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CME

Narcolepsy Abstract Highlights from AAN 2020

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What is Narcolopsy?

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

Thorpy, Hiller. *Am Health Drug Ben*. 2017; 10:233-21. Mahoney et al *Nat Rev Neurosci* 2019;20:83-93. Morse. *Med Sci* 2019; 15: 522-529. Black et al. *Sleep Med* 2014; 15: 522-529.

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 nacroplepsy patients interviewed twice, 5 to 7 years apart

	First interview	Second interview
Hypersomnolence	100%	78.5%
Cataplexy	87.3%	76.1%
Taking narcolepsy medications	71%	56%
CNS Stiulant	49.2%	37%
CNS depressant	19.1%	17%
Antidepressant	38.6%	29.6%
Antidepressant + CNS stimulant	21.2%	16.1%

- 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% previoused 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%)

AE	% of Patients
Headache	10.8%
Nausea	7.2%
Anxiety	5.9%
Insomnia	5.4%

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

	Total sleep time	Sleep efficacy	Arousal index	Slow wave sleep	REM sleep	PSQI
Baseline	361.5 min	78.8%	18.7	17%	19%	8.9
On-treatment	362.5 min	79.7%	17.7	15%	18.5%	9.1

- Authors concluded that real-world data would suggest there is no significant change in sleep artchitecture 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

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

Foldvary-Schaefer N et al. *Neurol.* 2020; 94 (suppl).

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

	Placebo (n=58)	Solriamfetol (75 mg; n=59)	Solriamfetol (150 mg; n=55)	Solriamfetol (300 mg; n=59)
% with ESS score $\leq$ 10	15.5%	30.5%	40.0%	49.2%
% with $\geq$ 25% decrease in ESS score from baseline	27.6%	44.1%	47.3%	62.7%

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

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

Treatment Options: In Development

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.

Dubow J et al. *Neurol.* 2020; 94 (suppl).

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 weely cataplexy attacks (comparing end of 2 week stable dose phase to end of 2 week randomized phase)

Foldvary-Schaefar N et al. *Neurol.* 2020; 94 (suppl).

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**

	JAZ-258 to Placebo	JZP-258 continued	P-value
Median weekly catapelexy attacks	2.35	0	< .0001
Median ESS scores	2.0	0	< .0001
% of patients who thought narcolepsy worsened	44.6%	4.3%	< .0001
% of patients who thought narcolepsy worsened	60.0%	5.9%	< .0001

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

Foldvary-Schaefar N et al. *Neurol.* 2020; 94 (suppl).

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 catalepsy 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)

Median Weekly Catelepsy

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

Thorpy M et al. *Neurol.* 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