Thomas Roth
Henry Ford Hospital
Narcolepsy Network

September 28, 2017
Tools for Diagnosing Narcolepsy

• Clinical history
• Sleep diary
• Questionnaires
• Sleep laboratory evaluation
  – Polysomnography
  – Multiple Sleep Latency Test (MSLT)
• International Classification of Sleep Disorder (ICSD-2) criteria
Narcolepsy: Validation of a Daily Electronic Diary

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# Epworth Sleepiness Scale

0 = would never doze  
1 = slight chance of dozing  
2 = moderate chance of dozing  
3 = high chance of dozing

<table>
<thead>
<tr>
<th>Situation</th>
<th>Chance of Dozing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting and reading</td>
<td>_______</td>
</tr>
<tr>
<td>Watching television</td>
<td>_______</td>
</tr>
<tr>
<td>Sitting inactive in a public place</td>
<td>_______</td>
</tr>
<tr>
<td>As a passenger in a car for an hour without a break</td>
<td>_______</td>
</tr>
<tr>
<td>Lying down to rest in the afternoon</td>
<td>_______</td>
</tr>
<tr>
<td>Sitting and talking to someone</td>
<td>_______</td>
</tr>
<tr>
<td>Sitting quietly after a lunch without alcohol</td>
<td>_______</td>
</tr>
<tr>
<td>In a car while stopped for a few minutes in traffic</td>
<td>_______</td>
</tr>
</tbody>
</table>

Adapted with permission from Johns. *Sleep*. 1991;14:540-545.
ES Severity Across Disorders

Baseline ESS Scores in Clinical Studies:

- Narcolepsy (N=254)\(^1\)
- Severe untreated OSA (N=13)\(^2\)
- Parkinson’s disease (N=20)\(^3\)
- Seasonal affective disorder (N=12)\(^4\)
- MDD with ES/fatigue (N=38)\(^5\)
- Depression, untreated (N=135)\(^6\)
- Depression, partial response to antidepressant (N=135)\(^7\)
- Multiple sclerosis (N=72)\(^8\)


OSA, obstructive sleep apnea; MDD, major depressive disorder.
Cataplexy is Pathognomonic to Narcolepsy
Specific But Not Sensitive

- Cataplexy present in the majority of patients (64%-90%)
- First episode of cataplexy typically occurs several weeks or months after the onset of EDS, although it may be delayed for decades
- In ~10% of cases, cataplexy is the first symptom to appear
- Cataplexy is often misdiagnosed as a seizure

Swiss Narcolepsy Scale (SNS)

- Brief screening tool for narcolepsy with cataplexy\(^1\)
- Patients assign a value to each of 5 questions based on frequency of symptom occurrence\(^1,2\):
  - 1 = “never”, 5 = “almost always” or “almost daily”
  - Score calculated based on weighted equation
- Score <0 is suggestive of narcolepsy with cataplexy\(^1,2\)
  - Sensitivity of 96% and specificity of 98% in narcolepsy with cataplexy\(^2\)

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The Swiss Narcolepsy Score (SNS)


<table>
<thead>
<tr>
<th>Q1</th>
<th>How often are you unable to fall asleep?</th>
</tr>
</thead>
<tbody>
<tr>
<td>[5] almost always</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q2</th>
<th>How often do you feel bad or not well rested in the morning?</th>
</tr>
</thead>
<tbody>
<tr>
<td>[5] almost always</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q3</th>
<th>How often do you take a nap during the day?</th>
</tr>
</thead>
<tbody>
<tr>
<td>[5] almost daily</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q4</th>
<th>How often have you experienced weak knees/buckling of the knees during emotions like laughing, happiness, or anger?</th>
</tr>
</thead>
<tbody>
<tr>
<td>[5] almost always</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q5</th>
<th>How often have you experienced sagging of the jaw during emotions like laughing, happiness, or anger?</th>
</tr>
</thead>
<tbody>
<tr>
<td>[5] almost always</td>
<td></td>
</tr>
</tbody>
</table>

**Calculation:**

Narcolepsy score = \(6 \times Q_1 + 9 \times Q_2 - 5 \times Q_3 - 11 \times Q_4 - 13 \times Q_5 + 20\)

**Evaluation/Analysis:**

Narcolepsy score <0: narcoleptic
Narcolepsy score >0: non-narcoleptic hypersonniac

In a bicenter study (Zürich–Leyden), a SNS score <0 was found to have a sensitivity of 94% and a specificity of 89% for the diagnosis of hypocretin-deficient narcolepsy (in preparation)

The SNS is scored using a weighted equation: \(6 \times Q_1 + 9 \times Q_2 - 5 \times Q_3 - 11 \times Q_4 - 13 \times Q_5 + 20\)

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*Figure adapted from* Bassetti CL. In: Baumann CR et al, eds. *Narcolepsy*. Springer New York; 2011:309-319.
Cataplexy

- How often do you experience Cataplexy?
- What is a mild manifestation?
- What is a severe manifestation?
- What triggers it?
- Can you prevent it?
• All cataplexy events to be captured on ePRO

• Careful ePRO training required to ensure accurate capture of events.

  ▪ Ensure all cataplexy events captured not just collapse at the knees events.

  ▪ Patient discussion using terminology that resonates with subjects: (Patient feedback)

    ➢ “Melting in knees” “Knees Buckling”
    ➢ “Head nod” Head Thing”
    ➢ “Eye Drop” “Eye Trickle”
    ➢ “Jaw Droop”
Other Diagnostic Tools

• Human leukocyte antigen (HLA) testing

• Hypocretin assays in CSF
HLA Testing*
Utility in Aiding or Ruling Out Diagnosis of Narcolepsy

- HLA DRB1*15 and DQB1*0602 genotypes associated with narcolepsy
- DQB1*0602 strongly associated with presence and severity of cataplexy
  - Present in 76% of patients with cataplexy vs 41% of those without cataplexy vs 24% of general population
- DQB1*0602 common in patients without narcolepsy
  - Not definitive for diagnosing narcolepsy as much as its absence argues against a diagnosis of narcolepsy
- DQB1*0602 positivity less helpful in familial narcolepsy than in “sporadic” narcolepsy

* Commercially available.
HLA in Cases With and Without Cataplexy

Hypocretin system. The sleep-wake cycle is governed by a complex, multilevel neuronal system in the brain stem, thalamus, hypothalamus, and basal forebrain. Neurones in the hypothalamus producing hypocretin stabilize the activity of other key neuronal groups involved in the control of sleep and waking: these nuclei and their principal neurotransmitters are shown here in highly schematic fashion.
CSF Hypocretin-1 as a Diagnostic Test

Mignot et al. 2002.
Clinical Evaluation

• Hallmark symptoms of narcolepsy:
  – EDS
  – Cataplexy
  – Vivid hallucinations upon falling sleep or awakening from sleep
  – Brief episodes of total paralysis upon falling asleep or awakening from sleep

• EDS is the most common initial symptom, occurring alone in ~46% of patients and with other symptoms in ~33% of patients

• >60% of patients present with only 1 hallmark symptom

• <10% of patients present with all 4 hallmark symptoms


Additional Symptoms

- Disturbed Nocturnal Sleep
- Mental Fog
Disturbed Nocturnal Sleep

• How often do you experience it

• Nature (can't fall asleep, can't fall back to sleep, frequent awakenings)

• How troublesome is it? Does it make sleepiness worse
Narcolepsy: Sleep-Wake State Instability

Normal Sleep-Wake Pattern

Wakefulness
REM Sleep
NREM Sleep

Time of Day

Narcolepsy Sleep-Wake Pattern

Wakefulness
REM Sleep
NREM Sleep

Time of Day

Wake and Sleep are Poorly Consolidated in Narcolepsy
Hypnograms From 24-Hour Polysomnographic Recordings

Control Subject

Untreated Narcolepsy

Adapted with permission from Rogers et al. Sleep. 1994;17:590-597.
Mental Fog

• How often do you experience it?

• What is the subjective experience?

• When does it occur and How long does it last?

• Do you think it is related to your sleepiness?

• Do your stimulant medication help?
Key Features to Query for in the Clinical History

- Age at onset
- Duration of symptoms
- Length of naps and their recuperative quality
- Duration and quality of nocturnal sleep
- Family history
Age of Onset of EDS and Cataplexy in Narcolepsy

Peaks in Late Teens

Other Symptoms (if present) Lag by 4-5 Years

Adapted with permission from Ohayon al. J Psychosom Res. 2005;59:399-405.
Age at Onset of Common Sleep Disorders

- Obstructive sleep apnea
  - Increases with age up to age 65 y
  - Highest prevalence in 50-64 year olds

- Chronic insomnia
  - Older adults, particularly postmenopausal women

- RLS
  - Increases with age up to age 60 y
  - Highest prevalence in 50-59 year olds

Heistand et al. *Chest*. 2006;130;780-786.
Narcolepsy Is Underdiagnosed

- Prevalence
  - General US population estimate: 1 in 2000\(^1\)
- Onset typically before the age of 25 years\(^2\)
- Often >10-year delay in diagnosis\(^3,4\)
- Estimated approximately 50% or more of patients with narcolepsy remain undiagnosed\(^1\)
- In a sample of US sleep clinics, narcolepsy was the primary sleep diagnosis in approximately 5% of patients\(^5\)

Time to Diagnosis Delayed

- Median time to diagnosis of narcolepsy is 10.5 years (range, 1-61 years)
  - Diagnosis occurring more rapidly with increased awareness and improved tools for diagnosis
    - Since 1980; median, 3.5 years (range, 1.5-7.25 years)
  - Time to diagnosis shorter when cataplexy is a presenting symptom
    - Median, 5.5 years with cataplexy vs 14.5 years without cataplexy
Delay in Diagnosis

• What are the main causes of the delay?

• What are common misdiagnoses?

• Why is it getting better?

• Where is education need to be directed?
  Pediatricians, Educators, Parents, Neurologists?
Differentiating Narcolepsy From Idiopathic Hypersomnia

- **Narcolepsy**
  - Naps are more refreshing
  - Higher propensity to fall asleep (higher Epworth Sleepiness Scale [ESS] scores)
  - Patients experience more frequent and longer nocturnal awakenings

- **Idiopathic Hypersomnia**
  - Naps are typically unrefreshing
  - Nocturnal sleep is typically longer (>10 hours) and not punctuated by awakenings
  - Tendency for improvement in ESS over time
  - High frequency of comorbid psychoaffective complaints

Polysomnographic Findings in Narcolepsy

- Short nocturnal REM latency
  - 50% time <60 minutes - sleep onset REM periods (SOREMPs)
- Signs of disruptive nocturnal sleep include:
  - Increased proportion of stage 1 sleep
  - Increased wake after sleep onset
  - Lower sleep efficiencies
- Periodic leg movements (>10/hour) in ~ 40% of subjects with cataplexy
PolysomnographyInsensitive in Diagnosing Narcolepsy –
MSLT Required

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polysomnography</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOREMP</td>
<td>29</td>
<td>99</td>
</tr>
<tr>
<td>SOREMP and sleep latency &lt;10 min</td>
<td>27</td>
<td>99</td>
</tr>
<tr>
<td><strong>MSLT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 SOREMPs</td>
<td>80</td>
<td>93</td>
</tr>
<tr>
<td>≥2 SOREMPs and MSL &lt;5 min</td>
<td>70</td>
<td>97</td>
</tr>
<tr>
<td>≥2 SOREMPs and MSL &lt;8 min*</td>
<td>78</td>
<td>95</td>
</tr>
</tbody>
</table>

* Consistent with ICSD-2 criteria.

Adapted with permission from Aldrich et al. *Sleep*. 1997;20:620-629.
## Summary

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Narcolepsy</th>
<th>Sleep Apnea</th>
<th>Insomnia</th>
<th>RLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDS</td>
<td>Always</td>
<td>Variable</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Cataplexy</td>
<td>Usually</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Variable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep paralysis</td>
<td>Variable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset</td>
<td>Younger</td>
<td>Older</td>
<td>Older</td>
<td>Older</td>
</tr>
<tr>
<td>Family history</td>
<td>Occasional</td>
<td>Occasional</td>
<td>Frequent</td>
<td>Frequent</td>
</tr>
<tr>
<td>ESS (mean)</td>
<td>11.2</td>
<td>10.3</td>
<td>7.0</td>
<td>8.8</td>
</tr>
<tr>
<td>MSLT (mean)</td>
<td>6.5</td>
<td>10.4</td>
<td>15.0</td>
<td>12.8</td>
</tr>
</tbody>
</table>

Treatment of Narcolepsy
Behavioral Strategies

• Take short, regularly scheduled naps
• Adhere to a consistent sleep / wake schedule
• Exercise for at least 20 minutes per day at least 4 or 5 hours before bedtime
  – Regular exercise for prevention of obesity important in children with narcolepsy
• Maintain a comfortable, adequately warmed bedroom environment
• Engage in relaxing activities (eg, warm bath) before bedtime
• Avoid alcohol and caffeine-containing beverages for several hours before bedtime
• Avoid smoking, especially at night
• Take advantage of patient support groups (www.narcolepsynetwork.org)

Behavioral Strategies

• What behavioral strategies work best for you in managing daytime sleepiness

• What behavioral strategies work best for other narcolepsy symptoms?
Treatment of Narcolepsy
Pharmacologic Intervention

• EDS
  – Modafinil*
  – Amphetamine / methamphetamine / dextroamphetamine*
  – Methylphenidate*
  – Sodium oxybate*
  – Selegilene

• Cataplexy
  – Sodium oxybate*
  – Selegilene
  – Serotonin-norepinephrine reuptake inhibitors (SNRIs)
  – Tricyclic antidepressants (TCAs)
  – Selective serotonin reuptake inhibitors (SSRIs)

* Approved by the US FDA for the treatment of narcolepsy.
Combination Therapy

• Many patients require treatment with a wake-promoting agent and an anticataplectic

• Clinical trial evidence supporting efficacy is limited
  – To date, only 1 study evaluating combination therapy (modafinil plus sodium oxybate) has been published*

• Combination therapy can also consist of 1 short-acting and 1 long-acting psychostimulant
  – Achieve alertness quickly and maintain alertness for longer periods of time
  – Avoid insomnia as an unwanted side effect
  – Formulation and isomers are critical

## Psychostimulants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Level of Evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amphetamines</strong></td>
<td>Guideline - 3 level II, grade B studies - 2 level V, grade C studies - Long clinical practice</td>
<td>Not rated - 3 class II studies - 1 class IV study - 1 other study</td>
</tr>
<tr>
<td><strong>Methylphenidate</strong></td>
<td>Guideline - 1 level II, grade B study - 3 level V, grade C studies - Long clinical practice</td>
<td>Not rated - 1 class II study - 2 class IV study - 2 other studies</td>
</tr>
</tbody>
</table>

Sodium Oxybate (GHB) (Xyrem*)

- Might act via $\text{GABA}_B$ or specific gamma-hydroxybutyrate receptors
- Reduces DA release at night, likely to cause secondary DA increase during day
- Need bi-nightly dosing with immediate effects on disturbed nocturnal sleep
- Therapeutic effects on cataplexy and daytime sleepiness often delayed
- Dosage range: 4.5-9 grams total at night; half at HS, half 4 hours later

*Xyrem is indicated for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy; GHB = gamma-hydroxybutyrate; HS = bedtime; Sodium oxybate (2006), package insert, Available at: www.accessdata.fda.gov
Treatment of Narcolepsy With Stimulants

Mitler MM et al. (1990), J Clin Neurophysiol 7(1):93-118
Relative Efficacy of Drugs for the Treatment of Sleepiness in Narcolepsy

Long-Term ESS: Modafinil in Narcolepsy

ESS = Epworth Sleepiness Scale; Schwartz JR et al. (2004), Presented at the American College of Chest Physicians
Compared to baseline, the nightly administration of sodium oxybate was associated with dose-related improvements in Epworth Sleepiness Scale scores at the end of the 8-week trial; *p<0.001 compared to placebo; B = baseline, E = end point; Xyrem International Study Group (2005), J Clin Sleep Med 1(4):391-397
Long-Term Efficacy in the Management of EDS

Sodium Oxybate: 12-Month Open-Label Study

ESS Score (Median)

Entry in previous 4-week double-blind study (GHB-2)

* p<0.001 vs. baseline, N=117; GHB-3; Stimulant medications maintained; U.S. Xyrem Multicenter Study Group (2003), Sleep 26(1):31-35
Daytime Sleep Latency: Maintenance of Wakefulness

Daytime Sleep Latency (Minutes)

Visit 2 | Visit 3 | Visit 4 | Visit 5
--- | --- | --- | ---
Placebo | Modafinil | Sodium Oxybate/Modafinil

Black J, Houghton WC (2006), Sleep 29(7):939-946
# Future Possible Treatments of Narcolepsy

<table>
<thead>
<tr>
<th>Treatment Types</th>
<th>Advantages and Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-hypocretin-based therapies</td>
<td>Inhibitors of DA reuptake likely to be mild stimulants; inhibitors of adrenergic uptake likely to be anticataplectic agents. Possibly targeting multiple reuptake sites; may be developed in the context of depression, wake-promotion, attention-deficit/hyperactivity disorder treatments or as therapies for cocaine or stimulant abuse</td>
</tr>
<tr>
<td>Novel monoaminergic reuptake inhibitors</td>
<td>The efficacy of sodium oxybate (GHB) suggests that other hypnotics with SWS effect could have similar effects; possible agents in this class could include novel GABA-B agonists, GABA-A subtype specific compounds such as gaboxadol, longer-acting GBH analogues, and GABA reuptake inhibitors such as tiagabine or others</td>
</tr>
<tr>
<td>Histaminergic H3 antagonists/inverse agonists</td>
<td>Autoreceptor of histaminergic neurons; will stimulate histaminergic transmission; effective on sleepiness and cataplexy in animals models; Effects in humans still uncertain, but multiple compounds available preclinically or in early human trials</td>
</tr>
</tbody>
</table>

SWS = slow-wave sleep; H3 = histamine receptor 3; Mignot E, Nishino S (2005), Sleep 28(6):754-763
Future Possible Treatments of Narcolepsy (Cont.)

<table>
<thead>
<tr>
<th>Treatment Types</th>
<th>Advantages and Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRH analogues</td>
<td>Typically peptide analogues; effective in animal models but very high dose required; some compounds failed human trials on depression; limited activity for this area in the pharmaceutical industry</td>
</tr>
<tr>
<td>Hypocretin-Based Therapy</td>
<td>Disappointing effects after intravenous, intracisternal, and intranasal administration to date, but extremely high doses could still be effective; would likely be effective if could be delivered intracerebroventricularly</td>
</tr>
<tr>
<td>Hypocretin-1 itself</td>
<td></td>
</tr>
<tr>
<td>Hypocretin peptide agonists</td>
<td>Similarly to TRH analogues, could be effective at very high dose. Hypocretin is a larger peptide, and derivatives are unlikely to cross the blood-brain barrier sufficiently and will probably be unstable in vivo</td>
</tr>
<tr>
<td>Nonpeptide agonists</td>
<td>Best hope, especially if targeting the hertr2 receptor; with central penetration; impossible to predict success to date; peptide receptor agonists are often difficult if not impossible to make</td>
</tr>
<tr>
<td>Hypocretin cell transplantation</td>
<td>May one day provide a cure; results to date in other diseases are disappointing because of potential graft rejection, low survival rate of implant, and lack of supply for graft availability. This last problem could be solved on a long-term basis through stem cell technology, likely to be more than 10 years away</td>
</tr>
</tbody>
</table>

TRH = thyrotropin-releasing hormone; Mignot E, Nishino S (2005), Sleep 28(6):754-763
## Future Possible Treatments of Narcolepsy (Cont.)

<table>
<thead>
<tr>
<th>Treatment Types</th>
<th>Advantages and Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene therapy</td>
<td>Promising in the future but need appropriate vector; potentially dangerous side effects; could be combined with cell-based therapies</td>
</tr>
<tr>
<td>Immune-based therapies</td>
<td>Ineffective in 1 human and 1 canine case; unlikely to be useful</td>
</tr>
<tr>
<td>Steroids</td>
<td></td>
</tr>
<tr>
<td>IVIg</td>
<td>May be effective in decreasing symptoms but only if used before a year or so after onset; reported effects are still subjective and not confirmed through placebo-controlled trials; generally safe but occasionally life-threatening side effects</td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>Similar to IVIg but less available data; more invasive than IVIg</td>
</tr>
</tbody>
</table>

IVIg = intravenous immunoglobulins; Mignot E, Nishino S (2005), Sleep 28(6):754-763
What Patients Want

“A drug that would provide consistent and adequate control of the daytime sleepiness without the hard crash and one that would require one dose taken at bedtime resulting in 8 hours of restorative sleep.”
New Innovation in Narcolepsy Treatment

Sodium Oxybate is the only drug to be FDA approved to treat both excessive daytime sleepiness (EDS) AND cataplexy in patients with narcolepsy. Flamé has developed a NEW sodium oxybate drug product for the market which is based on its Micropump® technology:

This Controlled Release (CR) formulation of sodium oxybate needs to be tested in patients with narcolepsy to ensure that it is both safe and effective.

Single Nightly Dose

Elimination of the second dose translates to a more convenient dosing regimen for patients with Narcolepsy
Product Overview

Avadel’s Main program: Sodium Oxybate Micropump® (FT218)
Development of a controlled release (CR) powder for oral suspension of sodium oxybate using our patented technology Micropump®.

Micropump® microparticles
- are dispersed in the stomach and pass into the small intestine, where each microparticle releases the drug at an adjustable rate (controlled and/or delayed) and over an extended period of time.
- can be used separately or together to provide highly specialized delivery profiles
Achieving Recruitment Timelines

Timelines:

**First Subject First Visit:** November 2016  
**First Subject Dosed:** December 2016  
**Last Subject First Visit - Expected:** March 2018  

*Enrolment Period:*

*October 2016 – March 2018*
FLAMEL FT218 advantages

• Single Dose Nightly Formulation
  – Easier for the patient (and partners!)
  – Avoid waking up in the middle of the night
  – Avoid additional disruption of the sleep, or a dangerous walk to the bathroom
  – Lower total amount of water / night compared to 2 doses
  – Safety: Avoid a dose freely available on the nightstand

• Dosage form (Granules for suspension)
  – More convenient for travelling (powder, not liquid > 100ml)
  – Safety: Individual doses in Child–resistant packaging
Once Nightly Patient Questionnaire.
Please briefly describe any other concerns or problems that you have had associated with taking your middle of the night dose of sodium oxybate:

<table>
<thead>
<tr>
<th>Survey Number</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Disruption on vacation - in hotel or on vacation with other people, feel uncomfortable setting alarm for 2am, I would like to have a whole nights sleep without having to get up</td>
</tr>
<tr>
<td>5</td>
<td>mostly for convenience sake</td>
</tr>
<tr>
<td>9</td>
<td>Several times I sleep through alarm and can not take 2nd dose. Feel exhausted all day, once a night would be great</td>
</tr>
<tr>
<td>10</td>
<td>Before taking Xyrem, I very rarely woke up in the middle of the night. Now after taking it for 6 years, I wake up during the night even when it is not time to take my second dose</td>
</tr>
<tr>
<td>11</td>
<td>taking your dosage and trying to use the restroom or have other events that may cause you to need to be awake (taking out the dog, crying child)</td>
</tr>
<tr>
<td>12</td>
<td>1. having it and small children, 2. wake up too late and not take second dose and not enough time before work, 3. fall asleep in bathroom 5. yes would be wonderful too many times missed</td>
</tr>
<tr>
<td>13</td>
<td>I have had 2 concussions, 2 sprained ankles and many bruises</td>
</tr>
<tr>
<td>14</td>
<td>When I was taking sodium oxybate my life revolved around counting the hours until I could drive</td>
</tr>
<tr>
<td>16</td>
<td>In relation to Question 3: often enough to cause stress but more like every few weeks. In relation to question 4, semi frequently</td>
</tr>
</tbody>
</table>
Question 3

How often have you taken your second dose of sodium oxybate later than planned or too close to the time you plan to get up?
Have you ever experienced amnesia or loss of balance before or after taking your middle of the night dose of sodium oxybate?
Question 5

Would a once a night formulation of sodium oxybate help with your medication compliance?

Number of Responses

No | Yes
---|---
5 | 9

9 responses indicated 'Yes', while 5 indicated 'No'.
Would a once a night formulation of sodium oxybate make you feel safer?
Phase III Rest-On Clinical Study Evaluating the Safety and Efficacy of FT218: Study Overview
Effectiveness of Recruiting Type 1 Narcolepsy Patients via Internet Based Pre-selection System


1; Sleep Disorders Center, Henry Ford Hospital, Detroit, United States 2; Flamel Ireland/Avadel, Dublin, Ireland 3; Link2Trials, 1223 HL Hilversum, The Netherlands
Creating an Efficient Protocol

• No placebo group for stimulant. Very big issue
• In majority of sites 16-18 (prime age for narcolepsy onset) will be included
• Doses evaluated in crossover design not parallel group
• Major efforts in recruitment and retention
Unique Efficient Study Design

• Only two groups, one active one placebo, thus overall fewer subjects needed
• Dose is studied within active group with all receiving 6, 7.5 and 9 grams
• Duration of treatment for any given dose is therefore less
• Screening period is carried out over time with extensive ongoing monitoring of eligibility and subjects compliance with protocol requirements
REST-ON Phase III Clinical Trial
USA & Canadian Sites
Key Study Eligibility Requirements

• Male or female subjects
  – 16 years of age or older
• Willing and able to give written informed consent for study participation
• Documented evidence of a diagnosis of NT1 (EDS & Cataplexy) or NT2 (EDS)
• No prior use of sodium oxybate
What to expect on study

Once determined eligible by your treating physician and once written Informed Consent & Assent *(where applicable)* subjects will be randomized *(like the flip of a coin)* to one of two treatment arms.

- **Treatment group 1** will receive FT218 (Sodium Oxybate Controlled Release)
- **Treatment Group 2** will receive Placebo.

  Study participation will last for approximately 17 weeks.

- Patients with Cataplexy will discontinue all anti-cataplexy medications for the duration of the study.
- **All** patients will be able to remain on stimulants.
What to expect on study

What to expect when on study:

- Study participants will be asked to visit the study clinic a total of 9 times for the duration of the study.
  - 4 of these visits will require an overnight stay for an overnight sleep study and a next day nap test.
- During the study you will record how sleepy you are on a study specific electronic diary.
- If you have cataplexy you will record how many cataplexy events you have daily on a study specific electronic diary.
- Your study Doctor and team are there to support you and monitor your health and well being for the duration of the study.
Clinical Study Considerations

- **Blinded Placebo Design**
  - Why placebo design is important in new product approval by the FDA.
    - Need for placebo design,
    - Benefits in the long term for the disease area.
  - What happens if I am assigned to Placebo?
    - All patients can remain on stimulants.
    - Cataplexy patients must discontinue anti-cataplexy medications.
    - How your health and wellbeing will be monitored.
      - Scheduled visits.
      - Study team close monitoring of your health and signs and symptoms while on study.
      - Access to study team at your sleep clinic.
      - You can come off the study at any time without having to give a reason.

- **Remaining on Study**
  - Critical not to discuss your signs and symptoms on social media platforms.
  - Dialogue with your Doctor and study team to closely monitor your health and wellbeing and concerns.
Discontinuation of anti-cataplexy medications

- Cataplexy medication control – willingness to discontinue anti-cataplexy medications.

  - Key patient concerns
  - Key patient considerations in the contexts of a clinical trial.
Flamel and Clinical Trial Conduct: Commitment to You

Ethical and Scientific Standards of GCP (Good Clinical Practice)

- Safety, rights and well being of study patients.
- Respecting the wishes of patients.
- Protecting patients personal information.
- Methods to assure ethical and scientific standards and conduct.

- Regulatory
- IRB/REC (Institutional Review Board/Research Ethics Committee).
- Clinical Staff and Clinical Units
- Flamel and its operational designees
Flamel Study Patient Advisory Group

Establishment of PAG made possible through Partnership with the Narcolepsy Network.

Founding Principals of the CLFT218-1501 PAG:

- Anchoring the needs and perspectives of patients in key trial development activities
- Recognition of the importance and critical value of patient centric approach in clinical trial development activities.
- Patient engagement promotes greater relevance and more meaningful trial design and conduct for target patient population.
- Creating greater awareness and understanding across broader Narcolepsy patient community on the importance of, the need for and the benefits of clinical research.

- Twin objectives of PAG:
  - Facilitating dialogue and patient centricity via a structured framework.
  - Promoting greater patient empowerment through information and education.
Patient-Centric Approach to Clinical Trial Activities

Flamel’s approach to targeted Patient Engagement

- 2014: Patient focus groups at NN Meeting 2014
- 2016:
  - Inaugural Patient Advisory Group Meeting April 2016
  - Second Patient Advisory Group Meeting October 2016

Objective:

*Establishing an aligned platform for Patient/Family engagement in the clinical trial process.*
Flamel Study Patient Advisory Group

- **PAG Inaugural Meeting Outcomes:**
  - Re-design and reformat of clinical trial patient facing materials and study specific ePRO device for use on study.
  - Awareness creation of critical importance of the patient support network and how this support network can play a crucial role in ensuring the success of individual patient trial participation.
  - Critical input and contribution to the design and generation of a trial specific social media awareness campaign.
  - Critical input on overcoming/managing key trial design requirements.
Flamel/Avadel Patient Engagement Milestones

✓ **2014**: Patient focus groups at NN Meeting 2014
✓ **2015**: Patient outreach to establish the Patient Advisory Group.

**2016: USPAG**

✓ Inaugural Patient Advisory Group Meeting April 2016
✓ Second Patient Advisory Group Meeting October 2016
✓ EU PAG Outreach Meeting – March 217
✓ Third Patient Advisory Group Meeting April 2017

*Establishing an aligned platform for Patient/Family engagement in the clinical trial process.*
Incorporating Patient Input into Clinical Trials.
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Importance of the Patient Support Network

How can you, as a member of the narcolepsy community, best support patients who may not have a strong support network or may have reservations about clinical trials?

• Why would patients, family/friends be skeptical of clinical trial participation? How can this be addressed?
• How do “we” try to create better awareness and understanding of clinical trials?
• What can sites do in order to promote empowerment through information about clinical trials?
What Patients Want

“A drug that would provide consistent and adequate control of the daytime sleepiness without the hard crash and one that would require one dose taken at bedtime resulting in 8 hours of restorative sleep.”