CME

Narcolepsy Abstract Highlights from AAN 2020

Maurice Ohayon, MD, PhD
Professor of Psychiatry and Behavioral Sciences
Stanford University
What is Narcolepsy?

A rare disorder characterized by excessive daytime sleepiness, often with periods of brief involuntary sleep and/or cataplexy

• Prevalence unknown and likely very under-diagnosed
• Susceptible to comorbidities (i.e., depression, anxiety, obesity)
• Pathophysiology linked to reduced orexin A and B
• Treatments focused on neurotransmitter systems believed to interact with orexins, including:
  • Catecholamine system (solriamfetol, amphetamines, methylphenidate, modafinil)
  • GABA system (sodium oxybate)
  • Histamine system (pitosilant)
• Numerous treatments in development

What is AAN 2020?

AAN Annual Meeting
• Scheduled for April
• Cancelled due to Covid-19
• Abstracts published in *Neurology Journal*
Natural History

Maurice Ohayon et al. Concomitant Evolution of Treatment and Symptoms of Narcolepsy in a Longitudinal Study

• 291 narcolepsy patients interviewed twice, 5 to 7 years apart

<table>
<thead>
<tr>
<th></th>
<th>First interview</th>
<th>Second interview</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersomnolence</td>
<td>100%</td>
<td>78.5%</td>
</tr>
<tr>
<td>Cataplexy</td>
<td>87.3%</td>
<td>76.1%</td>
</tr>
<tr>
<td>Taking narcolepsy medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS Stiulant</td>
<td>71%</td>
<td>56%</td>
</tr>
<tr>
<td>CNS depressant</td>
<td>49.2%</td>
<td>37%</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>19.1%</td>
<td>17%</td>
</tr>
<tr>
<td>Antidepressant + CNS stimulant</td>
<td>38.6%</td>
<td>29.6%</td>
</tr>
<tr>
<td></td>
<td>21.2%</td>
<td>16.1%</td>
</tr>
</tbody>
</table>

• Authors concluded narcolepsy is a chronic, debilitating disease that likely requires long term treatment

Ohayan M et al. Neurol. 2020; 94 (suppl).
FDA Approved Treatments

Sodium Oxybate

- Emmanuel Mignot et al. *Sodium Oxybate Treatment Effects on Sleep Architecture in Pediatric Patients With Narcolepsy With Cataplexy*
- Combined data from children (7-16 yrs) in a placebo-controlled trial (upto 1 year; n=86) plus open label extension (up to 2 years; n=44)
- In children switching from placebo to sodium oxybate, improvements in sleep architecture
  - Arousals/night measure (-43), N1% (-4.6%), N3% (12.6%).
- In children remaining on sodium oxybate, sleep architecture remained stable
- In placebo-controlled study: TEAEs included enuresis, nausea, vomiting, headache, weight loss
- In open-label extension: TEAEs included upper respiratory tract infection and nasopharyngitis

Mignot E et al. *Neurol.* 2020; 94 (suppl).
FDA Approved Treatments

Sodium Oxybate

- Emmanuel Mignot et al. Cataplexy-Free Days With Sodium Oxybate Treatment in Children/Adolescents With Narcolepsy With Cataplexy
  - Placebo-controlled randomized withdrawal study in children to determine if sodium oxybate can reduce cataplexy
  - Children/adolescents given SO (starting at a stable dose or titrated up to stable dose then remained at stable dose for 3 weeks. Followed by 2 week placebo-controlled withdrawal period and then a open label extension (up to 1 year)
  - In drug naïve patients (74), catalepsy free days/week changed from 0 at start of the study to 4 by end of the titration phase. During the stable dose phase, catalepsy free days/week remained similar in the ] drug naïve patients (4.2; n=66) and those previously taking SO (4.8; n=32)
  - During the withdrawal phase, participants randomized to placebo saw their catalepsy free days/week drop to 0 (n=32) while those remaining on SO saw no significant change (4.0 catalepsy free days/week; n=31)

Mignot E et al. Neurol. 2020; 94 (suppl).
FDA Approved Treatments

Pitolisant

• *Eric Bauer et al. Safety and Tolerability of Pitolisant in the Treatment of Adult Patients With Narcolepsy: An Open-Label, Expanded Access Program in the United States*

• Pitolisant Expanded Access Clinical Evaluation (PEACE) provided adult patients with narcolepsy access to treatment with pitolisant while it was an investigational medication (N=623; 88% previously used other narcolepsy medication)

• 35.2% discontinued
  • 16.7% due to AEs
  • 12.2% due to lack of efficacy

• Most AEs mild to moderate (94.8%)

<table>
<thead>
<tr>
<th>AE</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>10.8%</td>
</tr>
<tr>
<td>Nausea</td>
<td>7.2%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5.9%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5.4%</td>
</tr>
</tbody>
</table>

Bauer E et al. Neurol. 2020; 94 (suppl).
FDA Approved Treatments

Pitolisant

- **Craig Davis et al. Efficacy of Pitolisant in Patients With High Burden of Narcolepsy Symptoms**
- Pooled data from 2 placebo-controlled trials (7-8 weeks of treatment)
  - Post-hoc analysis #1 (108 patients w/ Epworth Sleepiness Scale > 16
    - Mean decrease in EES from baseline:
      - Pitolisant group (n=54); **6.1**
      - Placebo group (n=54); **2.6 (P = .0002)**
  - Post-hoc analysis #2 (105 patients w/ sleep latency ≤ 8 min in Maintenance of Wakefulness Test
    - Mean increase in sleep latency from baseline:
      - Pitolisant group (n=59); **7.0 minutes**
      - Placebo group (n=46); **3.4 minutes (P = .0089)**
  - Post-hoc analysis #3 (31 patients w/ > 15 catalepsy attacks per week
    - Mean decrease in attacks from baseline:
      - Pitolisant group (n=59); **17.9 attacks/week (21.8 baseline vs 3.9 final)**
      - Placebo group (n=46); **2.7 attacks/week (20.9 baseline vs 18.2 final) (P < .001)**

Davis C et al. *Neurol.* 2020; 94 (suppl).
FDA Approved Treatments

Pitolisant

• *Annika Triller et al. Effects of Pitolisant on Nighttime Sleep*
• Drug known to reduce daytime sleepiness but does it improve nighttime sleep?
• 15 patients with narcolepsy type 1 given pitolisant for 6 – 12 months

<table>
<thead>
<tr>
<th></th>
<th>Total sleep time</th>
<th>Sleep efficacy</th>
<th>Arousal index</th>
<th>Slow wave sleep</th>
<th>REM sleep</th>
<th>PSQI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>361.5 min</td>
<td>78.8%</td>
<td>18.7</td>
<td>17%</td>
<td>19%</td>
<td>8.9</td>
</tr>
<tr>
<td>On-treatment</td>
<td>362.5 min</td>
<td>79.7%</td>
<td>17.7</td>
<td>15%</td>
<td>18.5%</td>
<td>9.1</td>
</tr>
</tbody>
</table>

• Authors concluded that real-world data would suggest there is no significant change in sleep architecture in narcolepsy patients treated with pitolisant.

Triller A et al. *Neurol.* 2020; 94 (suppl).
FDA Approved Treatments

Solriamfetol

- *Nancy Foldvary-Schaefer et al.* Long-Term Effects of Solriamfetol on Functioning and Work Productivity in Participants With Excessive Daytime Sleepiness Associated With Narcolepsy
- Long-term extension study in patients taking solriamfetol (75/150/300 mg) for up to 50 weeks

<table>
<thead>
<tr>
<th>Efficacy (changes from baseline)</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOSQ-10 score (mean change)</td>
<td>Headache</td>
</tr>
<tr>
<td>WPAI-SHP</td>
<td>Nausea</td>
</tr>
<tr>
<td>• Activity impairment outside work</td>
<td>Anxiety</td>
</tr>
<tr>
<td>• Impairment while working</td>
<td>Nasopharyngitis</td>
</tr>
<tr>
<td>• Overall work impairment due to problem</td>
<td>Reduced appetite</td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
</tr>
<tr>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>-26.7%</td>
<td></td>
</tr>
<tr>
<td>-29.5%</td>
<td></td>
</tr>
<tr>
<td>-29.5%</td>
<td></td>
</tr>
</tbody>
</table>

FDA Approved Treatments

Solriamfetol

- *Russell Rosenberg et al.* Clinically Relevant Effects of Solriamfetol on Excessive Daytime Sleepiness: A Post-Hoc Analysis of the Magnitude of Change in a Clinical Trial of Adults With Narcolepsy
- 12-week, Phase 3 clinical trial comparing placebo to salriamfetol (3 doses)
- Baseline ESS scores ranged 17.0 – 17.3 in the 4 groups

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=58)</th>
<th>Solriamfetol (75 mg; n=59)</th>
<th>Solriamfetol (150 mg; n=55)</th>
<th>Solriamfetol (300 mg; n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with ESS score ≤ 10</td>
<td>15.5%</td>
<td>30.5%</td>
<td>40.0%</td>
<td>49.2%</td>
</tr>
<tr>
<td>% with ≥ 25% decrease in ESS score from baseline</td>
<td>27.6%</td>
<td>44.1%</td>
<td>47.3%</td>
<td>62.7%</td>
</tr>
</tbody>
</table>

- AEs mild to moderate (headache, nausea, decreased appetite, nasopharyngitis, dry mouth, anxiety)

Rosenberg R et al. *Neurol.* 2020; 94 (suppl).
FT218

- *Jordon Dubow et al. Pharmacokinetics and Formulation Selection of FT218, a Once-Nightly Sodium Oxybate Formulation for the Treatment of Narcolepsy*
  - FT201 is a once, nightly formulation of Micropump controlled-release sodium oxybate
  - Pilot PK study in 16 health volunteers to compare pharmacokinetics of once nightly FT218 with twice nightly sodium oxybate
  - Study observed favourable PK profiles favorable for sustained efficacy similar to twice nightly sodium oxybate
  - Drug is currently being evaluated in a Phase 3 pivotal study.
Treatment Options: In Development (or newly approved)

JZP-258

- **Nancy Foldvary-Schaefer et al.** Efficacy and Safety of JZP-258 in a Phase 3, Placebo-controlled, Double-blind, Randomized Withdrawal Study in Adults with Narcolepsy with Cataplexy
  - JZP-258 is a novel oxybate product (less sodium)
  - Currently under review by the FDA (PDUFA date July 21, 2020)
  - FDA review largely based on Phase 3 study – two abstracts focused on that study published for AAN 2020
- Trial design
  - 201 adults (18-70 yrs) with narcolepsy and catalepsy enrolled in the study
  - Initially, patients received titrating doses of JZP-258 got 12 weeks followed by 2 week stable dose period (open-label)
  - 134 patients then randomized to placebo (n=65) or JZP-258 (n=69) for 2 weeks
  - Primary endpoint was change in average weekly cataplexy attacks (comparing end of 2 week stable dose phase to end of 2 week randomized phase)

Treatment Options: In Development (or newly approved)

JZP-258

- Nancy Foldvary-Schaefer et al. Efficacy and Safety of JZP-258 in a Phase 3, Placebo-controlled, Double-blind, Randomized Withdrawal Study in Adults with Narcolepsy with Cataplexy
  - Results

<table>
<thead>
<tr>
<th></th>
<th>JAZ-258 to Placebo</th>
<th>JZP-258 continued</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median weekly cataplexy attacks</td>
<td>2.35</td>
<td>0</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Median ESS scores</td>
<td>2.0</td>
<td>0</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>% of patients who thought narcolepsy worsened</td>
<td>44.6%</td>
<td>4.3%</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>% of patients who thought narcolepsy worsened</td>
<td>60.0%</td>
<td>5.9%</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

- TEAEs: headache (20.4%), nausea (12.9%), dizziness (10.4%)

Treatment Options: In Development (or newly approved)

JZP-258

- *Michael Thorpy et al.* Changes in Cataplexy Frequency by Therapy at Study Entry in a Phase 3, Placebo-Controlled, Double-Blind, Randomized Withdrawal Study of JZP-258 in Adults With Narcolepsy With Cataplexy
  - Looked at cataplexy rates during open label phase of study when patients were being tapered off other treatments (off all other meds by week 10 of initial titration phase)

<table>
<thead>
<tr>
<th></th>
<th>Sodium oxybate (n=41)</th>
<th>Sodium oxybate + other anticateplectic (n=14)</th>
<th>Other anticateplectic (n=21)</th>
<th>Anticateplectic naïve (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1 of open-label 12 week titration phase</td>
<td>2.0</td>
<td>0.6</td>
<td>3.5</td>
<td>5.8</td>
</tr>
<tr>
<td>End of open-label 12 week titration phase</td>
<td>1.0</td>
<td>2.2</td>
<td>2.3</td>
<td>2.0</td>
</tr>
<tr>
<td>End of open-label 2 week steady dose phase</td>
<td>1.0</td>
<td>2.0</td>
<td>2.0</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Thorpy M et al. *Neurology.* 2020; 94 (suppl).
Summary

• Narcolepsy is a rare sleeping disorder
• Significant impact on person’s quality of life and productivity
• Treatment available and many more in development
• AAN 2020
• Approved treatments continue to show efficacy
• Newer treatments show promise