of life (QoL) and increased mortality. Yet, the burden of EDS is often underestimated and devising effective strategies for management poses a significant challenge.

Advances in sleep medicine have offered increasingly detailed insight into the physiology of the sleep-wake cycle and its associated neurotransmitters. Subsequently, recent clinical trials have revealed the efficacy and safety of novel therapies in improving outcomes in patients with OSA or narcolepsy experiencing EDS. Translating these data into evidence-based practices is critical to reduce the burden of EDS.

This virtual symposium will examine the impact of EDS on clinical outcomes, QoL, and psychosocial functioning as well as the subsequent need for early detection and effective treatment. In order to apply the latest scientific updates in sleep medicine, this symposium will feature Augmented Reality, enabling expert faculty to walk clinicians through the core physiological mechanisms involved in sleep and the means by which current and novel therapies exert their clinical impact. By navigating recent clinical trial data on these therapies, clinicians should be better able to apply the latest evidence to practice, optimizing the management of EDS in patients with narcolepsy or OSA.

Learning Objectives
At the end of this CME/CE activity, participants should be able to:
• Recognize the burden of EDS in patients with OSA or narcolepsy.
• Apply the science of sleep to novel treatments for EDS to optimize treatment selection.
• Integrate efficacy and safety data into treatment decisions for EDS in patients with OSA or narcolepsy to improve QoL and functioning.

The following learning objectives pertain only to those requesting CNE or CPE credit:
• Recognize the burden of EDS in patients with OSA or narcolepsy.
• Explain the science of sleep for novel treatment decisions for EDS in patients with OSA or narcolepsy to improve QoL and functioning.
• Recognize the burden of EDS in patients with OSA or narcolepsy.

Target Audience
Sleep specialists, pulmonologists, psychiatrists, neurologists, PCPs, PAs, NPs, nurses, and pharmacists

Financial Support
Supported by an educational grant from Jazz Pharmaceuticals, Inc.

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Type: knowledge-based
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CREDIT REQUIREMENTS

FACULTY BIOS & DISCLOSURES

Richard K. Bogan, MD, FCCP, FAASM
Dr. Bogan is the President of Bogan Sleep Consultants, LLC. He is serving as Chief Medical Officer of SleepMed, Inc., the largest sleep diagnostic company in the United States. He is also Associate Clinical Professor at the University of South Carolina School of Medicine and Associate Clinical Professor at the Medical University of South Carolina in Charleston, S.C.

Dr. Bogan received his bachelor’s degree in chemistry from Wofford College and his MD degree from the Medical University of South Carolina in Charleston. He served his internship and residency, as well as Chief Medical Resident, at the University of Alabama Hospital and Clinics in Birmingham. Thereafter, he completed a fellowship and assistant professorship in the Pulmonary Division of the Department of Medicine at the University of Alabama School of Medicine. He has been certified by the American boards of Sleep Medicine, Internal Medicine, and Pulmonary Diseases.

Dr. Bogan has served as principal investigator on numerous clinical trials in the past and continues to do so now. He has a variety of publications and research interests that focus on topics such as narcolepsy, insomnia, sleep apnea, shift work sleep disorder, restless legs syndrome/periodic limb movement disorder, chronic fatigue/fibromyalgia, and circadian rhythm abnormality.

Michael J. Thorpy, MD
Dr. Thorpy is a Professor of Neurology at Albert Einstein College of Medicine and Director of the Sleep-Wake Disorders Center in the Department of Neurology at Montefiore Medical Center, both in New York. In addition to treating patients with sleep disorders, he conducts research in narcolepsy, insomnia and sleep apnea. He is President of the New York State Society of Sleep Medicine, Past President of the Sleep Section of the Academy of Neurology, and Past Secretary of the National Sleep Foundation. In 1993 Dr. Thorpy received the Nathaniel Kleitman Award from the American Academy of Sleep Medicine, one of the field’s highest honors, and in 2012 he received the Lifetime Achievement Award from the National Sleep Foundation.

Born in New Zealand, Dr. Thorpy earned his medical degree from the University of Otago Medical School. After receiving postgraduate training in Dunedin, New Zealand; Bombay, India; and London, England, he completed his residency in neurology at the State University of New York in Syracuse and a neuroendocrinology fellowship at Albert Einstein College of Medicine and Montefiore Medical Center. Dr. Thorpy is board certified in sleep disorders medicine.

Dr. Thorpy has published extensively on narcolepsy, insomnia, and sleep disorders. He chaired the first International Classification of Sleep Disorders and has published more than 200 peer-reviewed articles and chapters, including publications in journals such as The New England Journal of Medicine. His numerous books include “The Encyclopedia of Sleep and Sleep Disorders”, Parasomnias (2010), Sleepiness (2011), Neuroimaging of Sleep and Sleep Disorders (2012), Genetics of Sleep and Sleep Disorders (2013), Narcolepsy: A Clinical Guide (2016), and SleepMultiMedia, a computerized textbook of sleep medicine (v11.0 2018).

Dr. Thorpy has given more than 100 television, radio, and print interviews on sleep disorders.
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Dr. Bogan reports that he is a consultant for Harmony Biosciences, LLC; and Jazz Pharmaceuticals, Inc. He participates in industry funded research with Avadel/Flamel Ireland LTD; Axsome Therapeutics, Inc.; Balance; Eisai Inc.; Fresca; Jazz Pharmaceuticals Inc.; and Merck & Co., Inc. He is on the speakers bureau for Jazz Pharmaceuticals, Inc.; and Merck & Co., Inc. He is a shareholder, member of the Board of Directors, and Chief Medical Officer and employee of SleepMed, Inc. He receives other financial or material support as a member of the Board of Directors, First Community Corporation, SC and National Sleep Foundation.

Dr. Thorpy reports he receives research support from Avadel Pharmaceuticals; Axsome Therapeutics, Inc.; Balance Therapeutics; Harmony Biosciences, LLC; Jazz Pharmaceuticals, Inc. and Takeda Pharmaceuticals U.S.A., Inc. He is a consultant for Avadel Pharmaceuticals; Axsome Therapeutics, Inc.; Balance Therapeutics; Eisai Inc.; Harmony Biosciences, LLC; Jazz Pharmaceuticals, Inc. and Takeda Pharmaceuticals U.S.A., Inc.

Tony Graham, MD (peer reviewer) has no disclosures to report.
Mae Ochoa, RPh (peer reviewer) has no disclosures to report.
Kashemi D. Rorie, PhD (planning committee) has no disclosures to report.
Evan Lubberger (planning committee) has no disclosures to report.
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3. Be sure to fill in your ABIM ID number and DOB (MM/DD) on the evaluation, so we can submit your credit to ABIM.

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Learning Objective 1
Recognize the burden of EDS in patients with OSA or narcolepsy.

Learning Objective 2
Apply the science of sleep to novel treatments for EDS to optimize treatment selection.
Learning Objective 3
Integrate efficacy and safety data into treatment decisions for EDS in patients with OSA or narcolepsy to improve QoL and functioning.

Sleepiness in OSA and Narcolepsy is Nothing to Snooze On

EDS in OSA and Narcolepsy

- EDS in OSA
  - Despite adequate treatment with CPAP, patients with OSA still have residual EDS
  - The prevalence of residual sleepiness in patients with OSA on CPAP is estimated to be 5% - 10%

- EDS in Narcolepsy
  - Often the first symptom of narcolepsy
  - Identified as the most disruptive symptom by both patients (87.5%) and physicians (92%)

Impact of EDS
An Animated Tour

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**EDS in OSA and Depressed Mood or QoL**

- EDS (n = 828) vs. No EDS (n = 828) *p* < 0.05
- Those with EDS often have higher rates of depression and QoL based on MCI and SF-12/36 indicators
- Employees with OSA or EDS are at least 2X more likely to be involved in occupational incidents
- Brain fog
- Memory problems
- Impaired critical thinking
- Falling asleep throughout the day
- Worsened QoL
- Increased risk of accidents while driving

**Neurotransmitters Involved in the Sleep-Wake Cycle and Their Anatomical Locations**

An Animated Tour

**Mechanisms of Action of Solriamfetol, Traditional Stimulants, and Other Wake-Promoting Agents**

<table>
<thead>
<tr>
<th>Affinities and Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional stimulants (e.g. methylphenidate, dextroamphetamine)</td>
</tr>
<tr>
<td>Wake-promoting agents (e.g. modafinil)</td>
</tr>
<tr>
<td>Solriamfetol</td>
</tr>
<tr>
<td>Pitolisant</td>
</tr>
<tr>
<td>Sodium oxybate</td>
</tr>
</tbody>
</table>

$^1$DAT = dopamine transporter; NET = norepinephrine transporter; SERT = serotonin transporter


**Treatment Decision-Making for EDS in Patients with OSA or Narcolepsy**

Provided by CME Queen
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**FDA-Approved Treatments for EDS**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modafinil</td>
<td>Adult patients with excessive sleepiness associated with narcolepsy, OSA, or shift work sleep disorder</td>
</tr>
<tr>
<td>Armodafinil</td>
<td>Adult patients with excessive sleepiness associated with narcolepsy, OSA, or shift work sleep disorder</td>
</tr>
<tr>
<td>Sodium oxybate</td>
<td>Patients 7 years and older with cataplexy or EDS associated with narcolepsy</td>
</tr>
<tr>
<td>Solatamfetol</td>
<td>Adult patients with EDS associated with narcolepsy or OSA</td>
</tr>
<tr>
<td>Pirolant</td>
<td>Adult patients with EDS associated with narcolepsy</td>
</tr>
</tbody>
</table>

*Amphetamines and methylphenidate are approved for ADHD and narcolepsy but not EDS.
ADHD = attention deficit hyperactivity disorder

**Modafinil and Armodafinil: Efficacy**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Modafinil</th>
<th>Armodafinil</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESS score</td>
<td>4 (459)</td>
<td>3 (665)</td>
</tr>
<tr>
<td>Studies, n (patients)</td>
<td>4 (459)</td>
<td>3 (665)</td>
</tr>
<tr>
<td>Change from baseline (95% CI)</td>
<td>-1.94 (-2.67, -1.21)</td>
<td>-2.24 (-3.1, -1.32)</td>
</tr>
<tr>
<td>MWT sleep latency, minutes</td>
<td>3 (356)</td>
<td>2 (624)</td>
</tr>
<tr>
<td>Studies, n (patients)</td>
<td>3 (356)</td>
<td>2 (624)</td>
</tr>
<tr>
<td>Change from baseline (95% CI)</td>
<td>+3.55 (2.33, 4.78)</td>
<td>+3.60 (2.33, 4.87)</td>
</tr>
</tbody>
</table>

ESS = Epworth Sleepiness Scale; MWT = maintenance of wakefulness test

**Modafinil and Armodafinil: Safety**

- Most common AEs (≥ 5%)
  - Headache
  - Nausea
  - Nervousness
  - Rhinitis
  - Diarrhea
  - Back pain
  - Anxiety
  - Dizziness
  - Insomnia
  - Dyspepsia
- Reports of rash, including Stevens-Johnson
- May decrease effectiveness of hormonal contraceptive agents
- May increase heart rate and diastolic and systolic BP

*∝ is not a significant difference from placebo
**References:**
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Stimulants: Safety

- 58 patients who were taking high-dose stimulants for narcolepsy or idiopathic hypersomnia were compared with 58 control patients.1
  - High dose stimulants were > 120% 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 amphetamines2
- In 2016, an estimated 5,647,000 persons aged 12 and older reported misuse of prescription stimulants3


Novel and Emerging Therapies for EDS in Narcolepsy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Developmental/ Approval Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pitolisant</td>
<td>H3 receptor antagonist/inverse agonist</td>
<td>FDA-approved indication: adult patients with EDS associated with narcolepsy</td>
</tr>
<tr>
<td>Solriamfetol</td>
<td>Dopamine and norepinephrine reuptake inhibitor</td>
<td>FDA-approved indication: adult patients with EDS associated with narcolepsy or OSA</td>
</tr>
<tr>
<td>JZP-258 (low-sodium oxybate formulation)</td>
<td>GABA_A receptor modulator</td>
<td>Submitted: patients 7 years and older with cataplexy or EDS associated with narcolepsy</td>
</tr>
<tr>
<td>FT218 (long-acting sodium oxybate)</td>
<td>GABA_A receptor agonist</td>
<td>FDA-designated orphan drug; EDS and cataplexy in patients with narcolepsy</td>
</tr>
</tbody>
</table>


Interaction of Solriamfetol and the Sleep-Wake Cycle

An Animated Tour

Solriamfetol: Efficacy in Narcolepsy

- AEs (≥ 5% and greater than placebo) included headache, nausea, decreased appetite, insomnia, and anxiety.
  - p < .05; 2 p < .001 vs placebo
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**Solriamfetol: Efficacy in Narcolepsy and OSA**

- Figure A: ESS in 51-Week Maintenance Phase Group
  - ESS Score Mean (SD)
  - Solriamfetol 150 mg (n=9)
  - Solriamfetol 300 mg (n=9)
  - Narcolepsy (n=46)

- Figure B: ESS in the Randomized Withdrawal Phase
  - ESS Score Mean (SD)
  - Baseline (n=51)

- Mathematics A. et al. Sleep. 2019;42;1174-1175

**Solriamfetol: Safety**

- In a study of 24 patients with narcolepsy, at 2 hours post-dose, solriamfetol produced significantly lower standard deviation of lateral position (SDLP), or weaving, when driving compared to placebo.
- Impact of solriamfetol alone or in conjunction with stimulants on blood pressure and heart rate:
  - At 8 weeks there was no increase in percentage of non-dippers relative to baseline (placebo, 44%; solriamfetol combined 150 and 300 mg doses, 39%).
  - Additon of solriamfetol to stimulant therapy did not lead to significant increases in systolic or diastolic blood pressure, heart rate, or mean arterial pressure.
- Unlike modafinil/armodafinil and pitolisant, solriamfetol is unlikely to reduce effectiveness of birth control.
- Abuse potential comparable to or lower than phentermine in recreational drug users.

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**Interaction of Pitolisant and the Sleep-Wake Cycle**

An Animated Tour

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**Pitolisant: Efficacy in Narcolepsy**

- Figure: ESS Score Over Time
  - Baseline
  - Month 1
  - Month 2
  - Month 3
  - Month 4

- Davies L. et al. Sleep. 2019;42;1174-1175
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**Pitolisant: Efficacy in OSA**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pitolisant (n=21)</th>
<th>Placebo (n=6)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final ESS Score</td>
<td>9.1 (4.7)</td>
<td>12.1 (6.8)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Sleep Diary Variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change in daily number of sleepiness episodes</td>
<td>-1.79</td>
<td>-1.30</td>
<td>.056</td>
</tr>
<tr>
<td>Mean change in daily duration of sleepiness episodes</td>
<td>-47.87</td>
<td>-32.24</td>
<td>.066</td>
</tr>
<tr>
<td>Leeds Sleep Evaluation Questionnaire</td>
<td>10.21</td>
<td>2.42</td>
<td>155</td>
</tr>
<tr>
<td>Mean change in quality of sleep</td>
<td>17.70</td>
<td>13.50</td>
<td>.058</td>
</tr>
<tr>
<td>Mean change in Global LSEQ score</td>
<td>17.28</td>
<td>10.69</td>
<td>.005</td>
</tr>
<tr>
<td>CGI improvement at end of DB treatment</td>
<td>84%</td>
<td>56%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Patient Global Opinion</td>
<td>86%</td>
<td>66%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Improvement at end of DB treatment</td>
<td>24%</td>
<td>19.4%</td>
<td>.377</td>
</tr>
</tbody>
</table>

*Pitolisant is not FDA-approved for OSS in OSA.

**Pitolisant: Safety**

- AEs (> 5% and twice placebo) include:¹
  - Nausea
  - Insomnia
  - Anxiety

- Prolongs QT interval; may be greater in patients with hepatic or renal impairment²

- May reduce effectiveness of hormonal contraceptives³

- In a study of 303 patients (pitolisant = 172; placebo, n = 131) with narcolepsy, no clinically relevant effects on vital signs, laboratory findings, or ECG parameters were noted²

- Lower abuse potential compared to phentermine and overall profile to placebo³

**JZP-258: Efficacy in Narcolepsy**

<table>
<thead>
<tr>
<th>Change in ESS Score</th>
<th>JZP-258 (n = 69)</th>
<th>Placebo (n = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>15</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>-5</td>
</tr>
<tr>
<td>0</td>
<td>-5</td>
<td>-10</td>
</tr>
</tbody>
</table>

*Sign wraps at 10 to 10.

**JZP-258: Safety**

<table>
<thead>
<tr>
<th>AEs, n (%)</th>
<th>SDB Sleep (n = 69)</th>
<th>SDB + Other Antidepressants (n = 23)</th>
<th>Other Antidepressants (n = 83)</th>
<th>Total (n = 205)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>7 (9.5)</td>
<td>3 (13.0)</td>
<td>7 (8.4)</td>
<td>24 (11.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (2.8)</td>
<td>2 (8.7)</td>
<td>2 (2.4)</td>
<td>6 (2.9)</td>
</tr>
<tr>
<td>Distress</td>
<td>1 (1.4)</td>
<td>1 (4.3)</td>
<td>6 (7.2)</td>
<td>12 (5.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>1 (4.3)</td>
<td>6 (7.2)</td>
<td>7 (3.4)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0</td>
<td>1 (4.3)</td>
<td>6 (7.2)</td>
<td>7 (3.4)</td>
</tr>
<tr>
<td>Somnambulism</td>
<td>2 (2.8)</td>
<td>1 (4.3)</td>
<td>6 (7.2)</td>
<td>10 (4.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (2.8)</td>
<td>1 (4.3)</td>
<td>6 (7.2)</td>
<td>10 (4.9)</td>
</tr>
</tbody>
</table>

Incidence of emesis and somnambulism were low (3.5% and 2.0% of total participants, respectively)
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Theoretical Treatment Algorithm for Narcolepsy

- Trial of SXB in all NT1 and NT2 patients if acceptable to patient and no contraindications
  - If SXB not fully effective for EDS, then add solriamfetol
  - If SXB not fully effective for cataplexy then add pitolisant
- If unable to take SXB: Trial of pitolisant
  - If pitolisant not fully effective for EDS, then add solriamfetol
  - If pitolisant not fully effective for cataplexy then add venlafaxine
- If pitolisant contraindicated or unacceptable, then use solriamfetol
  - After stabilizing on solriamfetol add a NERI, if cataplexy is present, such as venlafaxine
- Rational: SXB and pitolisant are the only medications that treat both REM abnormalities and EDS

*NXB is not recommended for cataplexy.

Conclusions

- The burden of EDS is vast, encompassing diminished QoL, impaired cognitive functioning, poor workplace performance, mood changes, and changes in cortical functioning
- Limitations of long-time first-line therapies such as stimulants have shown issues with safety (e.g., tolerance, rebound, and withdrawal), indicating the need for therapies with a different mechanism of action
- Sodium oxybate is an effective treatment for all the main symptoms of narcolepsy
- Solriamfetol improves EDS associated with narcolepsy or OSA
  - For patients who have just daytime sleepiness, this may be the only medication needed
- Targeting histamine pathways with agents such as pitolisant have demonstrated efficacy in EDS in adults

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Identify the potential CNS pathophysiology of EDS in narcolepsy and OSA
- Incorporate into practice, effective treatments with novel mechanisms of action that can reduce the burden of EDS in narcolepsy and OSA while also reducing the risk for abuse

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**Laying to Rest Challenges in Managing Excessive Daytime Sleepiness in Patients with Obstructive Sleep Apnea or Narcolepsy - An Augmented Reality Experience**

with Richard K. Bogan, MD, FCCP, FAASM (Chair) and Michael J. Thorpy, MD

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