Update on Idiopathic Hypersomnia

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Disclosures:

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Royalties: as inventor for sale/transfer of use and technology patent above to Balance Therapeutics
Differential Diagnosis

• Iatrogenic effect of medication
• Behaviorally insufficient sleep (BIS)
• Primary sleep disorder (e.g., sleep apnea; ‘narcolepsy’)
• Secondary to a medical/psychiatric condition
• Secondary to a neurological disorder (e.g., Parkinson’s disease, myotonic dystrophy)
• ‘Primary’, ‘Central’, or ‘Idiopathic’ Hypersomnia – viz., “sleepiness” occurring sui generis
Orexin/hypocretin cell loss causes Narcolepsy Type 1 (i.e., with cataplexy)
....and, it is immunogenetically mediated:
On the origins of hypersomnia/hypersomnolence:

- Loss of Function
  - Wakefulness
- Gain in Function - Sleep
HOWEVER:

NARCOLEPSY (Type 1)
(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
hypersomnia

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

Merriam-Webster Medical Dictionary
The $\text{GABA}_A$ receptor is a target for many allosteric modulators that dampen vigilance by way of enhancing GABA currents.
Modulation of Vigilance in the Primary Hypersomnias by Endogenous Enhancement of GABA<sub>A</sub> Receptors

David B. Rye, Donald L. Bliwise, Kathy Parker, Lynn Marie Trotti, Prabhjyot Saini, Jacqueline Fairley, Amanda Freeman, Paul S. Garcia, Michael J. Owens, James C. Ritchie, Andrew Jenkins

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<sub>A</sub> 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<sub>A</sub> 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<sub>A</sub> receptors and negligible for α4 subunit–containing ones. CSF samples from hypersomnolent patients also modestly enhanced benzodiazepine (BZD)–insensitive GABA<sub>A</sub> 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<sub>A</sub> receptors and to lack intrinsic activity—nevertheless reversed enhancement of GABA<sub>A</sub> 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.
*In vitro* potentiation of GABA$_A$ mediated Cl$^-$ currents by idiopathic hypersomnic CSF reversibility with the antagonist flumazenil
Biology (i.e., potentiation of GABA by hypersomnic CSF) disrespects ICSD-3 taxonomy

F=12.82, df 6, 49, P=0.0001) narcolepsy without cataplexy group (t=4.32, P=0.0118), narcolepsy with cataplexy group (t=3.78, P=0.0299), long sleepers (t=4.24, P=0.0136) and in the Spanish PH patients (t=4.85, P=0.0049) versus controls

Equivalence:

0.05mg/kg Versed ®

BAC = 0.10
Replication in 32 novel cases tested in 2 different laboratories on 2 continents (kappa coefficient = 0.79)

Normalization of attentional lapses by intravenous flumazenil in seven hypersomnolent subjects (humans)

• DROP IN VIDEO ------NBC TODAY SHOW
Sustained improvement in multiple domains with flumazenil (48-60mg SL per day +12mg transdermal at bedtime) in our index case

<table>
<thead>
<tr>
<th>Dependent Measure</th>
<th>FLUMAZENIL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OFF (February 2008)</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale</td>
<td>18</td>
</tr>
<tr>
<td>Reaction time median (ms)</td>
<td>292.3</td>
</tr>
<tr>
<td>Attentional lapses during PVT (0-100)</td>
<td>1</td>
</tr>
<tr>
<td>Short Form Beck Depression Inventory (0-39)</td>
<td>7</td>
</tr>
<tr>
<td>Functional Outcomes of Sleep (5-20)</td>
<td>10.0</td>
</tr>
<tr>
<td>Multidimensional Fatigue Inventory (MFI) (0-100)</td>
<td>85</td>
</tr>
</tbody>
</table>
THE GOOD NEWS? WE CAN HEAL YOU WITH FLUMAZENIL

THE BAD NEWS? NOBODY SELLS IT AND THE FDA DOES NOT APPROVE
Novel sleep-"lytic” therapies driven by inhibiting GABA-A receptor ‘tone”:

- Flumazenil
- Clarithromycin
- Pentylenetetrazol (aka BTD-001)
Flumazenil for the Treatment of Refractory Hypersomnolence: Clinical Experience with 153 Patients

Lynn Marie Trotti, MD, MSc; Prabhjot Saini, MSc; Catherine Koola, MPH; Vincent LaBarbera, MD; Donald L. Bliwise, PhD; David B. Rye, MD, PhD

1Emory University School of Medicine, Sleep Center and Department of Neurology, Atlanta, GA; 2Emory University Rollins School of Public Health, Atlanta, GA

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


Nathaniel F. Watson, MD, MSc

Department of Neurology, University of Washington, Seattle, WA
• 96 patients (62.8%) realized symptomatic benefit

• Responders reported a mean 4.7 point reduction in the Epworth Sleepiness Scale (+/- 4.7).

• 59 remained on flumazenil for a mean of 7.8 months (+/- 6.9 months).

• Responders were more often women with prominent sleep inertia.

• Adverse events did not result in treatment discontinuation.

• Sublingual and transdermal flumazenil provided sustained clinical benefit in 39% of patients.
Robust flumazenil prescription growth for hypersomnolence refractory to psychostimulants*

* Emory prescriptions filled at Pavilion Compounding Pharmacy, Atlanta, GA
** Refill defined as at least two consecutive months of refills
Flumazenil Prescribing Data (March 2013 – August 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
Exploring novel therapeutic alternatives: CLARITHROMYCIN (Biaxin®)
Improvement in daytime sleepiness with clarithromycin in patients with GABA-related hypersomnia: Clinical experience

Lynn Marie Trotti¹, Prabhjyot Saini¹, Amanda A Freeman¹, Donald L Bliwise¹, Paul S García²,³, Andrew Jenkins², and David B Rye¹
Clarithromycin in γ-Aminobutyric Acid–Related Hypersomnolence: A Randomized, Crossover Trial

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

Objective: Some central hypersomnolence syndromes are associated with a positive allosteric modulator of γ-aminobutyric acid (GABA)-A receptors in cerebrospinal fluid. Negative allosteric modulators of GABA-A receptors, including clarithromycin, have been reported to reduce sleepiness in these patients. We sought to systematically assess the effects of clarithromycin on objective vigilance and subjective sleepiness.

Methods: This was a 5-week, randomized, placebo-controlled, double-blind, crossover trial of clarithromycin 500mg with breakfast and lunch, in patients with hypersomnolence syndromes (excluding narcolepsy with cataplexy) and evidence for abnormal cerebrospinal fluid potentiation of GABA-A receptors. The study occurred at a university-affiliated medical center. The primary outcome measure was median reaction time on the psychomotor vigilance task (PVT) at week 2 in each condition. Secondary outcomes included the Epworth Sleepiness Scale, Stanford Sleepiness Scale, Functional Outcomes of Sleep Questionnaire, Pittsburgh Sleep Quality Index, SF-36, and additional PVT measures.

Results: Twenty-three patients began treatment. Three patients dropped out, and final analyses were performed on 20 complete cases. Median reaction time was not significantly different between clarithromycin and placebo. Subjective measures of sleepiness were significantly improved on clarithromycin versus placebo. Altered taste perception occurred, but was the only side effect more common on clarithromycin than placebo. No serious adverse events occurred.

Interpretation: Subjective sleepiness, but not psychomotor vigilance, improved during a 2-week course of clarithromycin. Although additional studies are needed, this suggests that clarithromycin may be a reasonable treatment option in patients with treatment-refractory hypersomnolence. This trial was registered at ClinicalTrials.gov (NCT01146600) and supported by the American Sleep Medicine Foundation.
Arise
INVIATION TO PARTICIPATE IN RESEARCH

For more detailed information, visit the study website
www.arisestudies.com

• Also see www.clinicaltrials.gov; ClinicalTrials.gov Identifier: NCT02512588
Where flumazenil ‘fails’ - Novel compounds (e.g., BTD-001) hold promise
The Influence of Cardiazol and Psychoton on the EEG in Narcolepsy

B. ROTH
Neurological Clinic, Charles University, Prague

Received 4. 5. 1954

Narcolepsy is a disease occurring in attacks, the relation of which to epilepsy has been much discussed in the literature. The majority of modern authors differentiate narcolepsy basically from epilepsy.
IH (N=30) 100mg vs. 200mg vs. placebo BID (DBCO design) Unblinded - analyzing

NT2 (N=30) 100 vs. 200 vs. placebo (DBCO design) Still recruiting

IH (N=30)

NT2 (N=30) 50 vs. 400 vs. placebo (DBCO design) BOTH ARMS ON HOLD
Conclusions:

• Hypersomnia with hypsomnia occurring *sui generis* appears to be mediated by a small peptide which acts at a site close to, but distinct from, the traditional BZD binding site of GABA-A receptors.

• A heritable component seems likely.

• In many subjects this appears to translate into clinical efficacy of flumazenil and clarithromycin (but not other macrolides).

• The “effect sizes” for subjective and objective improvements in vigilance in a select group of patients are robust. They surpass those reported for wake promoting agents inclusive of traditional psychostimulants for “narcolepsy” and shift work, and CPAP for OSA.
Where to now?

• What is the chemical nature of our biological endozepine-like activity?

• What are the critical molecular sites of action at the GABA-A receptor?

• What is the functional anatomy underlying hypersomnia & associated symptoms inclusive of treatment efficacy?

• Does this knowledge have implications for the study and treatment of dampened consciousness in other illnesses?
Thank you supporters!

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Paul Garcia MD, PhD

Emory School of Public Health
Prabhjyot Saini MSc
Historical Recognition of Hypersomnia

- Schlafrunkenheit
- Ivresse de sommeil
- Sleep drunkenness
- Svefn drungi
- Somnosis – Sir William Gowers
- Trance-like states – SW Kinnier Wilson
- Dysania
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Year Described</th>
<th>Prevalence</th>
<th>PubMed Entries (2010)</th>
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<tbody>
<tr>
<td>NARCOLEPSY Type 1 (with cataplexy)</td>
<td>1877-1890</td>
<td>0.0045</td>
<td>3178</td>
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<tr>
<td>NARCOLEPSY Type 2 (without cataplexy)</td>
<td>1929-1930</td>
<td>0.013 (est)</td>
<td></td>
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<tr>
<td>KLEINE-LEVIN SYNDROME</td>
<td>1925</td>
<td>0.00000010 (est.)</td>
<td>237</td>
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<tr>
<td>“IDIOPATHIC” HYPERSOMNIA</td>
<td>1972-1976</td>
<td>?</td>
<td>169</td>
</tr>
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</table>
Is bioactivity specific to ‘primary’ hypersomnias (e.g., might this be a biomarker of ‘trait’ sleepiness?)

- Disease Category
  - Sleep Apnea Patients
  - KLS Patients
  - Primary Hypersomnia Patients
  - Healthy Controls

- Screening - PSG
  - AHI 15/30/hr ESS ≥ 12
  - AHI 15-30/hr ESS < 8

- Screening - MSLT
  - ≤ 5 min
  - > 5 min
  - >10 min
  - ≤10 min

- Study Population
  - Hypersomnolent Sleep Apnea Subjects (n=16)
  - Non-Hypersomnolent Sleep Apnea Subjects (n=16)
  - Paired symptomatic & asymptomatic (n=8)
  - Primary Hypersomnia Subjects (n=16)
  - Non-sleepy Controls (n=16)