Delving into Hypersomnia: How we got to where we are – terms, tests, and causes
<table>
<thead>
<tr>
<th>External Industry Relationships *</th>
<th>Company Name(s)</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equity, stock, or options in biomedical industry companies or publishers**</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Board of Directors or officer</td>
<td>Narcolepsy Network</td>
<td>Medical Advisory Board</td>
</tr>
<tr>
<td>Royalties from Emory or from external entity</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Industry funds to Emory for my research</td>
<td></td>
<td>PI</td>
</tr>
</tbody>
</table>

*Consulting, scientific advisory board, industry-sponsored CME, expert witness for company, FDA representative for company, publishing contract, etc.

**Does not include stock in publicly-traded companies in retirement funds and other pooled investment accounts managed by others.
In the present state of my ignorance it seems more useful to gather facts than to formulate hypotheses.
hypersomnia

*n. sleep lasting for exceptionally long periods, as occurs in some cases of brain inflammation.*

Oxford Concise Medical Dictionary
THUS:

HYPERSOMNIA
(consumed by sleep)

≠

NARCOLEPSY
(1880, from Fr. narcolepsie, coined 1880 by French physician Jean-Baptiste-Édouard Gélineau from comb. form of Gk. narke "numbness, stupor" + lepsis "an attack, seizure." )
Hypersomnia
Consumed by Sleep

Narcolepsy
Seized by Sleep
Symptoms are the body's mother tongue; signs are in a foreign language.

(John Brown)
Translating that foreign language

• Cataplexy – problematic as:
  1) Only present in 20-30% of narcoleptics at onset of excessive sleepiness.
  2) Typically emerges 2.5-4 years after onset of sleepiness (and as many as 60 years)
  3) Rarely witnessed – highly reliant on self report

• Sleep onset dreaming on the Multiple Sleep Latency Test. Problematic as:
  1). A significant portion of the general population (2.5-4.0%) exhibits dream sleep during daytime napping (SOREMps).
  2). Test – re-test reliability is high for genuine narcolepsy without cataplexy, but poor for other causes of sleepiness/hypersomnia
Narcolepsy without cataplexy

• ~ 80% of subjects are NON-hypocretin deficient (and therefore not genuine narcoleptics)
• MANY experience HYPERSOMNIA!

NARCOLEPSY WITH LONG SLEEP TIME

Narcolepsy with Long Sleep Time: A Specific Entity?

Cyrille Vernet, MSc; Isabelle Arnulf, MD, PhD

Citation: Vernet C; Arnulf I. Narcolepsy with long sleep time: a specific entity? SLEEP 2009;32(9):1229-1235.
MUDR. BEDRICH ROTH

NARKOLEPSIE A HYPERSOMNIE
S HLEDISKA FYSIOLOGIE SPANKU

Statni zdravotnické nakladatelstvi, Prague, 1957
<table>
<thead>
<tr>
<th><strong>Narcolepsy</strong></th>
<th><strong>Sleep drunkenness</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Imperativness of daytime sleep episodes</td>
<td>typical for the disease</td>
</tr>
<tr>
<td>Daytime sleep duration</td>
<td>1 – 20 minutes</td>
</tr>
<tr>
<td>Cataplectic attacks</td>
<td>in most cases (80 – 90%) +</td>
</tr>
<tr>
<td>Sleep dissociation on awakening:</td>
<td></td>
</tr>
<tr>
<td>a) Postdormital paralysis</td>
<td>part of the cases +</td>
</tr>
<tr>
<td>b) Persistence of attenuation of higher nervous activity</td>
<td>exceptional</td>
</tr>
<tr>
<td>Falling asleep in the evening</td>
<td>quickly</td>
</tr>
<tr>
<td>Night sleep</td>
<td>restless, poor</td>
</tr>
<tr>
<td>Awakening at the end of night sleep</td>
<td>completely normal</td>
</tr>
<tr>
<td>REM-sleep during naps</td>
<td>Non-REM sleep naps</td>
</tr>
</tbody>
</table>
Wake and Sleep are Poorly Consolidated in Narcolepsy
Hypnograms From 24-Hour Polysomnographic Recordings

Control Subject

Untreated Narcolepsy

Time of Day

Sleep Stage

MT
W
R
1
2
3/4

Time of Day
Current Medications: Adderall 30mg 3x daily

At what age did your sleepiness begin? _13_ years old

How many hours of sleep do you get each week including naps and weekends? _84-90_ hours

How many hours of sleep do you feel that you need to feel rested? _8_ hours

What is the longest that you've ever slept continuously at one time? _12_ hours

Indicate by marking on the line below how “deep” a sleeper you are:
Hypersomnia with sleep drunkenness

« Patients rarely waken spontaneously at an appropriate time; they have to be awakened. They usually do not awaken to the ringing of a clock or telephone, or, if the ringing is prolonged, they shut it off and return to sleep. Many patients have special devices for waking them up such as repeating alarm clocks and resonators. In most cases, these devices are ineffective, and the patients have to be awakened by their family members. Awakening procedures must be vigorous and persistent; it is usually necessary to shake the patient repeatedly before he reacts. Even then the patients are confused, disoriented, very slow, and unable to react adequately to external stimuli. If left alone, they often return to sleep and later do not remember having been previously awakened…»

Roth B, Nevsimalova S. Arch Gen Psychiat 1972; 26: 456-62
Historical Recognition

- *Schlafrunkenheit*
- *Ivresse de sommeil*
- *Sleep drunkenness*
- *Somnosis*
- *Dysania*
Sleep onset REM periods versus sleep onset NREM periods

• Subjects with excessive daytime sleepiness but no cataplexy, sleep paralysis or sleep onset REM periods do not have narcolepsy and should be relegated to another diagnostic category (Dement et al. 1966)

• Essential (slow sleep) narcolepsy (Berti-Ceroni et al. 1967)

• Non-rapid eye-movement (NREM) sleep narcolepsy (Passouant et al. 1968)
Narcolepsy and Hypersomnia: Review and Classification of
642 Personally Observed Cases

By B. ROTH

DEPARTMENT OF NEUROLOGY, CHARLES UNIVERSITY MEDICAL FACULTY,
PRAGUE, CZECHOSLOVAKIA
Review and classification of 642 personally observed cases (Roth, 1976)

Narcolepsy 368
  Idiopathic 293
  Symptomatic 75

Hypersomnia 274
  Functional 213
    Short cycle 191
      Monosymptomatic idiopathic hypers. 71
      Polysymptomatic idiopathic hypers. 103
  Symptomatic 61
    Long cycle 22
      Neurotic 5
      Sleep related breathing disorder 12
ASSOCIATION FOR THE PSYCHOPHYSIOLOGICAL STUDY OF SLEEP
EUROPEAN SOCIETY FOR SLEEP RESEARCH
ASSOCIATION OF SLEEP DISORDERS CENTERS

RAVEN PRESS

AUTUMN ISSUE
INTERNATIONAL CLASSIFICATION OF SLEEP DISORDERS (ICSD-3 – just released)

Hypersomnolence disorders

1. Narcolepsy Type 2 – narcolepsy without cataplexy
2. Narcolepsy Type 1 – « genuine » hypocretin deficient narcolepsy
3. **Idiopathic hypersomnia**
4. Kleine-Levin syndrome
5. Hypersomnia due to Medical Conditions
6. Hypersomnia due to Medications or Drugs
7. Hypersomnia associated with Psychiatric Conditions
8. Behaviorally Induced Insufficient Sleep Syndrome
9. Isolated symptoms and normal variants
   - Long sleep
Idiopathic hypersomnia: a study of 77 cases
(Anderson et al. Sleep, 2007)

23 patients with nighttime sleep of 10 hours or longer
Mean ESS score: 16 +/- 2.7
Mean MSLT: 8.9 +/- 3.5
Sleep drunkenness in 16 patients

54 patients with nighttime sleep of less than 10 hours
Mean ESS score: 16.8 +/- 3.5
Mean MSLT: 7.9 +/- 2.6
Sleep drunkenness in 25 patients

→ « We did not find the distinction between those with normal and those with prolonged night sleep to be important when assessing symptoms »
The Multiple Sleep Latency Test – viz., the gold standard test key to these taxonomies, is invalid

- Outside of Type 1 narcolepsy, the test/re-test reliability of the MSLT is poor.
Figure 2—MSLT-based diagnosis on repeat MSLT

Arrows represent patients whose diagnosis changed from the first to the second MSLT. MSLT1, first MSLT; MSLT2, second MSLT; SOREM, sleep onset REM periods. N-C, narcolepsy without cataplexy; IH, idiopathic hypersomnia.
Primary Hypersomnias

- **Idiopathic Hypersomnia**: 1:300
- **Narcolepsy Lacking Cataplexy**: 1:2000, or with Cataplexy 1:2,000
- **Long Sleepers (>10 hrs/day)**: 1:11 - 1:65

Sleep Drunkenness
These men of the AASM - Disputed loud and long - Each in his own opinion
Exceeding stiff and strong - Though each was partly in the right,
And all were in the wrong!

It’s Narcolepsy

It’s Depression

It’s Sleep Apnea

It’s Fatigue

It’s Hypersomnia

It’s ADD

Modified from: The Blind Men and the Elephant—John Godfrey Saxe (1816-1887)
Differential Diagnosis of Hypersomnia

- Iatrogenic effect of medication
- Insufficient sleep
- Primary sleep disorder (e.g., sleep apnea)
- Secondary to a medical/psychiatric condition
- Secondary to a neurological disorder
- Primary Hypersomnia – viz., “sleepiness” sui generis
Disorders in which hypersomnia is fairly well established – *i.e.*, ‘secondary’ hypersomnia

- Parkinson’s Disease
- End-Stage Renal Disease
- Myotonic Dystrophy (type I)
Disorders in which hypersomnina is suspected

- Hypothyroidism
- Iron-deficiency
- Carnitine deficiency
- Chronic Fatigue Syndrome
- Attention Deficit Disorder (ADD) – inattentive type
- Ehlers–Danlos syndrome (EDS)
- Adrenal insufficiency
Low or marginally low thyroxine may contribute to hypersomnia.
Iron deficiency (not necessarily with anemia) may contribute to hypersomnbia

- The brain contains nearly one gram of elemental iron
- Iron is concentrated in wake promoting neural regions, particularly, dopamine containing cells
- Synaptic dopamine release is impaired with iron deficiency and would be expected to influence response to medications such as traditional psychostimulants
Brain iron imaging – concentrated in dopamine cells and their targets (e.g., basal ganglia)

Source: http://www.magnetics.uwa.edu
Carnitine deficiency may contribute to hypersomnia.

Deficiency in short-chain fatty acid β-oxidation affects theta oscillations during sleep

Mehdi Tafti¹, Brice Petit¹, Didier Chollet¹, Elisabeth Neidhart¹, Fabienne de Bilbao², Jozsef Z Kiss³, Philip A Wood⁴ & Paul Franken⁵

Polymorphism Located between CPT1B and CHKB, and HLA-DRB1*1501-DQB1*0602 Haplotype Confer Susceptibility to CNS Hypersomnias (Essential Hypersomnia)

Taku Miyagawa¹ , Makoto Honda²,³, Minae Kawashima¹,⁴, Mihoko Shimada¹, Susumu Tanaka², Yutaka Honda³, Katsushi Tokunaga¹

SERUM ACYLCARNITINE IN NARCOLPESY PATIENTS

Abnormally Low Serum Acylcarnitine Levels in Narcolepsy Patients

Taku Miyagawa, PhD¹; Hiroko Miyadera, PhD¹; Susumu Tanaka, PhD²; Minae Kawashima, PhD¹; Mihoko Shimada, MHSc¹; Yutaka Honda, MD, PhD³; Katsushi Tokunaga PhD¹; Makoto Honda MD PhD³

Effects of Oral L-Carnitine Administration in Narcolepsy Patients: A Randomized, Double-Blind, Cross-Over and Placebo-Controlled Trial

Taku Miyagawa¹, Hiromi Kawamura², Mariko Obuchi², Asuka Ikesaki², Akiko Ozaki³, Katsushi Tokunaga¹, Yuichi Inoue⁴,⁵, Makoto Honda⁴,⁶
ADHD subjects exhibit daytime sleepiness by MSLT testing

**Sleepiness evident on all naps (10:00 – Noon – 1400 – 1600); M. Lecendreux et al. (2000) JCCP 41(6): 803-812
Figure 2 (MSL): Population-based control MSLs (n=1019) derived from ([1, 2] courtesy of E. Mignot (Stanford Center of Narcolepsy Research) vs. CFS (n=46) from Wichita, KS [4].
Summary #1

- The MSLT has high sensitivity for genuine, hypocretin deficient narcolepsy (with cataplexy)
- The MSLT has poor specificity for the diagnosis of narcolepsy
- The MSLT has marginal sensitivity AND specificity for the diagnosis of other primary hypersomnias – 30-40% of MSLTs in hypersomnics are “normal”
Summary #2

• The MSLT is labor intensive
• The MSLT is impractical
• The MSLT is expensive
• Specialists are incentivized to rely on the MSLT ($ - and the “gold standard”).
• Specialists are not de-incentivized to rely upon the MSLT
Summary #3

• We desperately need a better metric the more faithfully captures the main clinical complaints: hypersomnia, sleep drunkenness, sleep inertia

• Extension of study to other common disorders in which hypersomnia manifests in order to gain additional mechanistic insights.
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