Emerging Treatments and Diagnostic Strategies for Hypersomnolence

David T. Plante, M.D.
Assistant Professor of Psychiatry
Program Director, Sleep Medicine Fellowship
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Overview

• Update on nosology
• Novel measures of hypersomnia
• GABA-related hypersomnia
• Future Directions

Before We Begin

• Focus will be on non-narcoleptic disorders of hypersomnia (i.e. Idiopathic Hypersomnia)
• Covering potentially controversial topics
• Majority of talk will cover diagnostics and therapeutics that are outside standard of care
• Many are not available currently
• Refer to AASM guidelines and professional updates
ICSD-3 Idiopathic Hypersomnia

A. The patient has **daily periods** of **irrepressible need to sleep or daytime lapses into sleep** occurring for **at least three months**.

B. Cataplexy is absent.

C. An MSLT performed according to standard techniques shows **fewer than two sleep onset REM periods** or no sleep onset REM periods if the REM latency on the preceding polysomnogram was less than or equal to 15 minutes.
ICSD-3 IH Continued

D. The presence of at least one of the following:

1. The **MSLT shows a mean sleep latency of ≤ 8 minutes**.

2. Total **24-hour sleep time is ≥ 660 minutes** (typically 12–14 hours) on 24-hour polysomnographic monitoring (performed after correction of chronic sleep deprivation), or by **wrist actigraphy** in association with a sleep log (averaged over at least seven days with unrestricted sleep).

ICSD-3 IH Continued

E. Insufficient sleep syndrome is ruled out (if deemed necessary, by lack of improvement of sleepiness after an adequate trial of increased nocturnal time in bed, preferably confirmed by at least a week of wrist actigraphy).

F. The hypersomnolence and/or MSLT findings are not better explained by another sleep disorder, other medical or psychiatric disorder, or use of drugs or medications.
ICSD-3 IH Notes

1. Severe and prolonged sleep inertia, known as sleep drunkenness (defined as prolonged difficulty waking up with repeated returns to sleep, irritability, automatic behavior, and confusion) and/or long (> 1 hour), unrefreshing naps are additional supportive clinical features.

2. A high sleep efficiency (≥ 90%) on the preceding polysomnogram is a supportive finding (as long as sleep insufficiency is ruled out).

ICSD-3 IH Notes Continued

3. The total 24-hour sleep time required for diagnosis may need to be adapted to account for normal changes in sleep time associated with stages of development in children and adolescents as well as for variability across cultures in all age groups.

4. Occasionally, patients fulfilling other criteria may have an MSLT mean sleep latency longer than 8 minutes and total 24-hour sleep time shorter than 660 minutes. Clinical judgment should be used in deciding if these patients should be considered to have idiopathic hypersomnia (IH). Great caution should be exercised to exclude other conditions that might mimic the disorder. A repeat MSLT at a later date is advisable if the clinical suspicion for IH remains high.
Multiple Sleep Latency Test

- Originally developed in mid 1980s
- 4-5 nap opportunities ~2 hours apart
- Occurs after night of sleep (minimum 6 hours, though more ideal)
- Measure time from lights off to first to first epoch of sleep (sleep onset latency)
- Measure time from sleep onset to first epoch of REM sleep (REM latency)
- If no sleep after 20 minutes, nap opportunity ends
- If no REM within 15 minutes of sleep onset, nap opportunity ends

Normative MSLT Findings

- **Mean Sleep Latency**
- ~20% of people will have MSLT values at or below the ICSD-3 defined pathologic cutpoint of 8 minutes

MSL 11.6±5.2 (5-nap protocol)
Arand et al., SLEEP 2005
MSLT in Idiopathic Hypersomnia

- Used as a diagnostic criterion in ICSD-3
- Average MSLT values in large studies (7.8 and 8.3 minutes) in IH surround defined pathologic cutoffs
- MSL>8 is commonly observed in IH patients with excessive total sleep time
  - 71% of IH patients with long sleep time may have MSL>8 minutes and 54% have MSL>10 minutes

\[1\] Vernet and Arnulf, SLEEP 2009

Test-Retest Reliability of MSLT in IH

- Over 40% of patients (IH & Narcolepsy without Cataplexy) had MSLT that crossed cutpoint of 8 minutes
- 12/36 patients had “resolution” of sleepiness using MSL 8 as cutoff
- 30% of patients crossed 2 SOREM threshold

Trotti et al. JCSM 2013
Is there a nosology for hypersomnia that doesn’t rely as heavily on the MSLT?

Hypersomnolence Disorder: DSM-5

- Shift from “secondary” to “comorbid” descriptions of both insomnia and hypersomnia in DSM-5
- DSM-5 includes “Hypersomnolence Disorder” which can co-occur with depressive episode
- Diagnostic criteria are based on epidemiologic data$^{1,2}$

$^1$Ohayon et al., Arch Gen Psychiatry 2012
$^2$Ohayon et al., Ann Neurol 2013
DSM-5 Hypersomnolence D/O

• Self-reported excessive daytime sleepiness (EDS) despite a main sleep period lasting at least 7 hours with at least one or more of the following:
  – Recurrent periods of sleep or lapses into sleep within the same day
  – A prolonged main sleep episode of more than 9 hours per day that is nonrestorative (i.e. unrefreshing)
  – Difficulty being fully awake after abrupt awakening

DSM-5 Hypersomnolence D/O

• Hypersomnolence occurs ≥3x/week for at least 3 months
• Accompanied by significant distress or impairment in cognitive, social, occupational, or other areas of functioning
• Not better explained by and does not occur exclusively during the course of another sleep disorder (e.g. narcolepsy, sleep apnea, circadian rhythm disorder, or parasomnia)
• Not attributable to medication or drug of abuse
• Coexisting mental and medical disorders do not adequately explain the predominant complaint of hypersomnolence
  – Similar to change for Insomnia Disorder
Why 9 hours?

![Diagram showing the prevalence of insomnia and related disorders]

Ohayon et al, Arch Gen Psych 2012
Ohayon et al, Ann Neuro 2013

Nosology Affects Prevalence

- Limited data regarding prevalence of IH using ICSD-3 criteria
- Hypersomnolence Disorder (DSM-5)$^1$
  - 1.5% (95%CI: 1.3-1.7%)
- TST >9 hours$^2$
  - 8.4% (95%CI: 8.0-8.8%) of population
- TST >9 hours with distress/impairment$^2$
  - 1.6% (95%CI: 1.4-1.8%)

$^1$Ohayon et al, Arch Gen Psych 2012
$^2$Ohayon et al, Ann Neuro 2013
Hypersomnia is Multi-faceted

• Daytime Sleepiness
• Ability to fall asleep/stay awake under soporific conditions
• Sleep Duration
• Drowsiness
• Neurobehavioral alertness
• Sleep inertia
• REM-instability

Other Objective Measures

• Maintenance of Wakefulness Test (MWT)
• Pupillometry
• Psychomotor Vigilance Task (PVT)
• Sustained Attention to Response Task (SART)
• Others

• None are specific for a particular disorder!
Maintenance of Wakefulness Test (MWT)

- 4 x 20-40 minute sessions 2 hours apart
- Person sits in a chair or upright in bed while supported
- Room is quiet and dark
- Instructed to try to look straight ahead, remain awake, and avoid extreme behaviors to stay awake
- Nap terminated after 40 min of no sleep, 3 consecutive epochs of N1, or any other sleep stage

Maintenance of Wakefulness Test in Unmedicated Narcoleptics

1. Narcolepsy patients have lower mean sleep latency values on MWT
2. Sizeable percentage of narcoleptics still have normal MWT

Mitler, Electroenceph and Clin Neurophys, 1998
MWT Interpretation

- Challenging because of limited normative data
- Rule of thumb is that MSL<11 minutes suggestive of impaired ability to maintain wakefulness\(^1\)
- Not used in nosology
- Often discordant with MSLT findings, particularly in non-narcoleptic disorders of hypersomnolence\(^2\)
- Significant but small correlation with MSLT (r=0.41)\(^2\)

\(^1\)Doghramji et al., Elect Clin Neurophysiol 1997
\(^2\)Sangal et al, Chest 1992

MWT in Idiopathic Hypersomnia

- Limited data confirms difficulties of applying MWT in the diagnosis of IH
- 52% of patients with IH will have “high” MSL (>29.4 minutes) on MWT\(^1\)
- 2/6 IH patients without long sleep time had MSL below 11 min\(^2\)
- 0/4 IH with long sleep time had MSL<11min (3/4 had MSL=40 min)\(^2\)

\(^1\)Sangal et al, Chest 1992
\(^2\)Philip Int J Psychopharm 2013
Pupillometry

- Non-EEG based measure
- Examines spontaneous changes in pupil size that occur when sleepy
- Narcoleptics show increases in pupil oscillations
- Measure not specific to narcolepsy

Merritt, Int J Psychophysiol, 2004

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Pupillometry vs. MSLT

Small but significant correlation between PUI and MSL

\[ r = -0.402 \]

\[ p < 0.01 \]

Yamamoto et al Environ Health Prev 2013
Psychomotor Vigilance Task (PVT)

- Subjects press a button as quickly as possible when counter appears on screen
- Reaction time provided in real time
- Stimuli appear at random intervals
- Several outcome variables
  - Reaction time
  - Lapses
  - False Starts

PVT

- Association between ESS and PVT\(^1\)
- No association between MSLT and PVT\(^1\)
- Generally, sleepy patients have worse performance on PVT\(^2\)
- IH and narcoleptic patients differ from insufficient sleep syndrome on some, but not all PVT measures\(^2\)
- Cutoffs for abnormal are not standardized
  - \(\geq 4\) Lapses\(^3,4\)
  - \(\geq 3\) False starts\(^3\)

\(^1\)Kim et al Sleep 2007  \(^2\)Thomann et al JCSM 2014  \(^3\)Yun et al Sleep Med 2015  \(^4\)Sunwoo et al Sleep 2012
**Sustained Attention to Response Task (SART)**

- Numbers 1-9 appear 225 times in random order and different sizes on a computer screen.
- Respond to appearance of each number, except the number 3 (appears 25 times).
- Error score = errors of omission and commission.
- Does not necessarily correlate with MSLT scores.

VanSchie, J Sleep Res, 2012

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**AEPs and Sleep Inertia**

P300 Delay and/or Sleep Negatives observed during Forced Awakenings in all Patient Groups Except Psychogenic Hypersomnia

Peter-Derex et al, Neurophysiologie Clinique 2013
Measures of Sleep Duration

• Excessive sleep duration now included in diagnostic criteria
• Cutoff values are debatable
• Available options
  – 24hr or ad libitum polysomnography
  – Actigraphy

Ad libitum PSG

• Should be done in concert with actigraphy/sleep diaries given concern for sleep deprivation causing false positives
• Can be very helpful clinically
• Few sleep labs currently allow patients to sleep ad libitum
Actigraphy in IH

• Limited data
• Actigraphic TST in IH 6.95h (±1.2)\(^1\) to 7.5h (±1.0)\(^2\)
• IH not different from controls on TST, SE, WASO during nightly sleep\(^1\)
• Did have more awakenings at night\(^1\)
• IH had less daytime activity and more naps\(^1\)
• Caveat: long sleep duration not generally considered in reported results

Filardi et al, Sleep Med 2015

Discrepancy between Actigraphy and Sleep Diaries in IH

*Overestimates of Diaries versus Actigraphy >1 hour also occur in ~25% of the population (Van Den Berg J Sleep Res 2008)
Subjective Hypersomnolence Measures

Epworth Sleepiness Scale

- Individual rates (0-3) how likely they are to doze off in 8 situations
- Score ≥11 suggests significant EDS
- Correlation coefficient ESS vs. MSLT= ~-0.3

Narcoleptics tend to have very high ESS scores

Johns 1991, 2000
Other Novel Scales
(In various stages of development)

• Sleep Inertia Questionnaire\(^1\)
  – 22 item survey focused on sleep inertia
• Hypersomnia Severity Index\(^2\)
  – 9 item scale
  – Factor 1=frequency of sleeping too much at night, difficulty waking up, sleeping during the day, feeling sleepy during the day
  – Factor 2=impact of hypersomnia

\(^1\)Kanaday and Harvey, Cogn Ther Res 2015
\(^2\)Kaplan et al, SLEEP Abstract Suppl 2015

Transdiagnostic Approach: NIMH RDoC

• RDoC=Research Domain Criteria
• Elucidate fundamental biobehavioral dimensions that cut across heterogeneous disorder categories
• Hypersomnia spans core Domain of Arousal/Modulatory Systems
• Goal is to utilize multiple scientific methods/paradigms to examine different units of analysis
Summary thus far

- Hypersomnolence is multifaceted
- Objective/subjective measures have marginal correlations with one another
- One approach is to try to understand the neurobiology of individual aspects of hypersomnolence
- Need to clarify cause(s) of hypersomnolence rather than relying solely on descriptive tests
CSF from Hypersomnia Patients Enhances Effects of GABA

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Endogenous GABAergic Substance in IH?

Endogenous GABAergic Substance in IH?

Participants with elevated response of GABA receptors from their CSF showed improvements with flumazenil (GABA antagonist)

Other (indirect) evidence of GABA-related hypersomnia

- Increased sleep spindles in patients with IH
- Clinical reports of improvements in some patients with flumazenil and clarithromycin

Trotti, J Psychopharm 2013
Kelty, J Psychopharm 2014
Bové, Sleep 1994
Rationale for Clarithromycin in IH

- Clinical anecdote of a patient with GABA-related hypersomnia who developed severe insomnia when given the drug for bronchitis

- Known CNS side effects (insomnia, mania)

- Acts as a GABA antagonist *in vitro*
  - (Garcia and Jenkins 2009)

Initial Chart Review

- 53 patients treated at Emory
  - Failed 2.6 (1.4) standard wake-promoting agents
  - All had CSF which enhanced GABA-A receptor function

- Started 500mg AM and lunch
  - some patients increased to 1000mg BID

Trotti et al., J Psychopharm 2014
Initial Chart Review

• 34 out of 53 patients (64%) reported subjective improvement in sleepiness during initial two weeks

• 10 patients did not tolerate
  – GI distress (n=5), bad taste (n=2)

• Some PVT measures improved among those deriving benefit
  – Mean reaction time & $1/RT_{10\%}$
  – Not number of lapses

Trotti et al., J Psychopharm 2014

Initial Chart Review

• 23 patients (68%) chose to continue taking on a long term basis
  – 16 remained on daily use
  – 4 used on intermittent basis
  – 3 ultimately discontinued

Trotti et al., J Psychopharm 2014
Clarithromycin RCT

- Double blind, crossover trial
- 5 weeks (randomized order)
  - 2 weeks clarithromycin 500 BID
  - 1 week washout
  - 2 weeks placebo
- Final analysis on 20 completed participants
- All participants had GABA-related hypersomnolence

Trotti et al., Ann Neurol 2015

Clarithromycin RCT

- Primary outcome
  - Δ median RT at week 2
- Secondary outcomes (weeks 1&2)
  - PVT lapses
  - Epworth Sleepiness Scale
  - Functional Outcomes of Sleep
  - SF-36
  - Stanford Sleepiness Scale
  - PSQI
  - Adverse Events
  - Median RT (week 1)

Trotti et al., Ann Neurol 2015
Clarithromycin RCT

• No significant difference on primary outcome
• Significant improvements in
  – ESS (4 point difference: 14.1 vs. 10.1)
  – FOSQ
  – Subscales of SF-36 (energy, general)
  – SSS (week 1 only)
• Clarithromycin associated with dysguesia
  15/22 vs. 0/20 placebo (p<0.001)

Trotti et al., Ann Neurol 2015

Clarithromycin in IH

• Currently not the standard of care
• All patients should try and fail standard therapies (unless contraindicated) before considering
• Currently GABA-A potentiation assay not commercially available
• Decision to try involves complicated risk-benefit discussion
Risks of Clarithromycin

- GI side effects
- Altered smell/taste
- Reversible ototoxicity (tinnitus)
- Psychiatric effects
- Rash (up to 10% of patients)
- Antibiotic resistance
- Drug interactions (inhibits P450 CYP3A4)
- Cardiovascular
  - Arrhythmias
  - Increased mortality those with cardiovascular disease (?)

Use of Flumazenil in IH

- Published results limited to case reports/case series
- NOT standard of care
- Significant logistic and pragmatic hurdles to prescribing it to patients
  - Obtaining drug
  - Compounding into lozenge, transdermal preparation

Kelty, J Psychopharm 2014
Risks of Flumazenil

- Minimal data on long term use
- Seizures
- GI (nausea/vomiting)
- Psychiatric (especially panic)
- Sweating/flushing
- Arrhythmias

Summary

- Hypersomnolence is a multi-faceted problem that no one measure will be able to quantify
- Sleep Medicine needs to develop other methods for assessing hypersomnolence and move them into clinical practice
- Need to advance our understanding of the biological causes of hypersomnolence and develop/test novel treatements
www.hypersomniafoundation.org/

- Patient-focused Foundation
- Annual Conference
- Educational Activities
- Patient Registry
- Links to Research Studies

Acknowledgements