# A Bird's Eye View: Progress & Challenges in the Diagnosis & Treatment of Idiopathic Hypersomnia

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## Disclosures

**Fees for service from:** UCB Pharmaceuticals, Jazz Pharma, Xenoport, Flamel Technologies (Avadel), Balance Therapeutics, Major League Baseball, several law firms as an expert witness, as well as patients and several branches of the US government (USPHS, USSS).

**US Patent US9616070B2**: Use of GABA-A receptor antagonists for the treatment of excessive sleepiness and disorders associated with excessive sleepiness

**Patent (submitted/pending) PCT/US18/32114:** Treatment of Conditions Associated with Myotonic Dystrophy

**Royalties:** as inventor for sale/transfer of use and technology US9616070B2 to Balance Therapeutics

# Progress on Many Fronts:

**Awareness:** Increasing (patients, providers, & researchers)

**Diagnostics:** Getting beyond the MSLT, but still a long road ahead

**Causes:** New and greater insights into the biology underlying many instances of 'idiopathic' hypersomnia

**Cure:** Symptomatic treatment choices are increasing, and new commercial interests are entering the arena

**Resources:** Growing from diverse sources – government (NIH), foundations, industry, and philanthropic

hypersomnia foundation.org



# Increased Attention at Professional Sleep Meetings:

SLEEP 2016 DENVER • JUNE 11-15

**APSS 2016** | Denver, CO

**Hypersomnolence: Diagnostic, scientific, and treatment challenges**

LM Trotti (Chair), J Black; D Plante, D Rye, P Zee

World Sleep 2017 OCTOBER 7-11, 2017 • PRAGUE, CZECH REPUBLIC

**World Sleep Congress 2017** | Prague

**Idiopathic hypersomnia: A neglected disorder**

Arnulf (Chair), K Sonka, D Rye, G Mayer

THE DENVER POST denverpost.com

**When 11 hours aren't enough: The rare disorder of perpetual sleepiness**

Idiopathic hypersomnia and "healthy sleep" among topics of national conference in Denver

By Kevin Simpson | ksimpson@denverpost.com | June 9, 2016 at 3:09 pm

## Memorable Comments at the 2017 World Sleep Society Congress in Prague

"The MSLT has **lead us astray** in the study of hypersomnia" – *E. Mignot*

"The MSLT is **not the way** to capture the phenotype of these (idiopathic hypersomnia) patients" – *I. Arnulf*

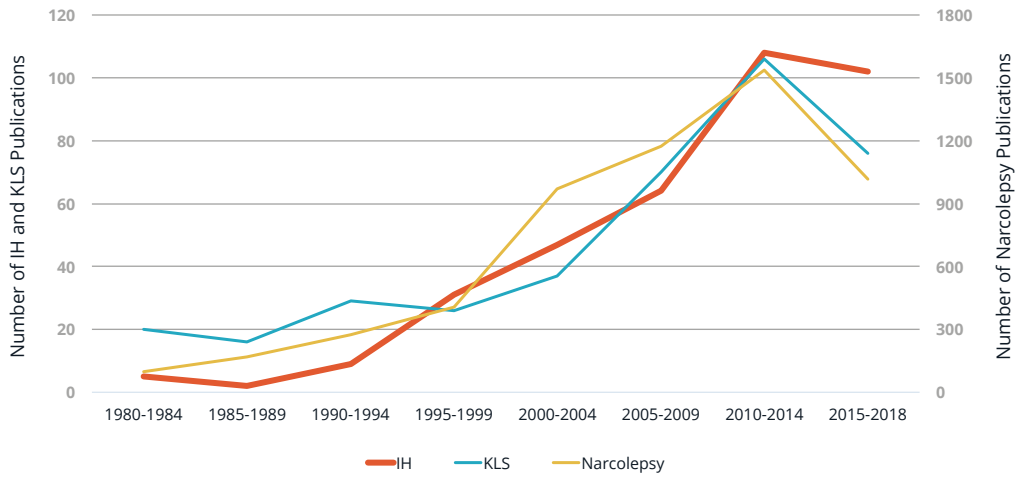
"The concept of Narcolepsy Type 2 is becoming more and more **meaningless**" – *E. Mignot*

"I believe idiopathic hypersomnia & Narcolepsy Type 2 to be the **same disease**" – *M. Partinen*

"Idiopathic hypersomnia with long sleep seems an **independent clinical entity** with a strong genetic predisposition" – *S. Nevsimalova*

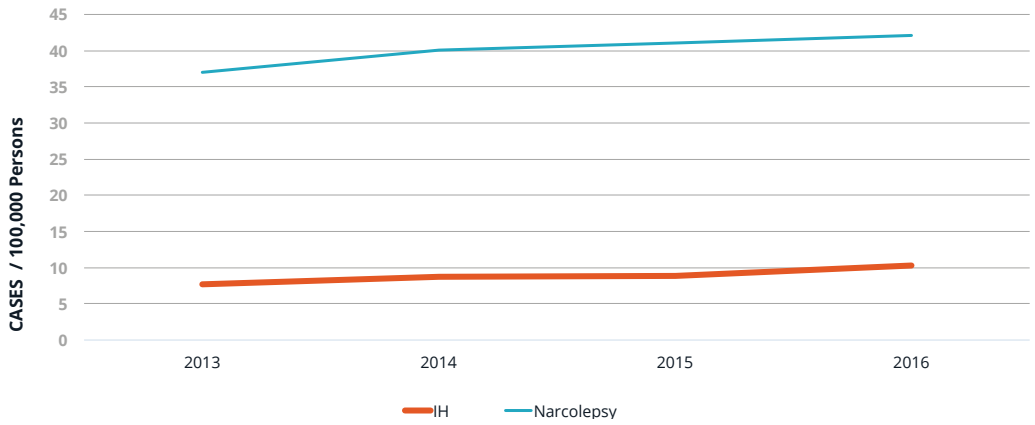


## Scientific Publications / 5 Year Periods




Source: ISI Web of Science search

# US Prevalence of IH versus any Narcolepsy / 100,000 Persons Insurance Claims Data (Symphony Health)



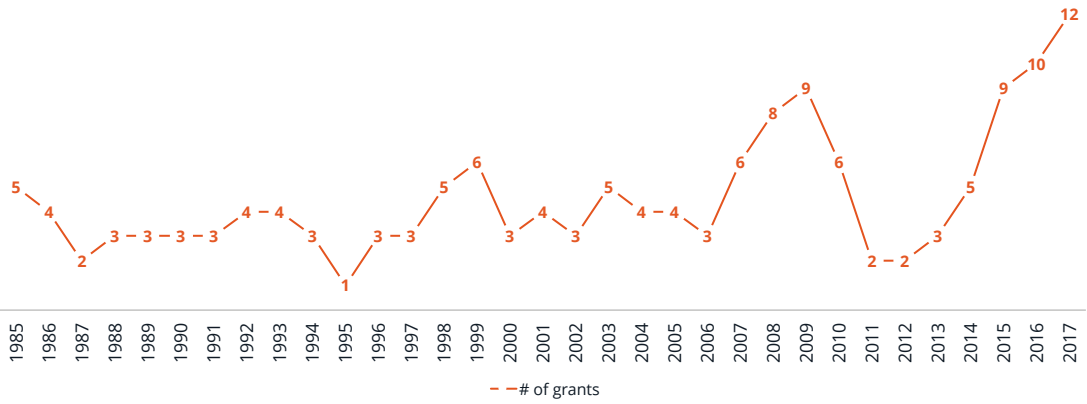

G Hess et al. (2018) – SLEEP Abst. Suppl 41: A232



# Patient 'Registries'

| Name | Location | # Centers | Year Updated | # Narcolepsy Cases | # IH Cases | Biospecimens |
|---|---|---|---|---|---|---|
| EU – Narcolepsy Network | Europe | 37 | 2015 | 542 (NT1)<br>120 (NT2) | 38 (IH) | Yes (some) |
| NarcoBank | France | 3 | 2017 | 290 (NT1) | 221 (IH)<br>168 Females<br>53 Males | Yes:<br>CSF<br>DNA |
| Emory Sleep Center | United States | 1 | 2018 | ~ 110 (NT1)<br>~ 220 (NT2) | ~ 560 IH + other hypersomnia | Whole blood > 850<br>CSF > 550<br>Fibroblasts 11 |
| CoRDS | Worldwide | --- | This meeting | This meeting | This meeting | Pending |

# # of Active NIH Grants: Key Search Word = "Hypersomnia"






# NIH Funding with Direct Relevance to Hypersomnia

| Principal Investigator | Specialty | University | Grant Type | Start | End | Topic |
|---|---|---|---|---|---|---|
| D Plante | Psychiatry/Sleep | Wisconsin | K23 | 12/1/12 | 11/31/17 | EEG/behavioral |
| L Trotti | Neurology/Sleep | Emory | K23 | 8/1/14 | 7/31/19 | Neuroimaging |
| D Rye | Neurology/Sleep | Emory | R01 | 9/1/15 | 8/31/19 | Multi-Disciplinary |
| J Cheung | Neurology/Sleep | Stanford | K23 | 9/25/17 | 8/31/22 | Genetics |
| N Bohnen | Neurology/Radiology | Michigan | R01 | 7/15/17 | 4/30/21 | PD/Neuroimaging |

## Pharmaceutical Industry Interest is Growing

Balance Therapeutics

Umecrine cognition

Jazz Pharmaceuticals®



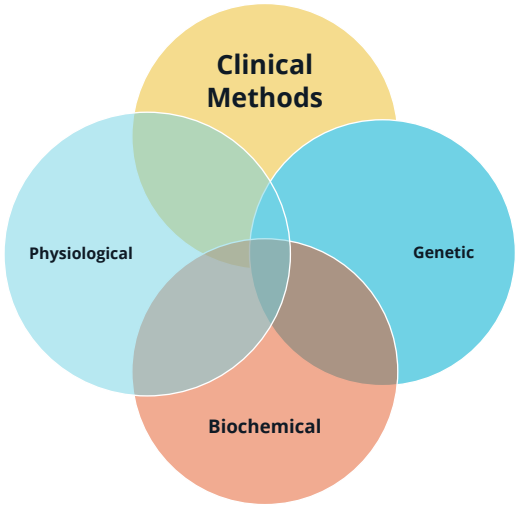
## Classification

As hypersomnia and hypersomnolence are **symptoms** – and ones not unique to a single disease …

might they be a disease in and of themselves (i.e., Sui generis)?

If so …

how might that 'disease' be distinguished from others that share these symptoms ?



# Gélineau's Syndrome

- **Patients with attacks of sleep are common, whereas patients with attacks of sleep and cataplexy are relatively rare**, and it would seem wise, for the present to regard the latter as a separate group.
- Since the term narcolepsy is often used rather loosely, confusion might be avoided by designating those cases presenting both attacks of sleep and cataplexy as Gélineau's syndrome".

NARCOLEPSY (GÉLINEAU'S SYNDROME) AND OTHER VARIETIES OF MORBID SOMNOLENCE *

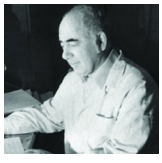
MAX LEVIN, M.D.

PHILADELPHIA

Archives of Neurology & Psychiatry (1929) 22: 1172-1200



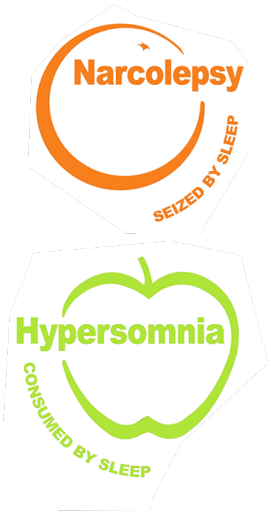
# Hypersomnia ≠ Narcolepsy



**French physician Jean-Baptiste-Édouard Gélineau**
**Narcolepsy** (from Fr. Narcolepsie) coined in 1880 from comb. form of Gk. narke "numbness, stupor" + lepsis "an attack, seizure."

**Sir William Gowers**
probably the greatest clinical neurologist of all time" – MacDonald Critchley, 1949: **'Somnosis'** (*circa 1890s*)

**Bedrich Roth**
**'Sleep Drunkenness'** *(1954)*
**'Idiopathic Hypersomnia'** *(1976)*



# Extending The Allegory

Whereas we can all agree that these are each apples (e.g., hypersomnia) – which is the Granny Smith (i.e., 'idiopathic' hypersomnia)? – which features allow us to make this distinction? – and with what level of confidence?



# Indeed, Self-reported Hypersomnia is Common in The General Population:

- 8.4% report > 9 hours of sleep / 24 hr. period
- 1.6% report Excessive Quantity of sleep (> 9 hrs) **and** "deteriorated quality of wakefulness" (viz., unintended excessive sleepiness) related to it
- 0.5% Hypersomnia Disorder (per DSM-IV)
- 0.038% with Narcolepsy with cataplexy

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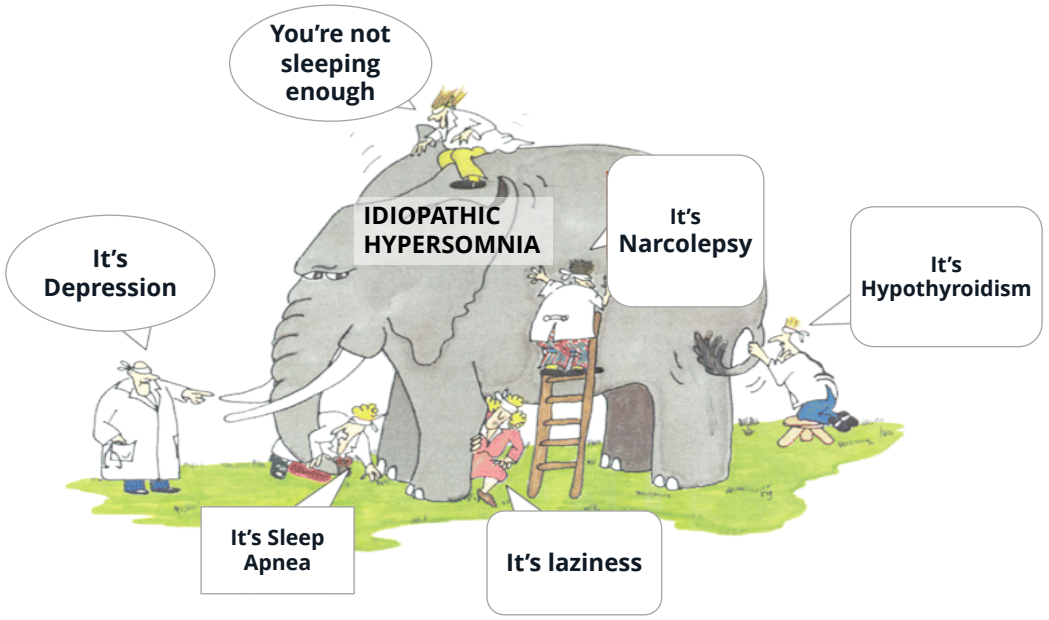
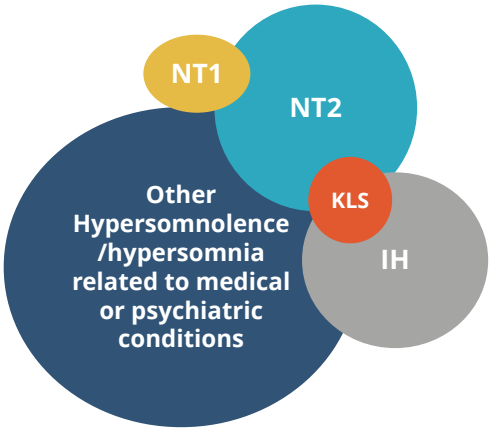
M Ohayon et al. Annals of Neurology (2013) 73: 785-794






# Central Disorders of Hypersomnolence International Classification of Sleep Disorders 3rd ed. (2014):




**NT1=** Narcolepsy with cataplexy due to loss of hypocretin

**NT2=** Narcolepsy without cataplexy

**IH=** Idiopathic Hypersomnia

**KLS=** Kleine-Levin Syndrome (episodic)

# ICSD-3 Criteria for Idiopathic Hypersomnia: Three Doorways to a Diagnosis

A. Irrepressible need to sleep or daytime lapses into sleep for at least 3 months

B. Cataplexy is absent

C. MSLT demonstrates ≤ 1 sleep onset REM-sleep periods

D. (**1**) MSLT demonstrates a mean latency to sleep of ≤ 8 minutes
(**2**) 11 hours of sleep/24 hr by polysomnography
(**3**) an average of 11 hours of sleep/24 hour by one week's actigraphy

E. Insufficient sleep is ruled out

F. Not better explained by medications, another sleep disorder, or medical or psychiatric disorder

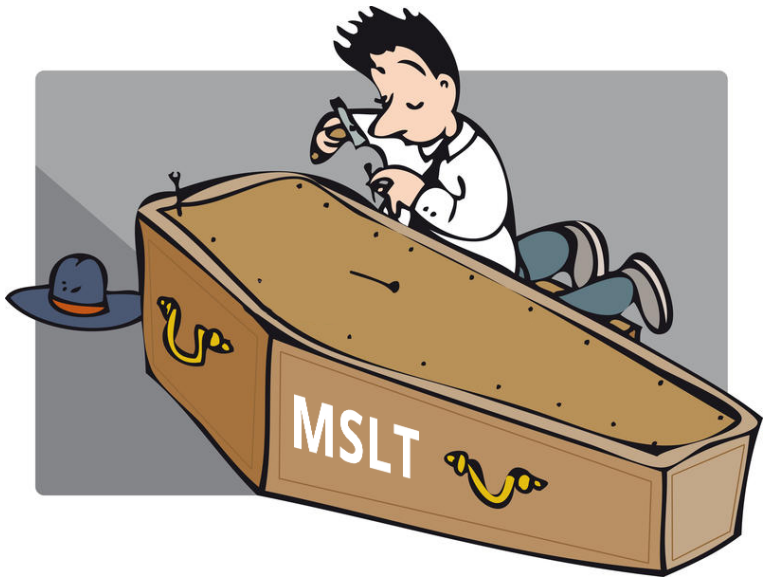


# Behind These 3 Doors do we Find the Same Patient?


A. Do patients 1,2, and 3 describe a similar course of disease?

B. Are treatment(s) equally effective for each of the 3 patients?

C. Does a common biology hide behind each door?



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JCSM Journal of Clinical Sleep Medicine

http://dx.doi.org/10.5665/sleep.3748

## The MSLT: More Objections than Benefits as a Diagnostic Gold Standard?

Commentary on Goldbart et al. Narcolepsy and predictors of positive MSLTs in the Wisconsin Sleep Cohort. SLEEP 2014;37:1043-1051.

Geert Mayer, MD[1,2]; Gert Jan Lammers, MD, PhD[3,4]

*[1]Hephata Klinik, Schwalmstadt Germany; [2]Department of Neurology, Philipps University, Marburg, Germany; [3]Department of Neurology and Clinical Neurophysiology, Leiden University Medical Center, Leiden, The Netherlands; [4]Sleep Wake Center SEIN, Heemstede, The Netherlands*

## Test–Retest Reliability of the Multiple Sleep Latency Test in Central Disorders of Hypersomnolence

Régis Lopez, MD, PhD[1,2,3]; Anis Doukkali, MD[2]; Lucie Barateau, MD[1,2,3]; Elisa Evangelista, MD[2,3]; Sofiene Chenini, MD[2]; Isabelle Jaussent, PhD[3]; Yves Dauvilliers, MD, PhD[1,2,3]

*SLEEP, Vol. 40, No. 12, 2017*

http://dx.doi.org/10.5664/jcsm.2922

## Test-Retest Reliability of the Multiple Sleep Latency Test in Narcolepsy without Cataplexy and Idiopathic Hypersomnia

Lynn Marie Trotti, M.D., M.Sc.; Beth A. Staab, M.D.; David B. Rye, M.D., Ph.D.

*Program in Sleep, Department of Neurology, Emory University School of Medicine, Atlanta, GA*

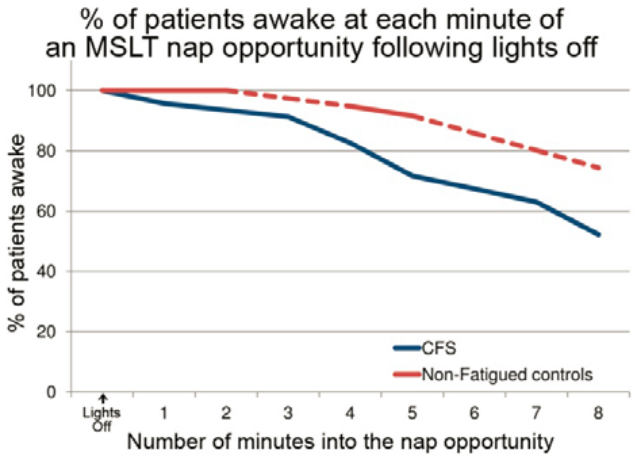
*Journal of Clinical Sleep Medicine, Vol. 9, No. 8, 2013*

## The MSLT is Repeatable in Narcolepsy Type 1 But Not Narcolepsy Type 2: A Retrospective Patient Study

Chad Ruoff, MD[1]; Fabio Pizza, MD[2,3]; Lynn Marie Trotti, MD, MSc[4]; Karel Sonka, MD[5]; Stefano Vandi, MD[2,3]; Joseph Cheung, MD, MS[1]; Swaroop Pinto, MD[6,7]; Mali Einen[1]; Narong Simakajornboon, MD[6,7]; Fang Han, MD[6]; Paul Peppard, PhD[8]; Sona Nevsimalova, MD[5,*]; Giuseppe Plazzi, MD, PhD[2,3,*]; David Rye, MD, PhD[4,*]; Emmanuel Mignot, MD, PhD[1,*]

*J Clin Sleep Med.* 2018;14(1):65–74.

# Many Non-complaining Population Controls as Well as Subjects with Chronic Fatigue Syndrome Meet MSLT Criteria for IH




Population-based control MSLTs (n=1019) courtesy of E. Mignot (Stanford Center of Narcolepsy Research) vs. CFS (n=46) from Wichita, KS (Reeves, W.C., et al., BMC Neurology, 2006. 6: p. 41).



# Desperate Need for Alternate Diagnostic Strategies:

- MSLT exhibits poor specificity and only reasonable sensitivity in discriminating between central disorders of hypersomnolence, hypersomnolence that occurs in 'other' disorders, and population 'norms' without complaints of excessive or perpetual sleepiness.
- MSLT exhibits poor test-retest reliability – i.e., repeat testing often results in discordant results/'diagnoses'
- MSLT is time, labor, and cost intensive
- Between laboratory differences in MSLT policies & procedures are substantial despite standard accreditation of testing laboratories

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# Payor/Market Trends (2013-2016) Also Emphasize Urgent Need For Alternate Diagnostic Strategies:

| Diagnostic Test | 2013 rate (per 100K) | 2016 rate | % Change |
|---|---|---|---|
| Polysomnography (PSG) | 677.6 | 583.6 | ↓13.9% |
| Multiple Sleep Latency Test (MSLT)<br>Maintenance of Wakefulness Test (MWT) | 17.2 | 13.4 | ↓ 22.1% |
| Home Sleep Apnea Testing (HSAT) | 96.8 | 211.2 | ↑118.2% |

G Hess et al. (2018) – SLEEP Abst. Suppl 41: A232



# New Tools Under Exploration to Diagnosis & Assess 'Idiopathic' Hypersomnia:

**SUBJECTIVE:**
- Hypersomnia Index
- Sleep Inertia Scale

**OBJECTIVE:**
- Extend sleep on diagnostic PSG
- *Ad lib* sleep/modified MSLT
- Ambulatory EEG (48-72 hr)
- Wearables (*viz.*, actigraphy)
- EEG signatures (*e.g.*, theta power)
- Psychomotor Vigilance (PVT)
- Critical Flicker Fusion
- Pupillometry
- Saccadic Eye Movement velocity
- Cognition
- Acute drug challenges (e.g., IV flumazenil)

**BIOMARKERS:**
- CSF – GABA-A
- CSF - proteomics
- CSF - metabolomics
- Genomics/Genetics

# Relevant Examples at this APSS Meeting:

- Multimodal Hypersomnolence Assessment Substantially Increases Objective Identification of Hypersomnolence in Patients Referred for Multiple Sleep Latency Testing (Poster 0613)
  DT Plante, JD Cook & ML Prairie Sleep (2018), Vol 41, Abst. Suppl: A227–A228
- Working Memory and Psychomotor Vigilance Performance After Brief Naps in Hypersomnolent Patients: MSLT Correlates (Poster 0617)
  P Saini, E Bremer, S Broyles, D Rye & LM Trotti Sleep (2018), Vol 41, Abst. Suppl: A229
- Improved Primary CNS Hypersomnia Diagnosis With Statistical Machine Learning (Poster 0627)
  L Jiang, J Cheung, E Mignot & LD Schneider Sleep (2018), Vol 41, Abst. Suppl: A233



EXPERT OPINION ON INVESTIGATIONAL DRUGS, 2018
VOL. 27, NO. 2, 187–192
https://doi.org/10.1080/13543784.2018.1417385



META-OPINION

## Update on treatment for idiopathic hypersomnia

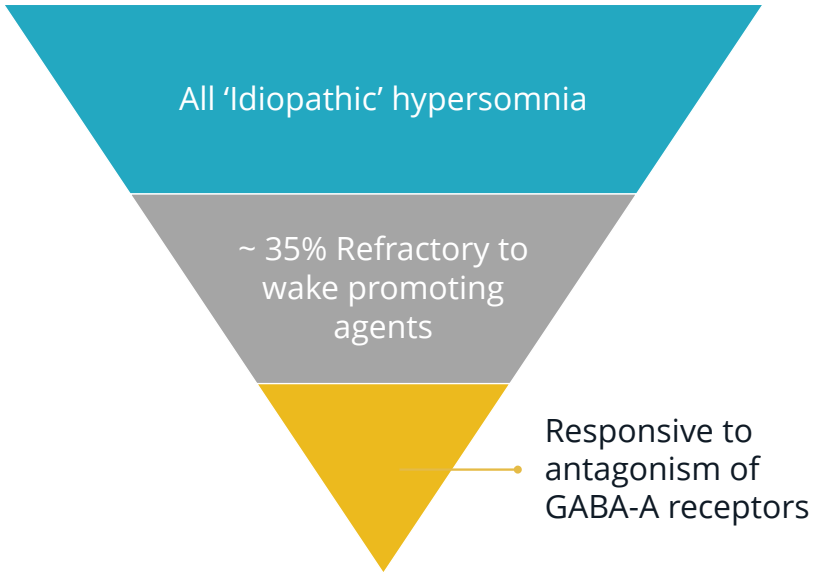
Elisa Evangelista[a,b], Régis Lopez[a,b,c] and Yves Dauvilliers[a,b,c]

[a]Centre National de Référence Narcolepsie Hypersomnies, Unité des Troubles du Sommeil, Service de Neurologie, Hôpital Gui-de-Chauliac Montpellier, Montpellier, France; [b]Inserm U1061, Montpellier, France; [c]Université de Montpellier, Montpellier, France

### Article highlights

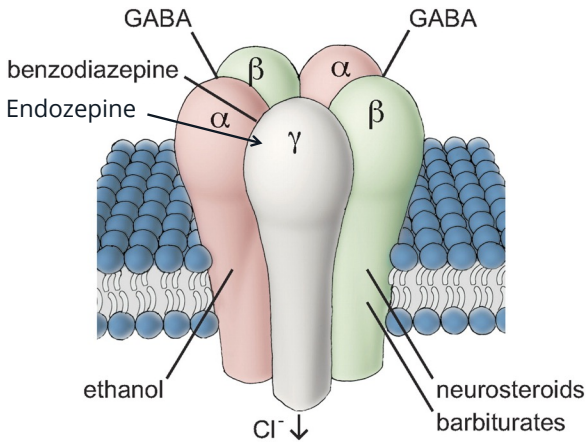
- Little is known about the pathophysiology, clinical characterization and treatment response of IH.
- Due to insufficient level of evidences, no treatment has currently an indication for the treatment of EDS in IH.
- Two recent well-designed studies confirmed the efficacy of modafinil for EDS in IH.
- Pitolisant and sodium oxybate are promising medications in IH
- More specific tools are needed to better assess the severity of the symptoms of IH and the treatment responsiveness

This box summarizes key points contained in the article






## The $GABA_A$ Receptor is a Target for Many Allosteric Modulators – Both Exogenous and Endogenous; Both Positive and Negative




Mikko Uusi-Oukari and Esa R. Korpi
Pharmacological Reviews March 2010, 62 (1) 97-135;

RESEARCH ARTICLE

SLEEP

# Modulation of Vigilance in the Primary Hypersomnias by Endogenous Enhancement of $GABA_A$ Receptors

David B. Rye,[1]* Donald L. Bliwise,[1] Kathy Parker,[2] Lynn Marie Trotti,[1] Prabhjyot Saini,[1] Jacqueline Fairley,[1] Amanda Freeman,[1] Paul S. Garcia,[3,4] Michael J. Owens,[5] James C. Ritchie,[6] Andrew Jenkins[3,7]

The biology underlying excessive daytime sleepiness (hypersomnolence) is incompletely understood. After excluding known causes of sleepiness in 32 hypersomnolent patients, we showed that, in the presence of 10 μM γ-aminobutyric acid (GABA), cerebrospinal fluid (CSF) from these subjects stimulated $GABA_A$ receptor function in vitro by 84.0 ± 40.7% (SD) relative to the 35.8 ± 7.5% (SD) stimulation obtained with CSF from control subjects (Student's *t* test, $t = 6.47$, $P < 0.0001$); CSF alone had no effect on $GABA_A$ signaling. The bioactive CSF component had a mass of 500 to 3000 daltons and was neutralized by trypsin. Enhancement was greater for α2 subunit– versus α1 subunit–containing $GABA_A$ receptors and negligible for α4 subunit–containing ones. CSF samples from hypersomnolent patients also modestly enhanced benzodiazepine (BZD)–insensitive $GABA_A$ receptors and did not competitively displace BZDs from human brain tissue. Flumazenil—a drug that is generally believed to antagonize the sedative-hypnotic actions of BZDs only at the classical BZD-binding domain in $GABA_A$ receptors and to lack intrinsic activity—nevertheless reversed enhancement of $GABA_A$ signaling by hypersomnolent CSF in vitro. Furthermore, flumazenil normalized vigilance in seven hypersomnolent patients. We conclude that a naturally occurring substance in CSF augments inhibitory GABA signaling, thus revealing a new pathophysiology associated with excessive daytime sleepiness.

Rye et al. Sci Transl Med. 2012 Nov 21;4(161):161ra151.



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Journal of Clinical Sleep Medicine

COMMENTARY

## What's Old is New Again: Fresh Hope for Treatment Refractory Hypersomnolence Patients

Commentary on Trotti et al. Flumazenil for the treatment of refractory hypersomnolence: clinical experience with 153 patients. *J Clin Sleep Med* 2016;12(10):1389–1394.

Nathaniel F. Watson, MD, MSc

*Department of Neurology, University of Washington, Seattle, WA*

# Flumazenil Prescribing Data
## (Pavilion Compounding Pharmacy, Atlanta, GA – March 2013/2016)

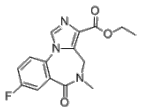
- Four (4) physicians:  344 individual subjects
- 45 subjects (13%) for at least 6 months continuously
- 18 subjects (5%) for at least 2 years continuously
- 89 additional prescribing physicians in the United States
- As of 2018 - > 100 prescribing physicians in the United States
- As of 2018 – 28 US physicians had prescribed to ≥ 5 unique patients

O Moody et al. Ann Neurol. 2017 Jun;81(6):904-907

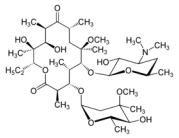


# Novel Sleep-"lytic" Therapies Driven by Inhibiting GABA-A Receptor 'Tone":

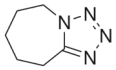
Flumazenil




Clarithromycin




Pentylenetetrazol (aka BTD-001; cardiazol; metrazol)



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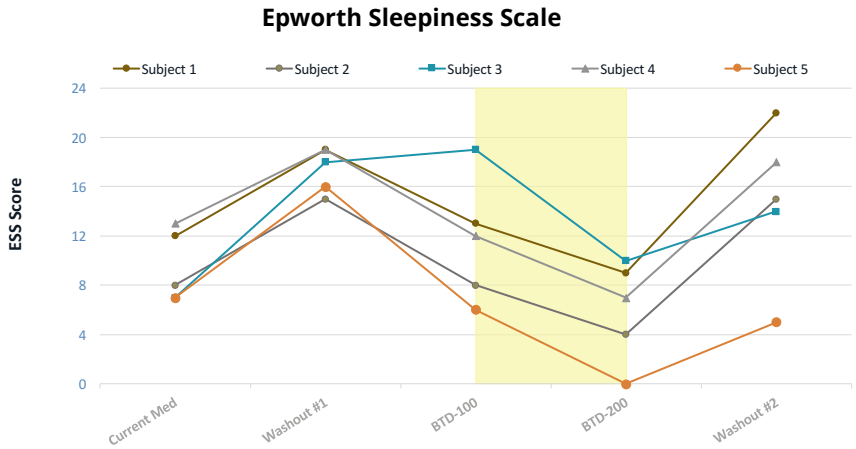
## An Open-label Study of the Efficacy, Safety and Tolerability of Oral BTD-001 in Adults with Idiopathic Hypersomnia or Narcolepsy Type 2




D Rye et al Sleep Medicine, Volume 40, Supplement 1, December 2017, Pages e285-e286



## Arise 2

- Coming soon to ~ 35 centers.
- Planned enrollment of 80 IH subjects (no NT2 as in ARISE 1).
- Double blind-crossover study lasting ~ 6 weeks (vs. 11-12 weeks in ARISE 1).
- Outcomes: ESS, Maintenance of Wakefulness Test, mental "fog" and additional.

Also monitor www.clinicaltrials.gov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# Are There Disorders That Phenocopy Idiopathic Hypersomnia?

1. Prodigious Sleep
2. Blunted Vigilance/Cognition
3. Responsive To Flumazenil

A **phenocopy** is an instance whereas the phenotype (generally referring to a specific trait such as hypersomnia or hypersomnolence) is mimicked by another condition whose phenotype is genetically determined.

"We must analyze, and seek to interpret partnerships in disease."

Sir Jonathan Hutchinson (1828-1913)
a pioneer syndromologist

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# Yes! And That Translates to Leverage

Leverage – The ability to influence a system, or an environment, in a way that multiplies the outcome of one's efforts without a corresponding increase in the consumption of resources. (www.businessdictionary.com)

- Expands the number of clinical and basic science researchers
- New biological and genetic knowledge serve as a foundation for inquiry
- Brings potentially powerful novel animal models to the playing field
- Opens dialogue with additional new funding sources in industry & foundations

## HYPERSOMNIA IN DYSTROPHIA MYOTONICA

BY

J. C. PHEMISTER and J. M. SMALL

*From the Department of Neurology, The London Hospital*

- Hypersomnia **co-occurs** with somnolence (EDS), but dominates the clinical picture
- **Sleep Inertia** – an "unmanageable liability to oversleep" – subjects needed to be "shaken awake in the morning"
- Bed times rarely later than 8:00 PM
- Hypersomnia fluctuated over weeks/months/years
- Seemingly unrelated to symptoms of muscle disease – predated myotonia in 1 of 4 subjects
- **Distinct from narcolepsy**
  - Absent cataplexy
  - Prodigious sleep amounts / 24 hours (such a propensity to sleep being atypical of narcolepsy)

J. Neurol. Neurosurg. Psychiat., 1961, 24,173.



## Case OM011 - Improved in Many Domains for > 12 Months With Flumazenil

**FLUMAZENIL**

| Dependent Measure | OFF (March 2017) | ON (April 2017) | Clinically meaningful |
|---|---|---|---|
| Epworth Sleepiness Scale | 13 | 5 | Δ 3-4 |
| Functional Outcomes of Sleep (5-20) | 9.96 | 18.70 | Δ 2-3 |
| Multidimensional Fatigue Inventory (0-100) | 66 | 47 | |
| General Fatigue (5-20)<br>Mental Fatigue (5-20)<br>Reduced Activity (5-20) | 17<br>17<br>13 | 11<br>10<br>8 | |
| Fatigue Severity Scale (7-63) | 57 | 38 | |
| Sleep Inertia Questionnaire (0-20) | 14.6 | 8 | |
| Hypersomnia Severity Index (0-36) | 32 | 17 | |

# Case KM031 – Improved in Many Domains With Flumazenil >> Armodafinil (Nuvigil®)

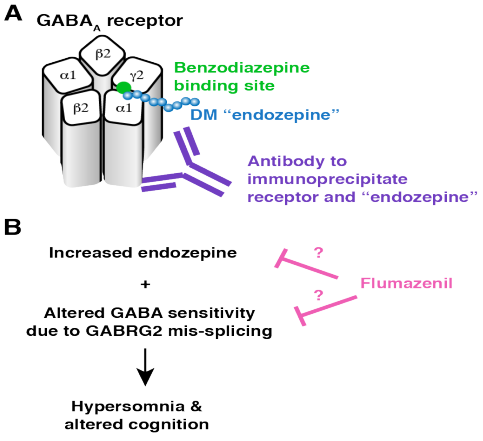
CASE KM031

| Dependent Measure | Off Rx (Jan 2018) | Armodafinil 250mg QAM (Feb 2018) | ON Flumazenil (no Armodafinil (March 2018) | Clinically meaningful |
|---|---|---|---|---|
| **Epworth Sleepiness Scale (0-24)** | **11** | **8** | **7** | Δ 3-4 |
| **Functional Outcomes of Sleep (5-20)** | **16.3** | **16.9** | **19.4** | Δ 2-3 |
| **Multidimensional Fatigue Inventory (0-100)** | **52** | **44** | **28** | |
| General Fatigue | **13** | **15** | **8** | |
| Mental Fatigue | **10** | **11** | **4** | |
| Reduced Activity | **13** | **7** | **6** | |
| **Fatigue Severity Scale (7-63)** | **54** | **47** | **24** | |
| **Sleep Inertia Questionnaire (0-20)** | **14.9** | **14.7** | **5.8** | |
| **Hypersomnia Severity Index (0-36)** | **26** | **25** | **10** | |



# GABA axis perturbation in Myotonic Dystrophy - a two hit hypothesis:

- **4 of 4 DM1 patient CSFs exhibit endozepine-like activity**
- **γ2 subunit of $GABA_A$ receptors is mis-spliced in human and murine brain**
  (Goodwin et al., 2015; Sergeant, Wang & Swanson; unpublished)
- **γ2S(short/fetal) is more abundant than γ2L (long/adult) in human DM1 brains and mouse models of DM1**
- **$GABA_A$ receptors are more sensitive to benzodiazepines**
  (Quinlan, Firestone and Homanics; 2000)



[Intervention Review]

# Flumazenil versus placebo or no intervention for people with cirrhosis and hepatic encephalopathy

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**Editorial group:** Cochrane Hepato-Biliary Group.
**Publication status and date:** New search for studies and content updated (no change to conclusions), published in Issue 8, 2017.

**Citation:** Goh ET, Andersen ML, Morgan MY, Gluud LL. Flumazenil versus placebo or no intervention for people with cirrhosis and hepatic encephalopathy. *Cochrane Database of Systematic Reviews* 2017, Issue 8. Art. No.: CD002798. DOI: 10.1002/14651858.CD002798.pub4.





| Disorder | Offending Agent(s) | Flumazenil Responsive | Clinical Development/ Trials |
|---|---|---|---|
| Idiopathic Hypersomnia/Nt2 | Endozepine "like" substance | Proportion – (~40-60%) | YES – BTD-001 (Pentylenetetrazol) Balance Therapeutics<br>YES – GR3027 (Umecrine) |
| Myotonic Dystrophy | Endozepine "like" substance; GABA-A receptor γ2 subunit mis-splicing | (Seemingly) | YES – Flumazenil (open-label) & complementary studies |
| Hepatic Encephalopathy | "Endozepines" and Neurosteroids e.g., – allopregnanolone; THDOC | YES | YES - GR3027 (Umecrine) |

# Clinical Trials for Idiopathic Hypersomnia:

| Sponsor | Location | Population | Study Type | Compound | Status |
|---|---|---|---|---|---|
| Balance | United States | IH & NT2 | Phase IIB | BTD-001 | June 2018 (recruiting) ------N=80 |
| Umecrine | Scandanavia | IH | Phase IIA | GR3027 | Ongoing |
| JAZZ | United States | IH | Phase III | JZP-258 | Sept. 2018 (recruiting) ----N=140 |



# Other Registered Clinical "Trials"

**Transcranial Direct Current Stimulation for Central Hypersomnia without cataplexy (tDCS)**
*United States, Ohio State University*

**The Role of the Circadian System in Neurological Sleep-wake Disorders (PNP)**
*Switzerland, University of Zurich*

**Importance of Sleep Deprivation in Differential Diagnosis of Primary Hypersomnia (Actisom dépistage)**
*France, Centre d'Investigation Clinique et Technologique 805*

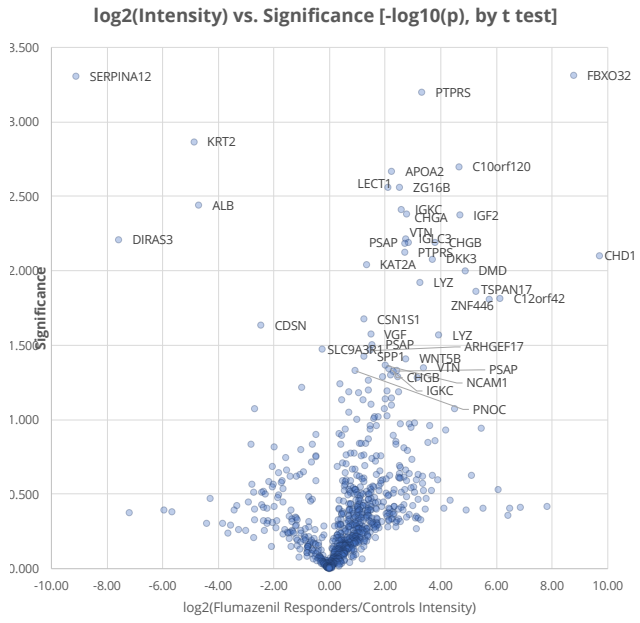
source: ClinicalTrials.gov

# Where Else Now?

- What is the chemical nature and source of endozepine-like activity?
- Where are the critical molecular sites of action for this endozepine at the GABA-A receptor and which subunits are engaged?
- What brain regions underly hypersomnia & associated symptoms inclusive of treatment efficacy?
- Are there genetic underpinnings to hypersomnia?
- Who is the target population and which symptoms are most tractable to treatment with $GABA_A$ receptor antagonists?



Proteomics of cerebrospinal fluid reveals a greater abundance of protein fragments in flumazenil responding patients versus non-complaining controls



# What Gene Variants Differentiate Idiopathic Hypersomnia From The General Population

Finding a gene by genome wide association

**Population 'Controls'**

**IH (± NT2) Subjects**



# Idiopathic Hypersomnia has Come a Very Long Way in a Relatively Short Period of Time:

1. A subgroup of patients refractory to traditional wake promoting medications exhibit a new biology with extra-ordinary diagnostic and treatment implications with potential broader relevance to the symptom of hypersomnia encountered in several other human diseases.
2. We have a growing number of new partners in our goal to meet an unmet clinical need by way of increasing awareness and encouraging discovery science. **Clinician Scientists // Basic Science Researchers // Industry // Disease Foundations**
3. Ongoing and anticipated clinical trials continue to grow in number
4. A passionate and engaged Hypersomnia Foundation & community continues to grow andprovide a strong voice in public discourse.

# WE Still Have a Lot To Do – Most Critically, In Anticipating "a" Treatment

**What Will the Package Insert Say We Are Treating?**

- "Once recognized, (disease) entities present problems in naming—and names are important".
- "A syndrome has 'arrived' if it has a name".
- "An unfortunate consequence of naming can be the mistaken impression that we understand the condition".
- "Differences in the phenotype are the most treacherous basis for decisions (… especially when heterogeneity/diversity is generally acknowledged …)."

Victor A. McKusick · On Lumpers and Splitters, or the Nosology of Genetic Disease in: Perspectives in Biology and Medicine · Winter 1969



# Thank you supporters!

**Individual patient contributions**
**Woodruff Health Sciences Research Fund**
**American Sleep Medicine Foundation (LMT)**
**National Institutes of Health: NS055015-(03S1)(DR);**
**K23-NS083748 (LMT); R01-NS089719 (DR)**
**Mind Science Foundation (DR)**
**Marigold Foundation (DR)**

## Acknowledgements

**Emory Program in Sleep**
Lynn Marie Trotti MD-MSc
Prabhjyot Saini MSc
Donald Bliwise PhD
Amanda Freeman PhD
Glenda Keating PhD
Jacqueline Fairley PhD
Justus Schwabedal PhD
Caroline Maness MD
Nigel Pederson MD
John Willie MD-PhD
Nursing & Technical Staff

**Emory Dept. of Pathology**
James Ritchie MD

**Emory Dept. of Anesthesiology**
Andrew Jenkins PhD
Paul Garcia MD-PhD
O Moody PhD

**Emory Dept. of Biochemistry**
Nicholas Seyfried PhD
Eric Dammer PhD

**Emory Dept. Of Biology**
Gary Bassell PhD

**Emory Dept. of Psychiatry**
Michael Owens PhD

**Boston Univ. Dept. of Physics**
Plamen Ivanov PhD
Ronny Bartsch PhD

**Hospital Clinic de Barcelona**
Alex Iranzo MD
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**Univ. of Florida**
Eric Wang PhD

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