Narcolepsy & Its Borderland: New Insights Into the Origins of Persistent Sleepiness

“SLEEP IS STRONGER THAN THE NOBLEST INSTINCT OF A LOVING HEART---------”
Halldor Laxness

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David Rye: Personal/Professional Financial Relationships with External Entities within the past year

<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>Balance Therapeutics</td>
<td>Stock related to sale of IP described in US 9,616,070 B2: Use of GABAA receptor antagonists for the Rx of excessive daytime sleepiness…..</td>
</tr>
<tr>
<td>Board of Directors or officer</td>
<td>Narcolepsy Network; Hypersomnia Foundation; Kleine-Levin Syndrome Foundation</td>
<td>Scientific or Medical Advisory Board member</td>
</tr>
<tr>
<td>Royalties from Emory or from external entity</td>
<td>Emory Univ/ Balance Therapeutics</td>
<td>Cash related to sale of IP described in US 9,616,070 B2: Use of GABAA receptor antagonists for the Rx of excessive daytime sleepiness…..</td>
</tr>
<tr>
<td>Industry funds to Emory for my research</td>
<td>Marigold Foundation</td>
<td>Principal Investigator: Hypersomnia in Myotonic Dystrophy Type 1</td>
</tr>
</tbody>
</table>

*Does not include stock in publicly-traded companies in retirement funds and other pooled investment accounts managed by others.
NARCOLEPSY (GÉLINEAU’S SYNDROME) AND OTHER VARIETIES OF MORBID SOMNOLENCE *

MAX LEVIN, M.D.

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”.

THE NARCOLEPSIES.1

BY S. A. KINNIER WILSON.

What has been called narcolepsy—a term that has always been loosely employed, various writers having described clinical examples of sleep disorder under this heading without staying to define the sense in which it is being used. As a consequence, current ideas are uncommonly fluctuating where narcolepsy is concerned....... Brain (1928) p. 63

Self reported hypersomnolence 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 related “deteriorated quality of wakefulness” (viz., unintended excessive sleepiness/napping)

- 0.5% Hypersomnolence Disorder (per DSM-5)

- Narcolepsy with cataplexy is a rare disorder - 0.038% with > 50% undiagnosed

• 20 year-old sophomore at Elon College referred for EDS since a high school sophomore. She began falling asleep in class in HS noting that “I’ve fallen asleep standing up in front of a classroom. Sleep has become more nonrestorative and excessive. In 2014 at time of presentation 90 hours per week – more recently, 102 hours. Polysomnogram in 2013 demonstrated 360 minutes of total sleep, sleep efficiency of 90.5%, an apnea/hypopnea index of 0.8/hour, and prominent “leg jerks”.

• **Sleep drunkenness.** “Don’t fell that any amount of sleep could make me fell rested – truly”. “Confused and agitated when others attempt to wake me up”. Has two sonic boom alarm clocks and additional five alarms on phone. Clumsy in “mornings” – often drops things. “Late 4-5 days each week to school”. Naps daily > 1 hour in duration. Withdrew from college at end of sophomore year.

• Leaden paralysis and post exertional fatigue. Denies carbohydrate cravings, interpersonal rejection, or positive mood reactivity. No appreciable change in symptoms around menses.

• Treatment Trials:
  Vyvanse – 30mg QAM – mother would wake her up at 4AM to deliver
  Dextroamphetamine 5mg PRN somewhat helpful.
  Armodafinil 250mg QAM – short lived “improved sense of wellbeing”. Stevens-Johnson.
  Wellbutrin (300mg XL) – QAM – 2014 – Helped with hypersomnolence but GI side effects
History (cont’d)

• PMHX: FTNSVD. No jaundice. Brief hypoxemic event at 2 yrs old. Normal development. No head trauma or encephalitis or meningitis. Mononucleosis in college.
  2009 – Postprandial GI discomfort – endoscopy/colonoscopy negative
  Propofol – well tolerated for GI procedures and wisdom tooth extraction in 2009
  “Inattentive ADD”
  “Depression” - initial treatment resulted in suicidality and brief hospital admission at which time Pristiq 75mg was started.
  Rare restless legs syndrome (RLS) – once-twice/month interferes with sleep onset. No parasomnias.

• FAMHX: Older sister – rare RLS & likes to sleep
  Mother - RLS and “falls asleep quickly and anywhere and has undiagnosed hypersomnolence”. Mother: “I’ve not been able to drive long distances.”. “I love to sleep”. “I don’t understand people who say that they can’t sleep”. “I think I have a degree of something but no more than the general population”. “This is not debilitating to me”.

<table>
<thead>
<tr>
<th>DEPENDENT MEASURE</th>
<th>JULY 2014</th>
<th>SEPTEMBER 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pristiq 75mg QAM Nortrel</td>
<td>Pristiq 100mg QAM Camila + estrogen</td>
</tr>
<tr>
<td>Sleep hours/week</td>
<td>90</td>
<td>102</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Hypersomnia Severity Index (0-36)</td>
<td>NA</td>
<td>31</td>
</tr>
<tr>
<td>Sleep Inertia Questionnaire (0-20)</td>
<td>NA</td>
<td>16.7</td>
</tr>
<tr>
<td>Functional Outcomes of Sleep (5-20)</td>
<td>6.7</td>
<td>5.6</td>
</tr>
<tr>
<td>Multidimensional Fatigue Inventory (0-100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental Fatigue (5-20)</td>
<td>91</td>
<td>92</td>
</tr>
<tr>
<td>Reduced Activity (5-20)</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Reduced Motivation (5-20)</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Reduced Motivation (5-20)</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Fatigue Severity Scale (7-63)</td>
<td>57</td>
<td>61</td>
</tr>
<tr>
<td>Owl-Lark Scale (Horne-Ostberg)</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>Beck Depression Inventory (Short-Form)</td>
<td>14</td>
<td>8</td>
</tr>
</tbody>
</table>
Examination:

- BMI: 17.7
- Vitals: Lying 103/65 – pulse 71
  Standing (5 min) 102/74 – pulse 98
  (i.e., ‘borderline’ POTS)

- No percussion or grip myotonia (i.e., no evidence for myotonic dystrophy)
- Joint hypermobility absent Beighton scale of 0
- Psychomotor Vigilance: Marked decrements in vigilance
  Lapses in attention (i.e., reaction times > 500ms) worse post-versus pre-nap and improve later in the day
Laboratory Findings:

Complete Blood Count & differential, Chem-17 and liver functions normal
Ferritin = 12-37 ug/L (30-400) - % transferrin saturation 24-43 (> 20)
Vitamin B12 = 474 pmol/L (210-800)
Folate = > 20 nmol/L
Thyroid Function Tests
  TSH = 1.31 uIU/ml (0.55-4.8)
  Free T4 = 1.1 ng/dL (0.82-1.77)   Total T4 = 10.5 mcg/dL (4.5-12.3)
  T3 = 97 ng/dL (60-181)
Cortisol, prolaction, LH, FSH, testosterone – “normal”
Carnitine free 24 mcmol/L (25-60)
Carnitine total 28 mcmol/L (34-86)
Vitamin D3 37.7 ng/ml (30-74)
C-Reactive Protein = 1.57 mg/L (0.3-8)
ESR – 2; ANA – negative; RF – 8.1 IU (0-13.9); HIV negative; HCV and HSV negative
CCP/transglutaminase/endomysial/gliadin antibodies absent

Sleep-Wake Disorders

• DSM-5 identifies a number of sleep-wake disorders: Dyssomnias and parasomnias
  – INSOMNIA DISORDER
  – HYPERSONOLOENCE DISORDER
  – NARCOLEPSY/HYPOCRETIN DEFICIENCY
  – SLEEP APNEA
  – CIRCADIAN RHYTHM SLEEP-WAKE DISORDER
  – NIGHTMARE DISORDER
  – DISORDER OF AROUSAL
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)

Other Hypersomnolence/hypersomnia related to medical or psychiatric conditions

Summary (cont)

- DSM-5 differs in requiring only sleepiness plus cataplexy OR MSLT findings OR hypocretin deficiency OR PSG SOREM.

- Accurate diagnosis requires:
  - Asking your patients about excessive sleepiness to diagnose a potential sleep disorder and refer patient to sleep center
  - Adequate preparation for MSLT, overnight PSG to rule out confounders, and careful follow-up assessment when the diagnosis is in question
<table>
<thead>
<tr>
<th></th>
<th>Narcolepsy Type 1 (with cataplexy)</th>
<th>Narcolepsy Type 2</th>
<th>Idiopathic Hypersomnia</th>
<th>“Long Sleeper”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive Daytime Sleepiness</td>
<td>3 months</td>
<td>3 months</td>
<td>3 months</td>
<td>Habitual</td>
</tr>
<tr>
<td>Cataplexy</td>
<td>YES (60-95%)</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Mean Sleep Latency &lt; 8 minutes</td>
<td>YES</td>
<td>YES</td>
<td>YES (35%) / NO (65%)</td>
<td>NO (?)</td>
</tr>
<tr>
<td>≥ 2 Sleep Onset REM-sleep (SOREMps)</td>
<td>YES</td>
<td>YES</td>
<td>NO ≤ 1 SOREMp</td>
<td>NO (?)</td>
</tr>
<tr>
<td>CSF Hypocretin &lt; 110 pg/ml</td>
<td>YES</td>
<td>15-20%</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>660’ of total sleep time (PSG + MSLT)</td>
<td>NO (normal)</td>
<td>Some (?)</td>
<td>OR</td>
<td>YES</td>
</tr>
<tr>
<td>660’ average total Sleep time 1 week</td>
<td>NO (normal)</td>
<td>N/A (?)</td>
<td>OR</td>
<td>YES</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Narcolepsy Type 1</th>
<th>Hypersomnia (&amp; Narcolepsy Type 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive Daytime Sleepiness</td>
<td>Imperative</td>
<td>Not as imperative</td>
</tr>
<tr>
<td>Daytime Sleep Duration</td>
<td>Minutes</td>
<td>Hours</td>
</tr>
<tr>
<td>Daytime Naps</td>
<td>With REM-sleep (dreams)</td>
<td>REM-sleep -inconsistent</td>
</tr>
<tr>
<td>Cataplectic Attacks</td>
<td>Most cases</td>
<td>ABSENT</td>
</tr>
<tr>
<td>REM-sleep dyscontrol</td>
<td>Many cases</td>
<td>RARE</td>
</tr>
<tr>
<td>Dampened sensorium or cognition</td>
<td>Exceptional</td>
<td>COMMON</td>
</tr>
<tr>
<td>Night-time Sleep</td>
<td>Normal Length &amp; Restless</td>
<td>Prolonged &amp; Very deep</td>
</tr>
<tr>
<td>Awakening from Sleep</td>
<td>Spontaneous</td>
<td>Can be LABORIOUS</td>
</tr>
<tr>
<td></td>
<td>Narcolepsy Type 1 (with cataplexy)</td>
<td>Idiopathic Hypersomnia</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td><strong>Prevalence</strong></td>
<td>1: 2,000</td>
<td>3: 10,000</td>
</tr>
<tr>
<td><strong>Age of Onset</strong></td>
<td>Pre-pubertal Teens Twenties</td>
<td>Pre-Pubertal Teens Twenties Adulthood</td>
</tr>
<tr>
<td><strong>Course</strong></td>
<td>Minimally Progressive Plateaus in 30s</td>
<td>Most likely progressive – modestly variable – “cyclical”</td>
</tr>
<tr>
<td><strong>Remissions</strong></td>
<td>NONE</td>
<td>RARE (15-20%)</td>
</tr>
<tr>
<td><strong>Heritability</strong></td>
<td>OR = 4 to 1° relative</td>
<td>Modest (~ 1/3 rd of subjects with 1° relative)</td>
</tr>
<tr>
<td><strong>FDA Approved Treatments</strong></td>
<td>YES</td>
<td>NONE</td>
</tr>
<tr>
<td><strong>Treatments</strong></td>
<td>Wake promoting agents (e.g., psychostimulants; modafinil)</td>
<td>Sleep “lytics” (e.g., GABA receptor antagonists)</td>
</tr>
</tbody>
</table>

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**NARCOLEPSY** with CATAPLEXY – aka “Type 1 narcolepsy”

**Idiopathic** – aka primary/central Hypersomnia
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Sleep Latency</td>
<td>10 minutes</td>
<td>32.5</td>
<td>14.5</td>
</tr>
<tr>
<td>REM-latency</td>
<td>129 minutes</td>
<td>N/A</td>
<td>101.5 min</td>
</tr>
<tr>
<td>Total Sleep Time</td>
<td>397 minutes</td>
<td>438.5</td>
<td>488 min</td>
</tr>
<tr>
<td>Sleep Maintenance Efficiency</td>
<td>92%</td>
<td>97.9%</td>
<td>94.3%</td>
</tr>
<tr>
<td>Stage N1</td>
<td>5 %</td>
<td>13.6%</td>
<td>3%</td>
</tr>
<tr>
<td>Stage REM-sleep</td>
<td>16 %</td>
<td>N/A</td>
<td>24 %</td>
</tr>
<tr>
<td>Apnea/hypopnea index</td>
<td>0.2 / hour</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>PLMi</td>
<td>48.5 / hour</td>
<td>0.0</td>
<td>10.4</td>
</tr>
<tr>
<td>Mean Sleep Latency</td>
<td>2.8</td>
<td>7.9</td>
<td>11.4</td>
</tr>
<tr>
<td># SOREMPs</td>
<td>1 of 5 (nap #2)</td>
<td>5 of 5</td>
<td>4 of 5 (no sleep #5)</td>
</tr>
<tr>
<td>Total overall sleep</td>
<td>464 minutes</td>
<td>498</td>
<td>550.4</td>
</tr>
</tbody>
</table>

**SOREMp ≥ 2**

- Narcolepsy with or without cataplexy
- TEST #2 - 2015
- Increased REM-sleep propensity
- TEST #3 - 2016

**SOREMp ≤ 1**

- Idiopathic Hypersomnia
- TEST #1 - 2014
- “Normal” sleepiness

Mean Sleep Latency – 8 minutes
- < 8 minutes
- ≥ 8 minutes
Alternate diagnostic & efficacy metrics are needed:

• The **multiple sleep latency test (MSLT)** exhibits poor specificity and modest sensitivity in identifying & discriminating between central disorders of hypersomnolence, hypersomnolence that occurs in ‘other’ disorders, and population ‘norms’.

• MSLT exhibits poor test-retest reliability – *i.e.*, repeat testing of non-hypocretin deficient narcolepsy, yields discordant results/diagnoses in 40-50% of instances

• 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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**NARCOLEPSY ≠ HYPERSOMNIA**

(1880, from Fr. narcolepsie, coined 1880 by French physician Jean-Baptiste-Edouard Gélineau 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)
Discovery of REM-sleep
Aserinsky & Kleitman (1953)
Association with narcolepsy/
cataplexy G Vogel (1960)

Idiopathic hypersomnia
& narcolepsy without cataplexy
(NT2)

~ 30-40% Refractory to
wake promoting agents

Responsive to
antagonism of
GABA-A receptors
On the origins of hypersomnolence/hypersomnia:

Loss of Function
Wakefulness

Gain in Function - Sleep

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

David B. Rye,1* Donald L. Bilwise,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 Jenkins3,7

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_A), 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.


Normalization of attentional lapses by i.v. flumazenil in seven hypersomnolent subjects

Summary of IV flumazenil data (N = 13 subjects with CDH unresponsive to wake promoting agents)

• Dose effect of flumazenil upon:
  a) EEG delta power reductions
  b) Improvement in vigilance (PVT)
  c) Subjective sleepiness
  • All of the above associate with CGI
  • Topographic differences in scalp EEG changes
  • Hysteresis observed in ~ 50% of subjects
  • % GABAA receptor potentiation by CSF is not specific to any single central disorder of hypersomnolence
  • % GABAA receptor potentiation by CSF does not predict sleepiness severity

"Lysing" somnosis by antagonizing GABAA receptors:

• Flumazenil
  ![Flumazenil](image)

• Clarithromycin
  ![Clarithromycin](image)

• Pentylenetetrazol
  (aka BTD-001; cardiazol; metrazol)
  ![Pentylenetetrazol](image)

Ciprofloxacin (and other fluoroquinolone antibiotics)
  ![Ciprofloxacin](image)

Br. J. clin. Pharmac. (1990), 30, 63-70

Tranexamic acid
  ![Tranexamic acid](image)

CLARITHROMYCIN (Biaxin®): A negative allosteric modulator of GABA-A receptors

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 Improvement in daytime sleepiness with clarithromycin in patients with GABA-related hypersomnia: Clinical experience

Lynn Marie Trotti, Prabhjot Saini, Amanda A. Freeman, Donald L. Billwise, Paul S. Garcia, Andrew Jenkins, and David B. Rye

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Clarithromycin in γ-Aminobutyric Acid-Related Hypersomnia: A Randomized, Crossover Trial

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

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Flumazenil for the Treatment of Refractory Hypersomnia: Clinical Experience with 153 Patients

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

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

Substantial fractions of CDH subjects refractory to conventional wake promoting agents respond favorably to GABAA receptor antagonism

<table>
<thead>
<tr>
<th>Drug</th>
<th>Design</th>
<th>Number of subjects ‘exposed’</th>
<th>Idiopathic Hypersomnia (% efficacious)</th>
<th>Narcolepsy Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin</td>
<td>Open-label</td>
<td>53 (43)</td>
<td>29 of 35 (83%)</td>
<td>5 of 8</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Double-Blind-Placebo Crossover</td>
<td>20</td>
<td>10 of 16 (63%)</td>
<td>2 of 4</td>
</tr>
<tr>
<td>Flumazenil</td>
<td>Single-Blind</td>
<td>13</td>
<td>4 of 8 (50%)</td>
<td>2 of 5</td>
</tr>
<tr>
<td>Flumazenil</td>
<td>Open-label</td>
<td>153</td>
<td>23 of 36 (64%)</td>
<td>9 of 19</td>
</tr>
<tr>
<td>Pentylenetetrazol</td>
<td>Open-label</td>
<td>7</td>
<td>4 of 4 (100%)</td>
<td>3 of 3</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>241</td>
<td>70 of 99 (71%)</td>
<td>21 of 39 (54%)</td>
</tr>
</tbody>
</table>

Flumazenil Prescribing Data (Pavilion Compounding Pharmacy, Atlanta, GA – March 2013 – March, 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
- As of 2018 - > 100 prescribing physicians in the United States
- As of 2018 – 28 US physicians had prescribed to ≥ 5 unique patients

Cerebrospinal Fluid Findings in our patient:

- **Cell count/differential:**
  - Tube #1 – 0 nucleated cells – 41 rbc
  - Tube #4 – 0 nucleated cells – 1 rbc
  - Protein 18 mg/dL (normal 15-45)
  - Glucose 56 mg/dL (normal 40-70)

- **Hypocretin concentrations:**
  - 206.7 & 243.7 pg/ml (2014) – normal > 200
  - 309.9 (2016)

- **In vitro** potentiation of GABA-A receptors:
  - 171.6% (2014) - (Non-sleepy controls ~ <60%)
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?
<table>
<thead>
<tr>
<th>DISORDER</th>
<th>OFFENDING AGENT(S)</th>
<th>FLUMAZENIL RESPONSIVE</th>
<th>CLINICAL DEVELOPMENT/ TRIALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Disorders of Hypersomnolence</td>
<td>Endozepine “like” substance</td>
<td>Proportion – (~40-60%)</td>
<td>YES – BTD-001 ARISE ARISE 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Pentylenetetrazol) Balance Therapeutics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>YES - GR3027 (Umecrine)</td>
</tr>
<tr>
<td>MYOTONIC DYSTROPHY</td>
<td>Endozepine “like” substance; GABA-A receptor γ2 subunit mis-splicing</td>
<td>(?)</td>
<td>YES – Flumazenil (open-label) &amp; complementary Animal models</td>
</tr>
<tr>
<td>HEPATIC ENCEPHALOPATHY</td>
<td>“Endozepines” Neurosteroids – allopregnanolone; THDOC</td>
<td>YES</td>
<td>YES - GR3027 (Umecrine)</td>
</tr>
</tbody>
</table>

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