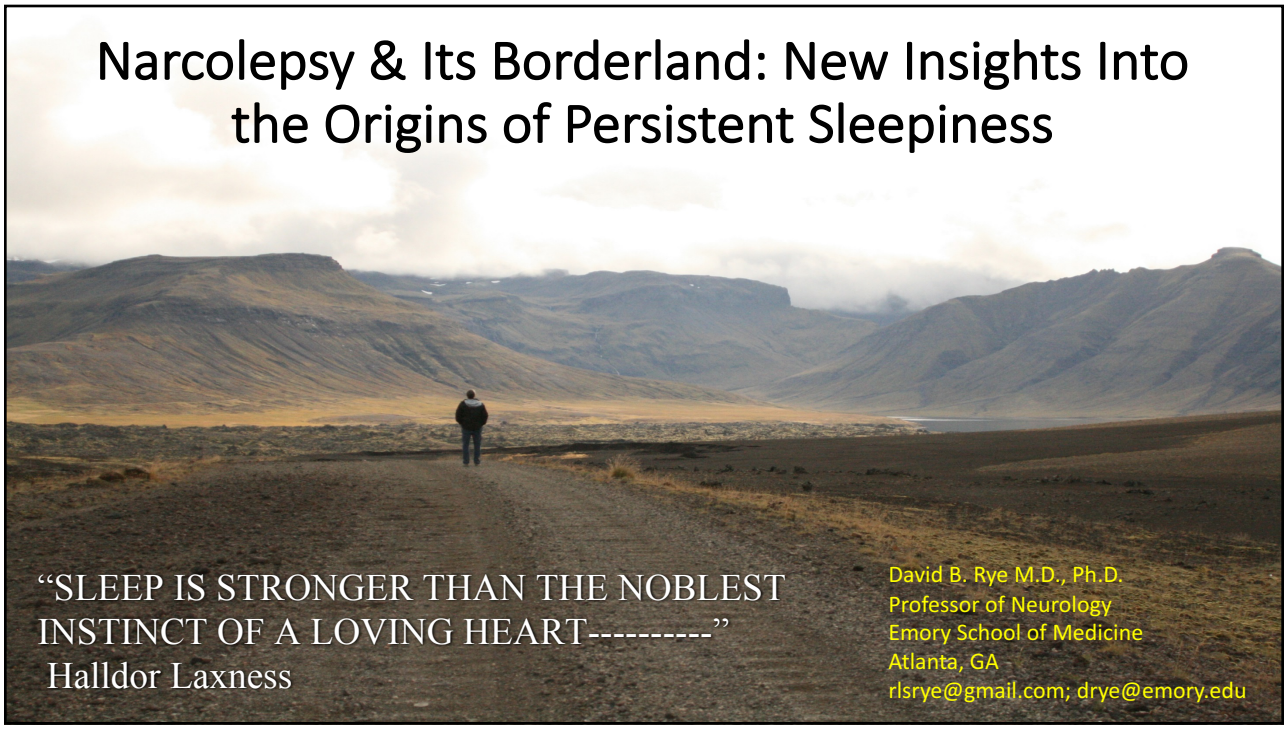
Narcolepsy & Its Borderland: New Insights Into the Origins of Persistent Sleepiness



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

David B. Rye M.D., Ph.D.
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Emory School of Medicine
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David Rye: Personal/Professional Financial Relationships with External Entities within the past year

External Industry Relationships *	Company Name(s)	Role
Equity, stock, or options in biomedical industry companies or publishers*	Balance Therapeutics	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…..*
Board of Directors or officer	Narcolepsy Network; Hypersomnia Foundation; Kleine-Levin Syndrome Foundation	Scientific or Medical Advisory Board member
Royalties from Emory or from external entity	Emory Univ./ Balance Therapeutics	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……*
Industry funds to Emory for my research	Marigold Foundation	Principal Investigator: *Hypersomnia in Myotonic Dystrophy Type 1*
Other	1). Jazz Pharmaceuticals 2). Balance Therapeutics 3). Major League Baseball 4). Garland, Samuel & Loeb, P.C.	1 & 2) Consultant 3) Expert Medical Record Reviews and Opinions 4) Expert Witness

*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.
PHILADELPHIA

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

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

C Hublin et al. Ann Neurol. (1994) 35:709-16.
M Ohayon et al. Ann Neurol. (2013) 73: 785-794

- 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".

- ***S*leep 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.

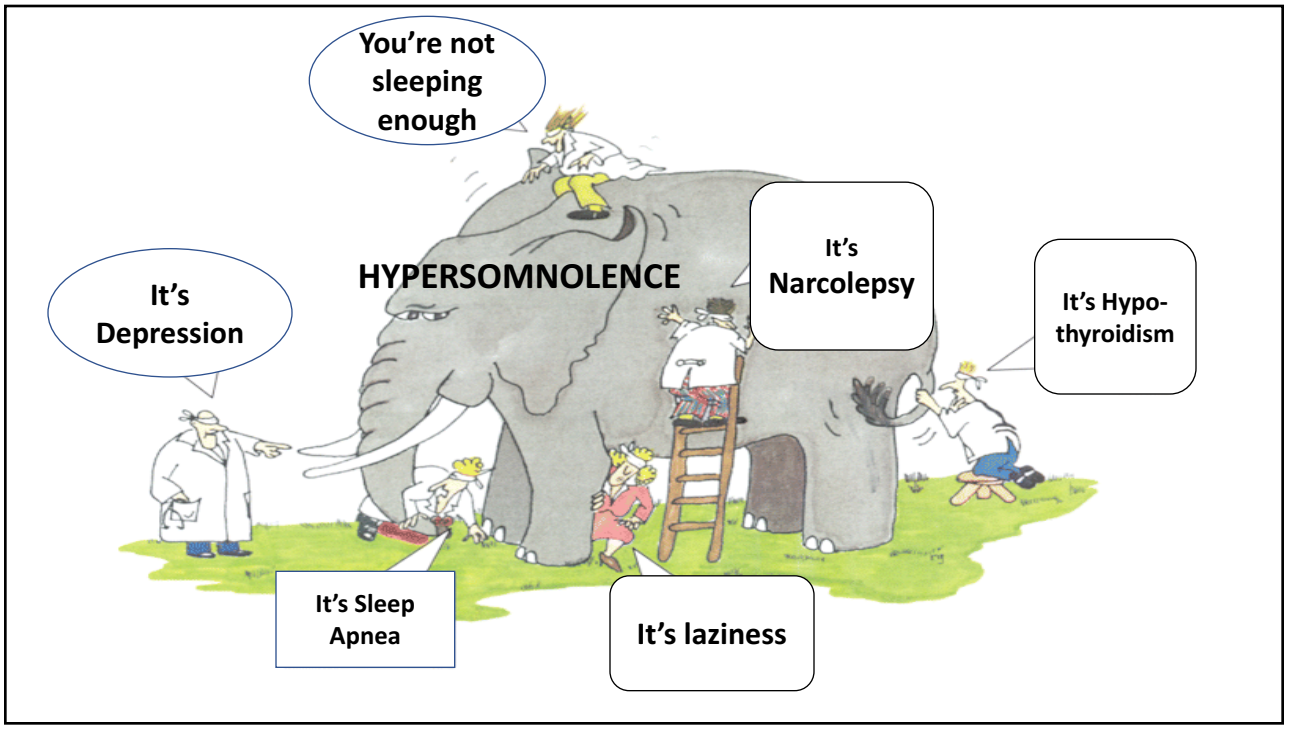
  Armodafinil 250mg QAM – short lived "improved sense of wellbeing". Stevens-Johnson.

  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".

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

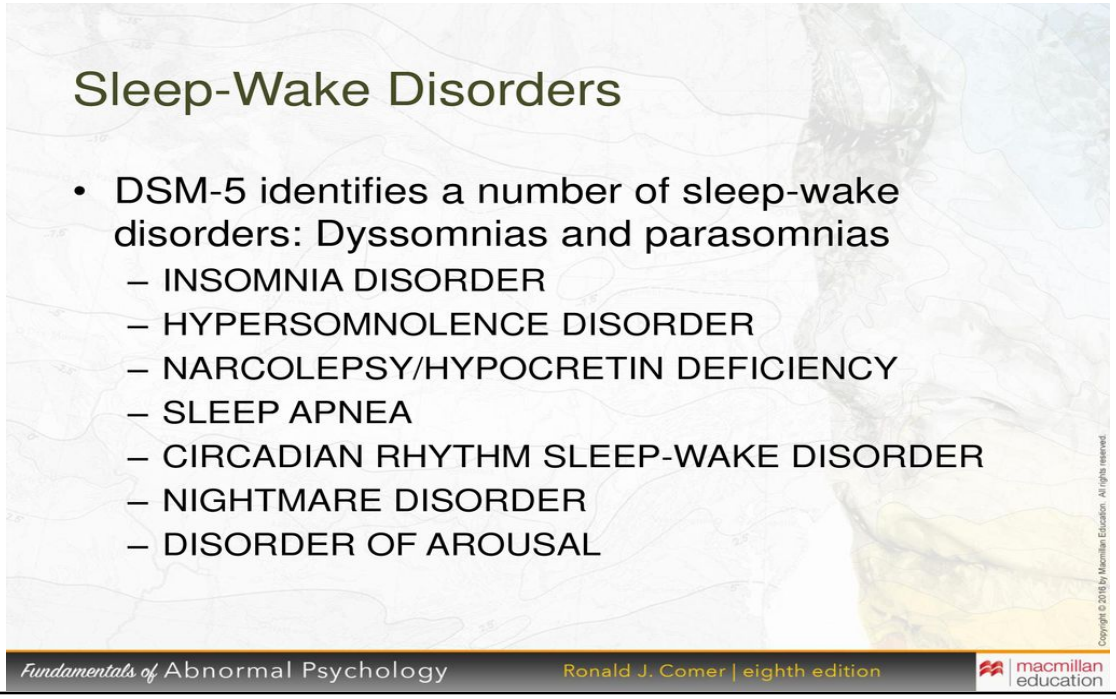


Examination:

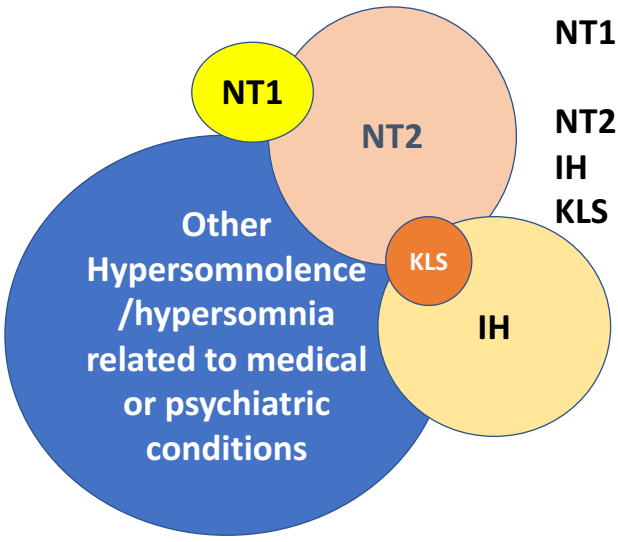
• BMI:		17.7
• Vitals:	Lying	103/65 – pulse 71
	Standing (5 min)	102/74 – pulse 98
		(*i.e.*, 'borderline' POTS)
• No percussion or grip myotonia		(*i.e.*, no evidence for myotonic dystrophy)
• Joint hypermobility absent		Beighton scale of 0
• Psychomotor Vigilance:		Marked decrements in vigilance
		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



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)**

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

	Narcolepsy Type 1 (with cataplexy)	Narcolepsy Type 2	Idiopathic Hypersomnia	"Long Sleeper"
Excessive Daytime Sleepiness	3 months	3 months	3 months	Habitual
Cataplexy	YES (60-95%)	NO	NO	NO
Mean Sleep Latency < 8 minutes	YES	YES	YES (35%) / NO (65%)	NO (?)
≥ 2 Sleep Onset REM-sleep (SOREMps	YES OR	YES	NO ≤ 1 SOREMp	NO (?)
CSF Hypocretin < 110 pg/ml	YES	15-20%	NO	NO
660' of total sleep time (PSG + MSLT)	NO (normal)	Some (?)	OR YES	YES
660' average total Sleep time 1 week	NO (normal)	N/A (?)	OR YES	YES

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	Narcolepsy Type 1	Hypersomnia (& Narcolepsy Type 2)
Excessive Daytime Sleepiness	Imperative	Not as imperative
Daytime Sleep Duration	Minutes	Hours
Daytime Naps	With REM-sleep (dreams)	REM-sleep -inconsistent
Cataplectic Attacks	Most cases	ABSENT
REM-sleep dyscontrol	Many cases	RARE
Dampened sensorium or cognition	Exceptional	COMMON
Night-time Sleep	Normal Length & Restless	Prolonged & Very deep
Awakening from Sleep	Spontaneous	Can be LABORIOUS

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	Narcolepsy Type 1 (with cataplexy)	Idiopathic Hypersomnia
Prevalence	1: 2,000	3: 10,000
Age of Onset	Pre-pubertal **Teens** Twenties	Pre-Pubertal **Teens** Twenties Adulthood
Course	Minimally Progressive Plateaus in 30s	Most likely progressive – modestly variable – "cyclical"
Remissions	NONE	RARE (15-20%)
Heritability	OR = 4 to 1^0 relative	Modest (~ 1/3 rd of subjects with 1^0 relative)
FDA Approved Treatments	YES	NONE
Treatments	Wake promoting agents (e.g., psychostimulants; modafinil;	Sleep "lytics" (e.g., GABA receptor antagonists) ?

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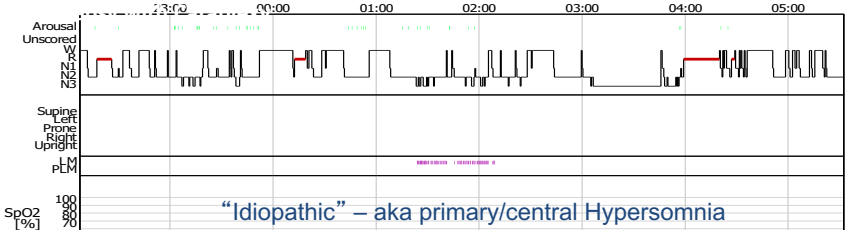
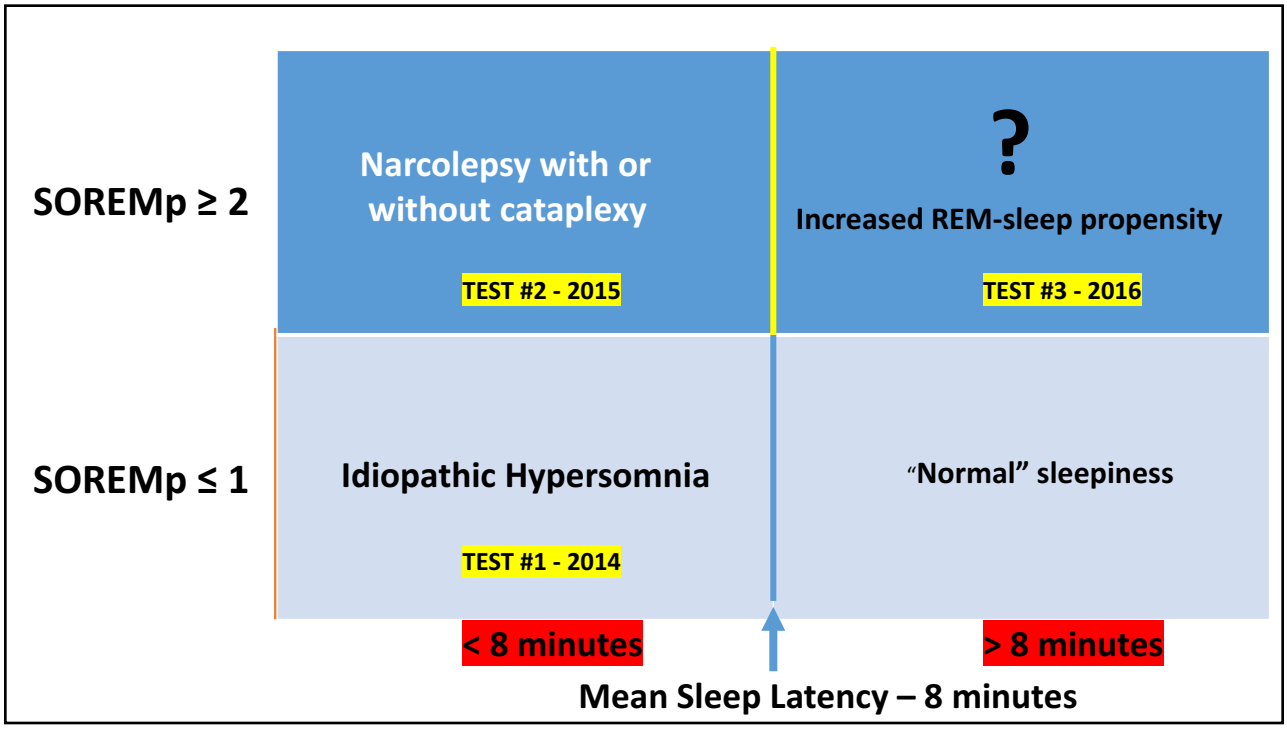
NARCOLEPSY with CATAPLEXY – aka "Type 1 narcolepsy"



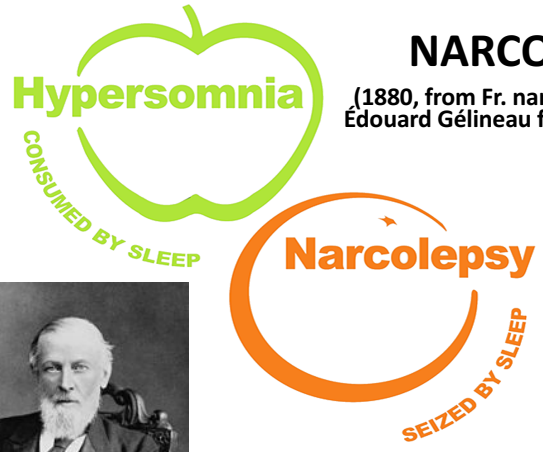
"Idiopathic" – aka primary/central Hypersomnia

Metric	PSG/MSLT - 2014	PSG/MSLT -2015	PSG/MSLT – 2016
Sleep Latency	10 minutes	32.5	14.5
REM-latency	129 minutes	N/A	101.5 min
Total Sleep Time	397 minutes	438.5	488 min
Sleep Maintenance Efficiency	92%	97.9%	94.3%
Stage N1	5 %	13.6%	3%
Stage REM-sleep	16 %	N/A	24 %
Apnea/hypopnea index	0.2 / hour	0.2	0.2
PLMi	48.5 / hour	0.0	10.4
Mean Sleep Latency	2.8	7.9	11.4
# SOREMPs	1 of 5 (nap #2)	5 of 5	4 of 5 (no sleep #5)
Total overall sleep	464 minutes	498	550.4



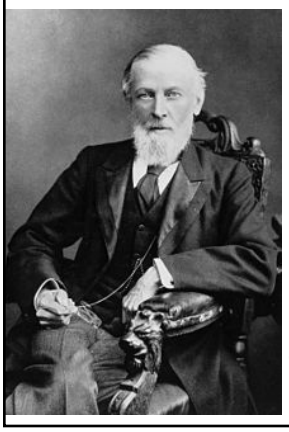
Alternate diagnostic & efficacy metrics are needed:

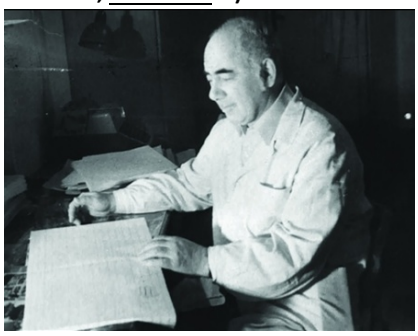
- The **multiple sleep latency test (MSLT)** exhibits poor specificity and modest sensitivity in identifying & discriminating between central disorders of hypersomnolence, hypersomnolence that occurs in 'other' disorders, and population 'norms'.
- MSLT exhibits poor test-retest reliability – *i.e.*, 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



NARCOLEPSY ≠ HYPERSOMNIA

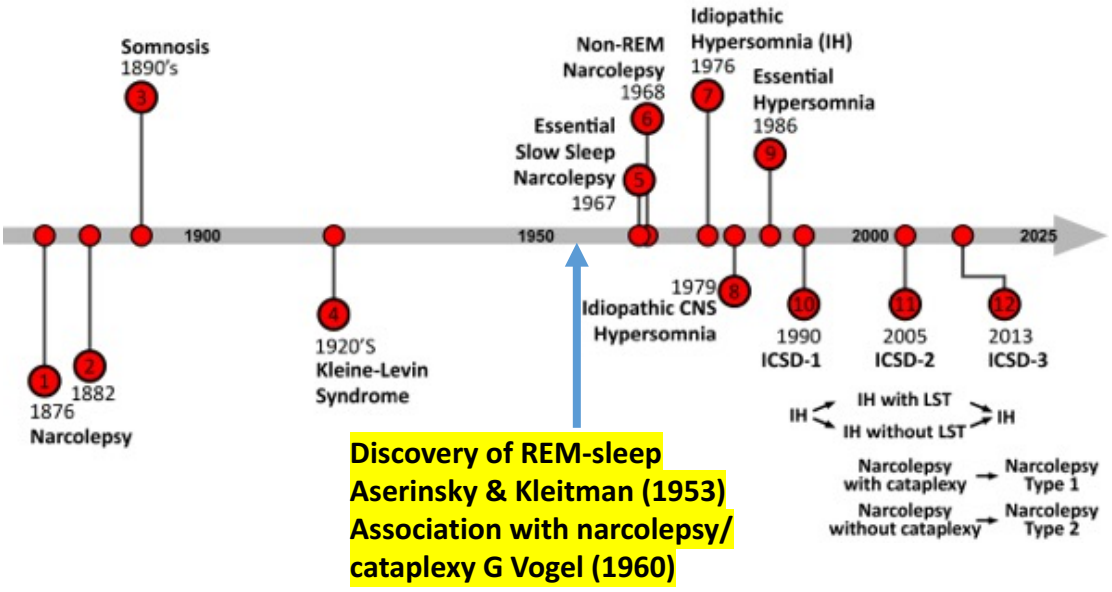
(1880, from Fr. narcolepsie, coined 1880 by French physician Jean-Baptiste-Édouard Gélineau from comb. form of Gk. narke "numbness, stupor" + lepsis "an attack, seizure.")

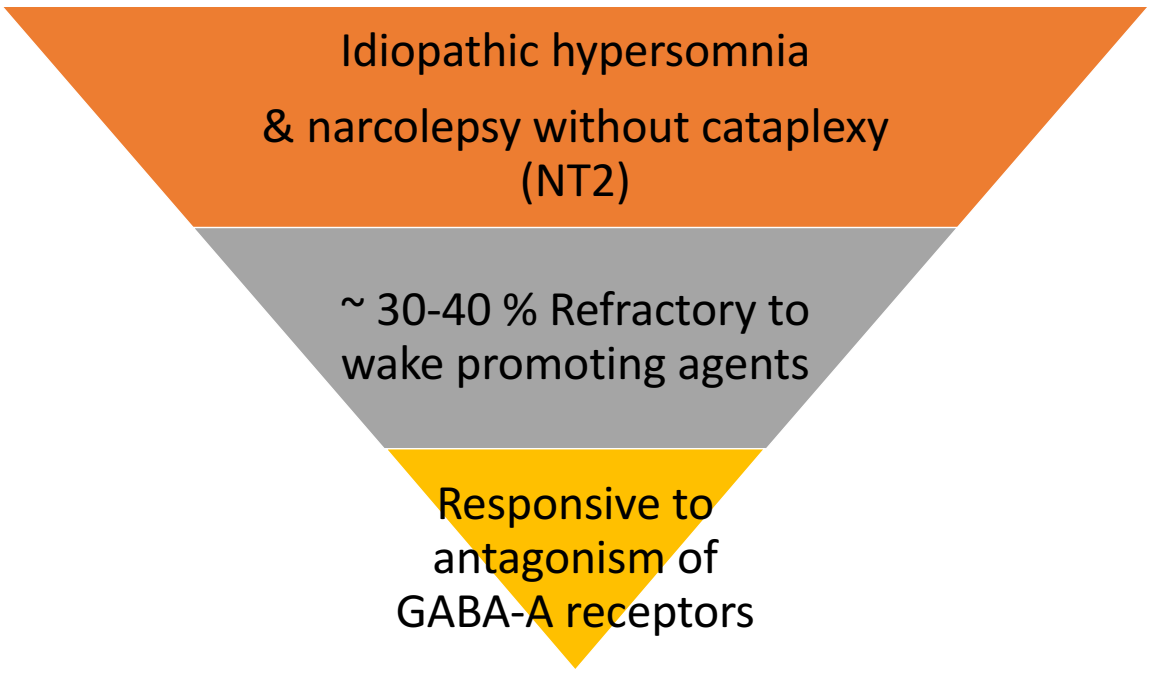




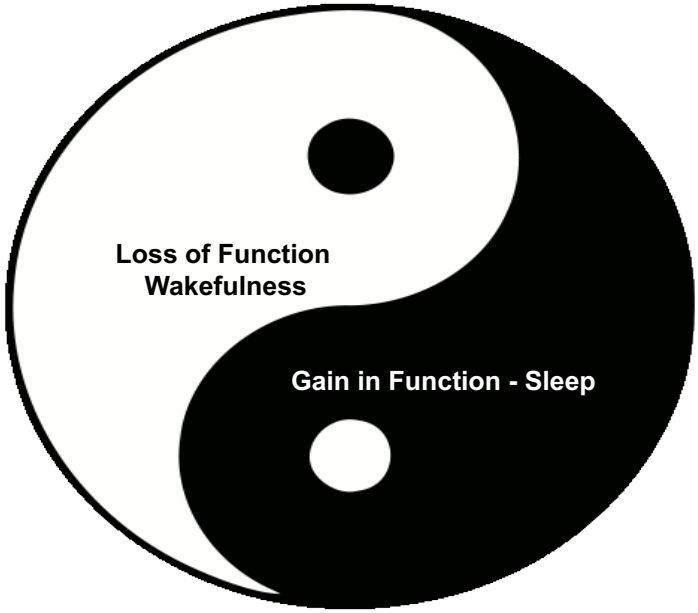
Bedrich Roth: 'Sleep Drunkenness' *(1954)*
'Idiopathic Hypersomnia' *(1976)*

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

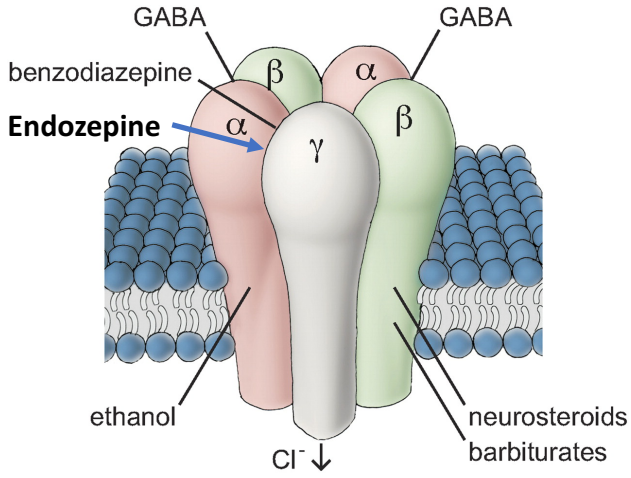

Somnosis
1890's
Non-REM
Narcolepsy
1968
Essential
Slow Sleep
Narcolepsy
1967
Idiopathic
Hypersomnia (IH)
1976
Essential
Hypersomnia
1986
1900
1950
2000
2025
1876
Narcolepsy
1882
1920'S
Kleine-Levin
Syndrome
1979
Idiopathic CNS
Hypersomnia
1990
ICSD-1
2005
ICSD-2
2013
ICSD-3
IH
IH with LST
IH without LST
IH
Narcolepsy
with cataplexy
Narcolepsy
Type 1
Narcolepsy
without cataplexy
Narcolepsy
Type 2
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:



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

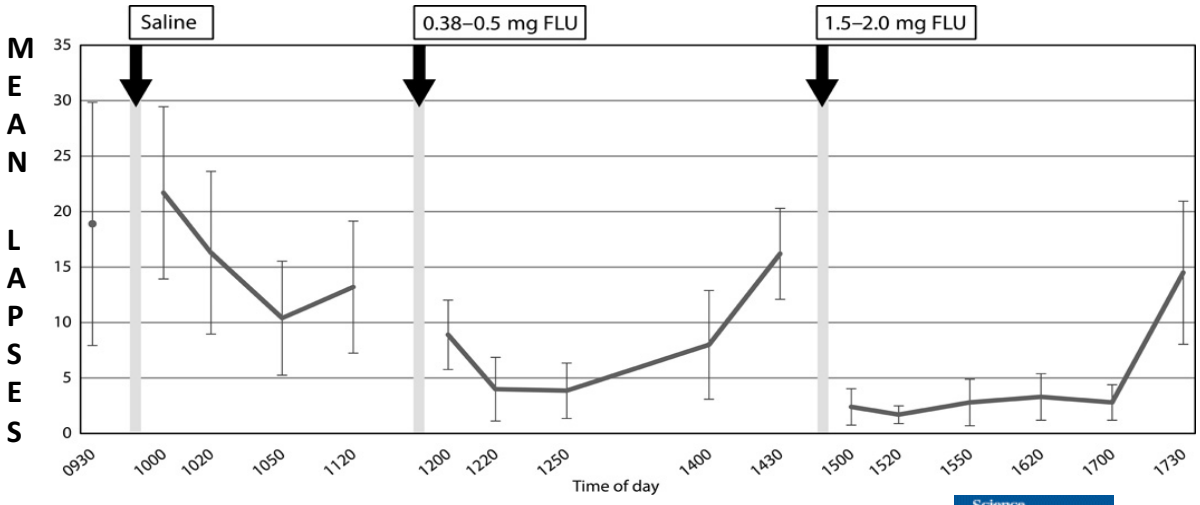
Modulation of Vigilance in the Primary Hypersomnias by Endogenous Enhancement of $GABA_A$ Receptors

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.

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



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

Science Translational Medicine AAAS

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

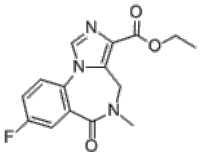
b) Improvement in vigilance (PVT)

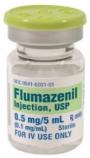
c) Subjective sleepiness

- 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

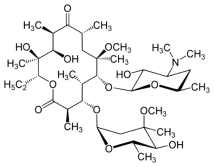
"Lysing" *somnosis* by antagonizing GABAA receptors:

- Flumazenil

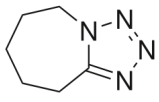


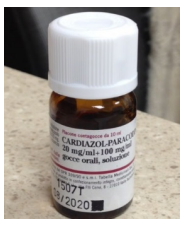


- Clarithromycin

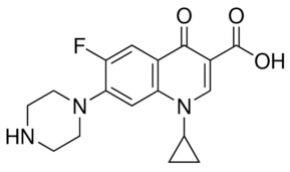


- Pentylenetetrazol (aka BTD-001; cardiazol; metrazol)



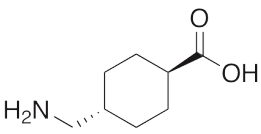


Ciprofloxacin (and other fluoroquinolone antibiotics



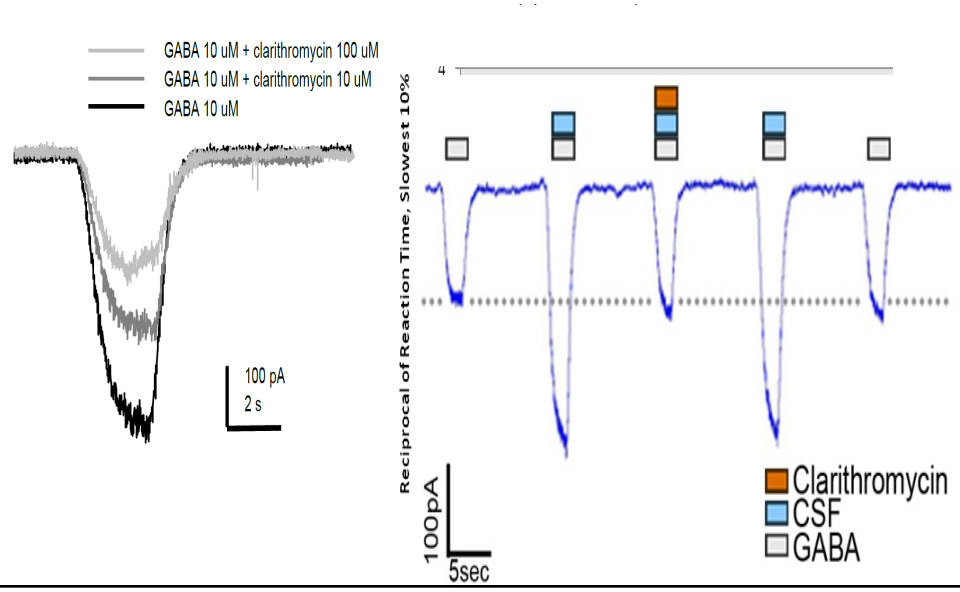
Br. J. clin. Pharmac. (1990), **30**, 63–70

Tranexamic acid



J Pharmacol Exp Ther. 2002 Apr;301(1):168-73.

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



Short Report

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

Lynn Marie Trotti[1], Prabhjyot Saini[1], Amanda A Freeman[1], Donald L Bliwise[1], Paul S Garcia[2,3], Andrew Jenkins[2], and David B Rye[1]

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Journal of Psychopharmacology
2014, Vol. 28(7) 697–702

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SAGE

RESEARCH ARTICLE

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

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ANN NEUROL 2015;78:454–465

JCSM
Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

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

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

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

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**

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

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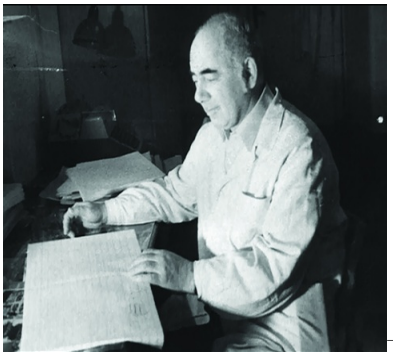
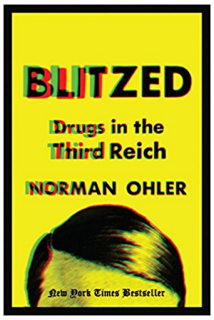


PHYSIOLOGIA
BOHEMOSLOVENICA
Vol. III. (1954) — Fasc. 4

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.

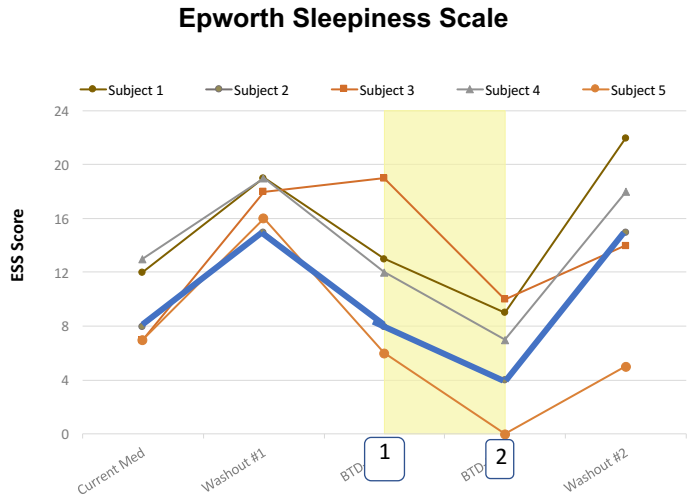


B. Roth – (1954) Chekhoslovatskaia Fiziologiia 3 (4): 420-423

Cerebrospinal Fluid Findings in our patient:

- Cell count/differential:
  - Tube #1 – 0 nucleated cells – 41 rbcs
  - 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%)

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, 2017, Pages e285-e286



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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?

Neuron
Previews

In Search of the Ever-Elusive Positive Endozepine

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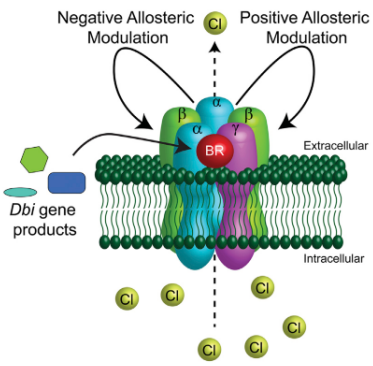
http://dx.doi.org/10.1016/j.neuron.2013.06.004

In this issue of *Neuron*, Christian et al. (2013) provide functional evidence for positive endozepines (positive allosteric modulators of $GABA_A$Rs) within the thalamic reticular nucleus. These molecules are encoded by the *Dbi* gene and modulate thalamocortical oscillations.



Endozepines

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2. PHYSIOLOGICAL EVIDENCE OF ENDOZEPINES

The synthesis of RO 15-1788 (or flumazenil, FLZ), the first known BZ antagonist (Hunkeler et al., 1981; Ramerstorfer, Furtmüller, Vogel, Huck, & Sieghart, 2010), facilitated a large body of research supporting the hypothesis that endogenous ligands to the BZ-binding site exist and are functionally relevant *in vitro* and *in vivo*. While FLZ has been a valuable

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DISORDER	OFFENDING AGENT(S)	FLUMAZENIL RESPONSIVE	CLINICAL DEVELOPMENT/ TRIALS
Central Disorders of Hypersomnolence	Endozepine "like" substance	Proportion – (~40-60%)	**YES – BTD-001 ARISE ARISE 2** (Pentylenetetrazol) Balance Therapeutics **YES - GR3027 (Umecrine)**
MYOTONIC DYSTROPHY	Endozepine "like" substance; GABA-A receptor γ2 subunit mis-splicing	(?)	YES – Flumazenil (open-label) & complementary Animal models
HEPATIC ENCEPHALOPATHY	"Endozepines" Neurosteroids – allopregnanolone; THDOC	YES	**YES - GR3027 (Umecrine)**

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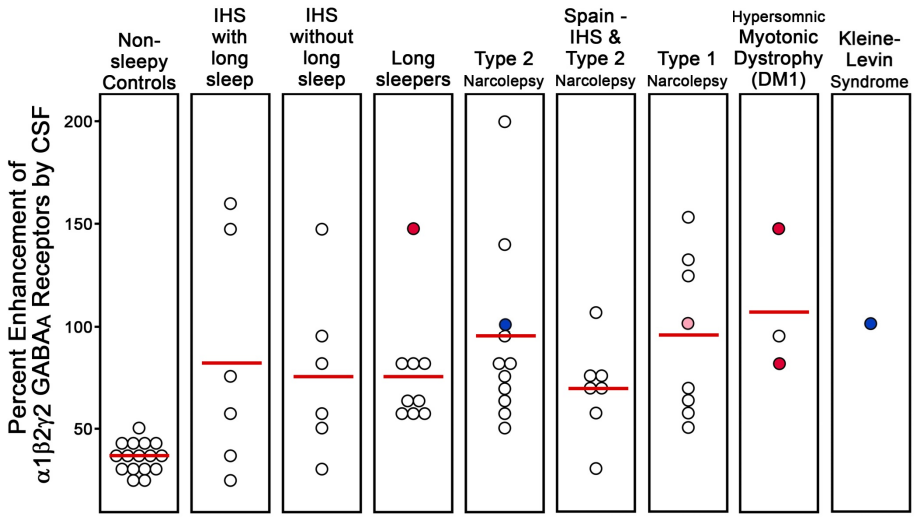

From Rye et al. Sci Transl Med. 2012 Nov 21;4(161):161ra151. Four columns to the right are new unpublished data.