Central Hypersomnias

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# Conflict of Interest Disclosures for Speakers

1. I do not have any relationships with any entities **producing, marketing, re-selling, or distributing** health care goods or services consumed by, or used on, patients, OR

2. I have the following relationships with entities **producing, marketing, re-selling, or distributing** health care goods or services consumed by, or used on, patients.

<table>
<thead>
<tr>
<th>Type of Potential Conflict</th>
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<tr>
<td>Grant/Research Support</td>
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<td>Other</td>
<td>Investigator of pitolisant (Bioprojet) trials</td>
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3. The material presented in this lecture has no relationship with any of these potential conflicts, OR

4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:

   1. 
   2. 
   3.
Plan

- Post-traumatic brain injury
- Narcolepsy
- Idiopathic hypersomnia
- Kleine-Levin syndrome
Post-Traumatic Hypersomnia
Sleepiness and loss of neurons after traumatic brain injury (TBI)


Objective sleepiness and sleep excess in TBI patients

N=42 patients, 0 and 6 months post-TBI

Imbach, Brain 2015
Underestimation of sleepiness and sleep excess in TBI patients

Imbach, Brain 2015
Predictors of sleep excess after 6 months

⇒ Severe trauma (Glasgow scale)
⇒ Intracranial haemorrhage

Imbach, Brain 2015
Loss of neurons after TBI

Valko, Ann Neurol 2015 and Valko, Sleep 2016
TBI: main messages

• Important sleep excess and objective sleepiness
• Underestimated by patients: no use of Epworth sleepiness score
• Damage in arousal systems, mostly in histamine system: future trials of new anti H3 drug (pitolisant, Wakix®)?
Narcolepsy
Basic: Class I HLA

Narcolepsy-Associated HLA Class I Alleles Implicate Cell-Mediated Cytotoxicity

Mehdi Tafti, PhD1,2; Gert J. Lammers, MD, PhD3,4; Yves Dauvilliers, MD, PhD5,6; Sebastiaan Overeem, MD, PhD7; Geert Mayer, MD8; Jacek Nowak, MD9; Corinne Pfister, MSc10; Valérie Dubois, MD11; Jean-François Eliaou, MD12; Hans-Peter Eberhard, PhD13; Roland Liblau, MD, PhD13; Aleksandra Wierzbicka, MD14; Peter Geisler, MD15; Claudio L. Bassetti, MD16; Johannes Mathis, MD17; Michel Lecendreux, MD17; Ramin Khatami, MD18; Raphaël Heinzer, MD19; José Haba-Rubio, MD20; Eva Feketeova, MD21; Christian R. Baumann, MD22; Zoltán Kutalik, PhD23,24; Jean-Marie Tiercy, PhD23,24
• HLA DQB1*06:02 is not expressed in the brain, whereas HLA class I genes are
• No CD4+ T-cell found in narcolepsy

• 944 European patients with NwC
• 4,043 control subjects matched by country
• Patients and controls were all DQB1*06:02 positive

• 3 positive associations with NwC
  • HLA-A*11:01 (OR = 1.49)
  • HLA-B*35:01 (OR = 1.46)
  • HLA-C*04:01 (OR = 1.34)

=>Suggest a cytotoxic (CD8+ T Cell or NK cell) mechanism
Improving narcolepsy diagnosis and clinical practice

• Kawai et al, Sleep 2015 Narcolepsy in African-Americans

• Dodet et al, Sleep 2015 Lucid dreaming in narcolepsy

• Cairns and Bogan, Sleep 2015. Prevalence and clinical correlates of a short onset REM period (SOREMP) during routine PSG.

• Reiter et al, Sleep 2015. Usefulness of a nocturnal SOREMP for diagnosing narcolepsy with cataplexy in a pediatric population
Narcolepsy in African American

- 182 African-Americans, 839 Caucasian-Americans

⇒ Higher ESS, earlier age at onset
⇒ Higher BMI
⇒ Higher HLA positivity in AA
⇒ Lower Hct-1 levels

⇒ Less cataplexy even in those with Hct deficiency (almost all AA without cataplexy were Hct deficient)
Lucid dreaming in narcolepsy

Dodet et al, Sleep 2015
Nightmare recall frequency

Nightmares, N/month

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<tr>
<th></th>
<th>NT1</th>
<th>NT2</th>
<th>Controls</th>
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<td>N=53</td>
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Dodet, Sleep 2015
Lucid dream frequency

Lucid Dreams, N/month

NT1: 7.7
NT2: 7.3
Controls: 0.3

Dodet, Sleep 2015
Awake, eye code

REM sleep, eye code
=> lucid REM sleep

REM sleep, usual REMs

Dodet, Sleep 2015
N= 30 lucid REM sleep episodes

Delta  Theta  Alpha  Beta  Gamma
Awake Eye closed

Non lucid REM sleep

Lucid REM sleep

Power ($\mu V^2$)

383  919  7.4  14.3  3  7  0.5  1  0.08  0.43

Dodet, Sleep 2015
What is lucid dreaming useful for?

- Having fun 30% of narcoleptic patients

Dodet, Sleep 2015
What is lucid dreaming useful for?

- Reducing nightmares (78% of narcoleptics)
Prevalence and Clinical Correlates of a Short Onset REM Period (SOREMP) during Routine PSG

Alyssa Cairns, PhD1; Richard Bogan, MD1,2,3

1SleepMed, Columbia, SC; 2University of South Carolina Medical School, Columbia, SC; 3Medical University of South Carolina, Charleston, SC

N= 3,059 pts with EDS; nSOREMP specificity for NT1: 99.5%
Sensitivity : 6.7%
N= 79,651 pts for routine PSG
Prevalence of nSOREMP in general population: 0.8% (shift work, African-American

Cairns, Sleep 2015
Usefulness of a Nocturnal SOREMP for Diagnosing Narcolepsy with Cataplexy in a Pediatric Population

Joel Reiter, MD¹; Eliot Katz, MD³; Thomas E. Scammell, MD¹; Kiran Maski, MD⁴

¹Division of Pulmonary, Critical Care and Sleep Medicine, Beth Israel Deaconess Medical Center, Boston, MA; ²Division of Pulmonary and Respiratory Diseases, Boston Children’s Hospital, Boston, MA; ³Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA; ⁴Department of Neurology, Boston Children’s Hospital, Boston, MA

N= 148 children, 28% with NT1
specificity for NT1: 97.3%
Sensitivity : 54.8% ; Positive predictive value: 88.5%
A new treatment in phase 2 in narcolepsy

Effect of oral JZP-110 (ADX-N05) on wakefulness and sleepiness in adults with narcolepsy: a phase 2b study

Ruoff C et al, Sleep 2016

- Drug: second-generation wake stimulant with dopaminergic and noradrenergic activity (inhibits reuptake at NE and DA transporters)
Study design:

- Placebo (n = 49)
- JZP-110 (n = 44)

- Screening
- Baseline
- Week 1: 150 mg/day
- Week 4: 300 mg/day
- Exit
A) Mean MWT Sleep Latency

Mean (SE) Change From Baseline, Minutes

- JZP-110 (n = 40): 12.8
- Placebo (n = 45): 2.1

P < 0.0001
• AE: insomnia (22%), headache (16%), nausea
• No benefit on cataplexy in the 33 patients with NT1
Narcolepsy: Main messages

• African-American: sleepiness without cataplexy in African-American patients: Warning: not always OSAS (despite obesity), it can be a narcolepsy

• High potential of lucid dreaming in narcolepsy: use it for reducing nightmares in your patients

• SOREMP during routine PSG in sleep disorders centers: highly specific of narcolepsy (adults and children), except night/shift work

• New therapies in narcolepsy
  – A new DA/NE reuptake inhibitor in development
  – The anti H3 pitolisant (Wakix) is now approved in France
Idiopathic hypersomnia
Treatments in idiopathic hypersomnia

- First time: 2 randomized placebo controlled trials

- A chart review:
Clarithromycin in γ-Aminobutyric Acid–Related Hypersomnolence: A Randomized, Crossover Trial

Lynn Marie Trotti, MD, MSc, Prabhjyot Saini, MSc, Donald L. Bliwise, PhD, Amanda A. Freeman, PhD, Andrew Jenkins, PhD, and David B. Rye, MD, PhD
Sample and methods

- N=23 randomized patients
- All with CSF GABA-A R potentiation
- IH n=10; Narco Type 2, n=4, subjective hypersomnia: 6
- Clarithromycin: 500 mg at breakfast and lunch

FIGURE 1: Study protocol. Subjects were randomized to order of presentation of clarithromycin (vertical lines) and placebo (checkerboard).

Trotti, Ann Neurol 2015
Benefit on sleepiness

![Graph showing Epworth sleepiness score for Baseline, Placebo, and Clarithromycin. Baseline score is higher than Placebo and Clarithromycin. Clarithromycin has a *-3.9 benefit compared to Placebo.](image)
Other changes

- Functional outcome of sleep Q: improved
- SF36 physical; energy; social: improved
- PVT time: p=0.16
- PVT lapses: no change
- SSS week 1: improved
- SSS week 2: no change
- AE: dysgueusia and gastrointestinal
Modafinil in the treatment of idiopathic hypersomnia without long sleep time—a randomized, double-blind, placebo-controlled study

GEERT MAYER\textsuperscript{1,2}, HEIKE BENES\textsuperscript{3}, PETER YOUNG\textsuperscript{4}, MARION BITTERLICH\textsuperscript{1} and ANDREA RODENBECK\textsuperscript{5}

\textsuperscript{1}Hephata Klinik, Schwalmstadt-Treysa, Germany, \textsuperscript{2}Department of Neurology, Philipps-Universität Marburg, Marburg, Germany, \textsuperscript{3}Department of Neurology, University of Rostock, Rostock, Germany, \textsuperscript{4}Department for Sleep Medicine and Neuromuscular Disorders, University of Münster, Münster, Germany, \textsuperscript{5}Charité-Universitätsmedizin Berlin, Berlin, Germany
- N = 33 patients with idiopathic hypersomnia and MSLT latency < 8 min
- Intervention: modafinil 100 mg*2 or placebo
Original Article

Benefits and risk of sodium oxybate in idiopathic hypersomnia versus narcolepsy type 1: a chart review

Smaranda Leu-Semenescu a,b, Pauline Louis a,c, Isabelle Arnulf a,b,c,d,*

a AP-HP, Hôpital Universitaire Pitié-Salpêtrière, Services des Pathologies du Sommeil, Paris, France
b Centre National de Référence: Narcolepsie et Hypersomnie, Paris, France
c Université Pierre et Marie Curie – Paris 6, Paris, France
d Institut Hospitalo-Universitaire de Neuroscience, Université Pierre et Marie Curie – Paris 6, Paris, France

• N= 107 with NT1 + SO
• N=52 with resistant IH + SO
Sodium oxybate (Xyrem) in IH (red) vs NT1 (blue)

- Stimulants tried before, No: 2.2 (blue), 3.2 (red)
- Daily dose, gr: 6.2 (blue), 4.3 (red)
- Time on treatment, months: 35.2 (blue), 15.8 (red)
- Could not tolerate the drug: 38 (blue), 30 (red)

Leu-Semenescu, Sleep Med 2016
Effect of SO (Xyrem) on sleepiness

Benefit on severe morning inertia: 72%

Leu-Semenescu, Sleep Med 2016
Side effects of Xyrem

- Nightmares
- Enuresis
- Sleep walking
- Sedation
- Vomiting
- Nausea
- Confusion
- Abnormal movements
- Paranoia
- Anxiety
- Depression
- Headaches
- Balance disorders
- Dizziness

Narcolepsy with cataplexy
Idiopathic hypersomnia

Leu-Semenescu, Sleep Med 2016
Idiopathic hypersomnia: main message

• Modafinil confirms its long-known benefit in IH with a level 1 study

• In patients with multi-resistant IH
  – Test with clarithromycin 500 mg*2: may help recognizing the hypersomnia with GABA-A modulation
  – Test with Xyrem single dose: may help for severe morning inertia
Kleine-Levin Syndrome
Kleine-Levin syndrome


Long episodes

- 28% have prolonged (>30 days) episodes
- Longer disease course
- More tired during asymptomatic periods

Lavault, Ann Neurol 2015
Familial Kleine-Levin syndrome: Paris and Stanford series

⇒ 4% multiplex families and 8% familial cases
⇒ Same clinical phenotype as sporadic cases

Nguyen QTR, Sleep 2015
CSF Hypocretin-1 levels: -33% during KLS episodes

Wang, Sleep 2016
Long term cognitive impairment in KLS

- Individual reports of occasional cognitive difficulties
- A single series of 18 patients (Engstrom, Sleep 2009, 2014): altered working memory, use different networks in fMRI
- In our patients, 50% report academic decline since KLS onset

Uguccioni, Sleep 2015
Visit 1: 124 KLS patients had cognitives tests

Visit 2: 44 KLS repeated cognitives tests, 1.3 y after visit 1

42 matched healthy controls

Uguccioni, Sleep 2015
FCSRT: Immediate free retrieval

Uguccioni, Sleep 2015
Conclusion

• Long term cognitive impairment in 33% patients
  – Attention
  – Speed processing
  – Progressive worsening of retrieval deficit
  – Not in visuospatial functions
• Cognitive function should be regularly assessed
• => Cognitive remediation and academic support
Lithium therapy in KLS

Leu-Semenescu, Neurology 2015
What was known

• Individual trials of lithium, Dr’s report (Arnulf, Brain 2005):
  – complete benefit in 41%,
  – partial in 26%
• Individual trials of lithium, patients’ report (Arnulf, Ann Neurol 2008)
  – Complete benefit 7% 
  – Partial benefit 17%

=> No idea of lithium serum levels, compliance
=> No series

Leu-Semenescu, Neurology 2015
Methods

• Among 131 patients in Paris
  – 71 received and took lithium (serum levels of 0.8-1.2 mmol/L)
  – 49 took nothing
  – 10 took valproate or contraceptive pill
• We compared the frequency and duration of episodes
  – before treatment/abstention (mean 5 years)
  – vs. after a mean 2 years of follow-up
Effect of lithium therapy vs abstention of treatment in Kleine-Levin syndrome

- Frequency of episodes per year
  - Visit 1: No treatment (green), Lithium (blue)
  - Visit 2: No treatment (green), Lithium (blue)

- Mean duration of episodes (days)
  - Visit 1: No treatment (green), Lithium (blue)
  - Visit 2: No treatment (green), Lithium (blue)

- Longest episode duration (days)
  - Visit 1: No treatment (green), Lithium (blue)
  - Visit 2: No treatment (green), Lithium (blue)

- Time spent incapacitated (days per year)
  - Visit 1: No treatment (green), Lithium (blue)
  - Visit 2: No treatment (green), Lithium (blue)

Leu-Semenescu, Neurology 2015
Open observational study

- Lithium
  - No more episode: 30%
  - Decreased frequency or duration: 50%
  - Non responders: 20%

  - Rapid relapse when stopped
  - «Mini-episodes » of 1 day

Leu-Semenescu, Neurology 2015
Side-effects of lithium

<table>
<thead>
<tr>
<th>Side-effect</th>
<th>% of patients with</th>
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<tbody>
<tr>
<td>Tremor</td>
<td>37</td>
</tr>
<tr>
<td>Polyuria-polydypsia</td>
<td>23</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>14</td>
</tr>
<tr>
<td>TSH increase</td>
<td>11</td>
</tr>
<tr>
<td>Weight increase</td>
<td>7</td>
</tr>
<tr>
<td>Acne</td>
<td>6</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4</td>
</tr>
<tr>
<td>Creatinin increase</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
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KLS: take home message

- 8% of familial cases: importance of genetic studies (exome sequencing)
- Mild impact on hypothalamic Hct-1 secretion
- Not a benign disease
  - 28% patients with long (>30 d) episodes
  - Long term memory problems (teenagers) in 1/3
- Benefit of lithium therapy