

Primary Hypersomnia: Diagnosis and Management

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Conflict of Interest Disclosures for Speakers

NOTHING TO DECLARE

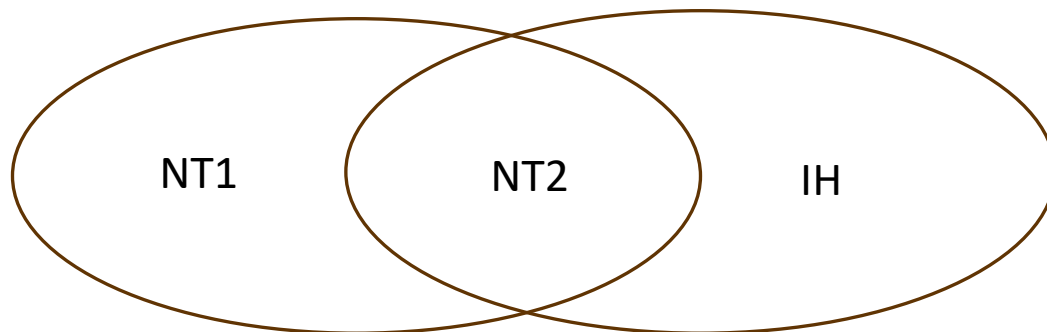
Learning Objectives

After attending this activity, the participant will demonstrate the ability to:

1. **Apply** formal diagnostic and diagnostic testing results to accurately diagnose Narcolepsy Type 1 and Type 2 and idiopathic hypersomnia.
2. **Explain** the neurobiological mechanisms of narcolepsy, specifically focusing on orexin/hypocretin deficiency and the auto-immune hypothesis.
3. **Formulate** a comprehensive clinical management plan combining lifestyle interventions and evidence-based pharmacotherapy for narcolepsy and idiopathic hypersomnia.

Categories of Primary Hypersomnia

	Narcolepsy Type 1	Narcolepsy Type 2	Idiopathic Hypersomnia
Diagnostic testing			
PSG/MSLT	Sleep latency ≤ 8 min 2 or more SOREMPs	Sleep latency ≤ 8 min 2 or more SOREMPs	Sleep latency ≤ 8 min 1–1 SOREMPs Alternative: ≥ 11 h in 24-h PSG, or average ≥ 11 h over 1-wk actigraphy
CSF Orexin (hypocretin)	Low (<110 pg/mL)	Normal, sometimes intermediate	Normal (usually >200 pg/mL)



Narcolepsy: Categories of Clinical Symptoms

- Problems with attention/alertness
- REM-related phenomena
- Ancillary clinical features

Problems with Attention/Alertness

Difficulty in maintaining attention/alertness

Rest versus Active environment

Performance problems (learning)

Automatic behavior

Excessive daytime sleepiness

Sleep attack

REM-Related Phenomena

Cataplexy:

- emotion-induced (laughter, fear, anger)
- direct inhibition of only α -motor neurons
- weakness without loss of consciousness

Hypnagogic hallucination

- sleep-onset; consist pattern; non-emotive

Hypnopompic hallucination

- out of sleep; night terror/nightmares

Sleep paralysis

- out of sleep; awake; cannot move or talk
- direct inhibition of only α -motor neurons

Ancillary Features

Sleep fragmentation

- Late-life presentation
- Contributes to worsening daytime symptoms?

Periodic legs movements (PLMS)

- Contributes to sleep fragmentation?

Sleep Apnea

- Obesity or independent

Differential Diagnosis for Excessive Daytime Sleepiness

Chronic insufficient sleep

Sleep-Phase delay syndrome (night owl)

Disruption of sleep quality (sleep apnea, PLMD)

Idiopathic hypersomnia

Differential of Hallucination

Primary Hypnagogic Hallucination

Night terrors/nightmares/PTSD

REM behavioral disorder

Charles Bonnet syndrome (room lighting a factor)

Seizures

Psychogenic (usually highly emotive)

Differential for Cataplexy

Familial periodic paralyses (K^+ channelopathy)

Syncope

Seizures

Sleep Attacks

(note: the later 3 are associated with change in mental status)

Assessments in Making the Diagnosis

Clinical – hypersomnia + cataplexy

Polysomnogram – rule out secondary causes (apnea, PLMD)

Multi sleep latency study (MSLT)

- < 8 min mean/median latency
- 2 or more REM onsets

HLA typing

CSF hypocretin/orexin levels

Pathophysiology

Prevalence: 25-50/100,000 population

Familial Risk: 1-2%

HLA: DQA1-0102/DQB1-0602 (90-99%)
(unaffected population = 22 -33%)

Hypocretin (Orexin) deficiency

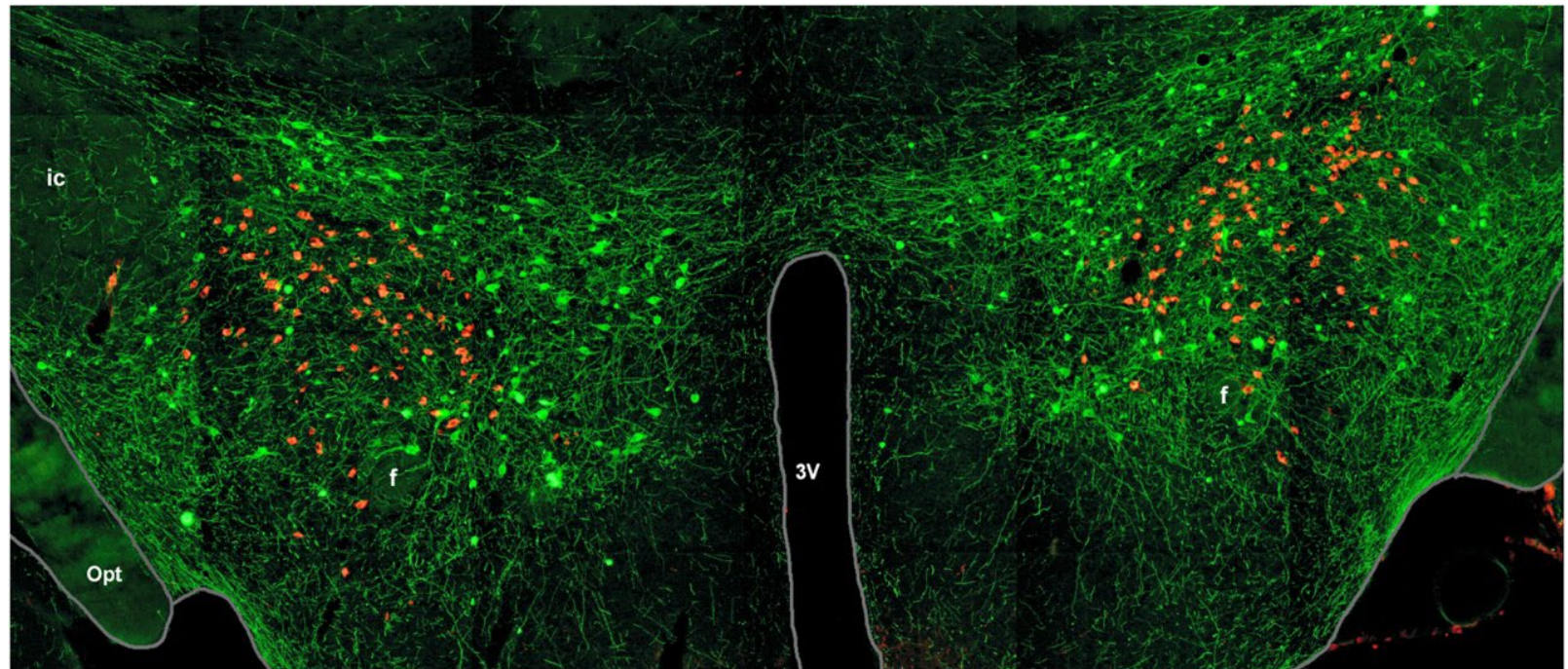
Discovery of Hypocretin/Orexin System

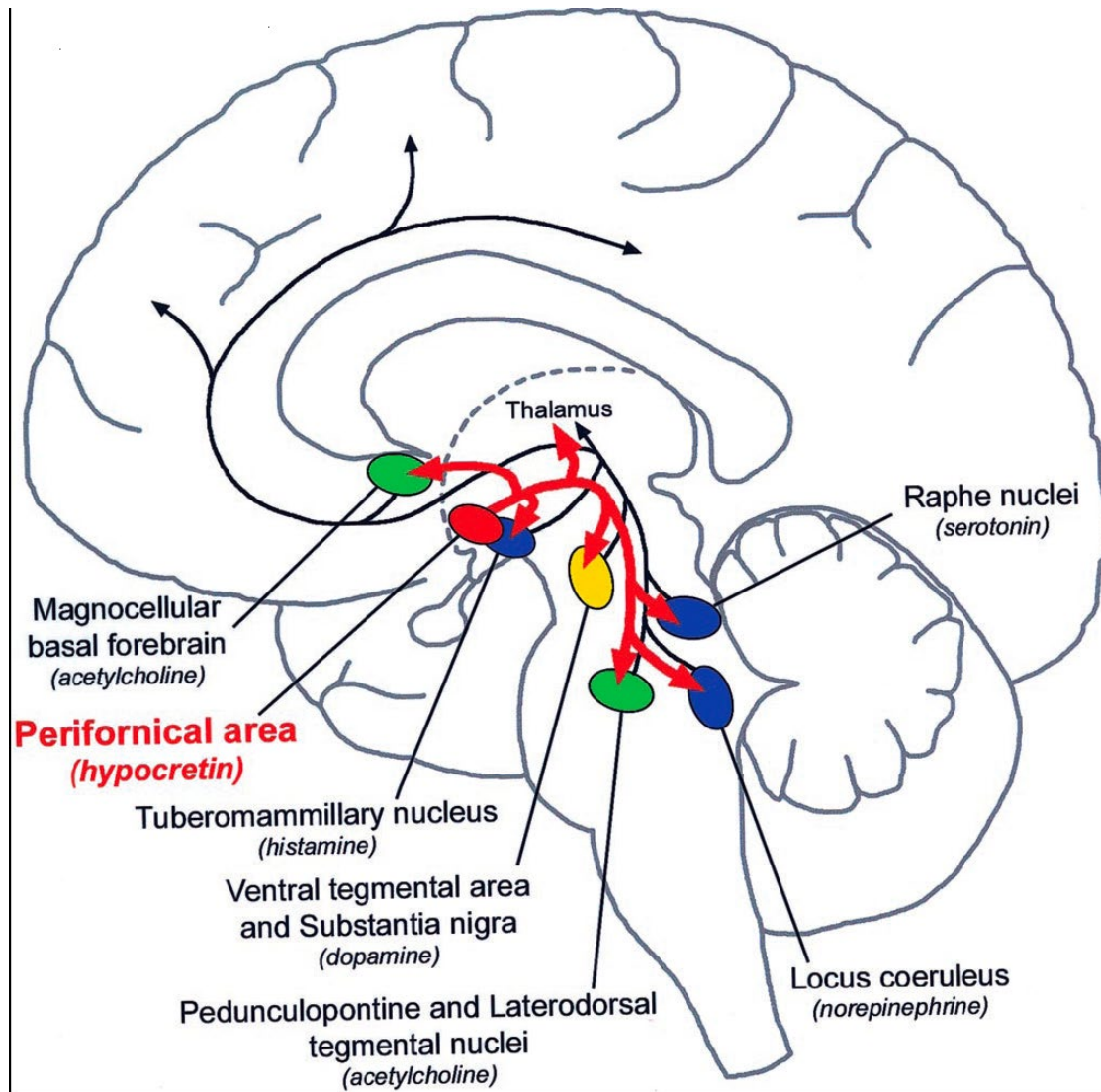
The hypocretins: Hypothalamus-specific peptides with neuroexcitatory activity. **De Lecea et al. PNAS Jan 1998.**
(Sutcliffe's Lab at Scripps (hypothalamus + secretin = **hypocretin**))

Orexins and orexin receptors: A family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. **Sakurai et al. Cell Feb 1998.**
(Yanagisawa's Lab at UTex Southwestern. "orexis", Greek for appetite = **orexin**)

Neurons containing hypocretin (orexin) project to multiple neuronal systems. **Peyron et al J Neurosci Dec 1998.** (Sutcliffe's Lab at Scripps)

Orexin/Hypocretin (green) and Melanin-Concentrating Hormone (orange) in the Rat Hypothalamus





Orexin/Hypocretin(Hcrt)

Preprohypocretin/orexin protein cleaved to Hcrt-1 and Hcrt-2 peptides

Hcrt-1 and -2 receptors: G protein-coupled receptors

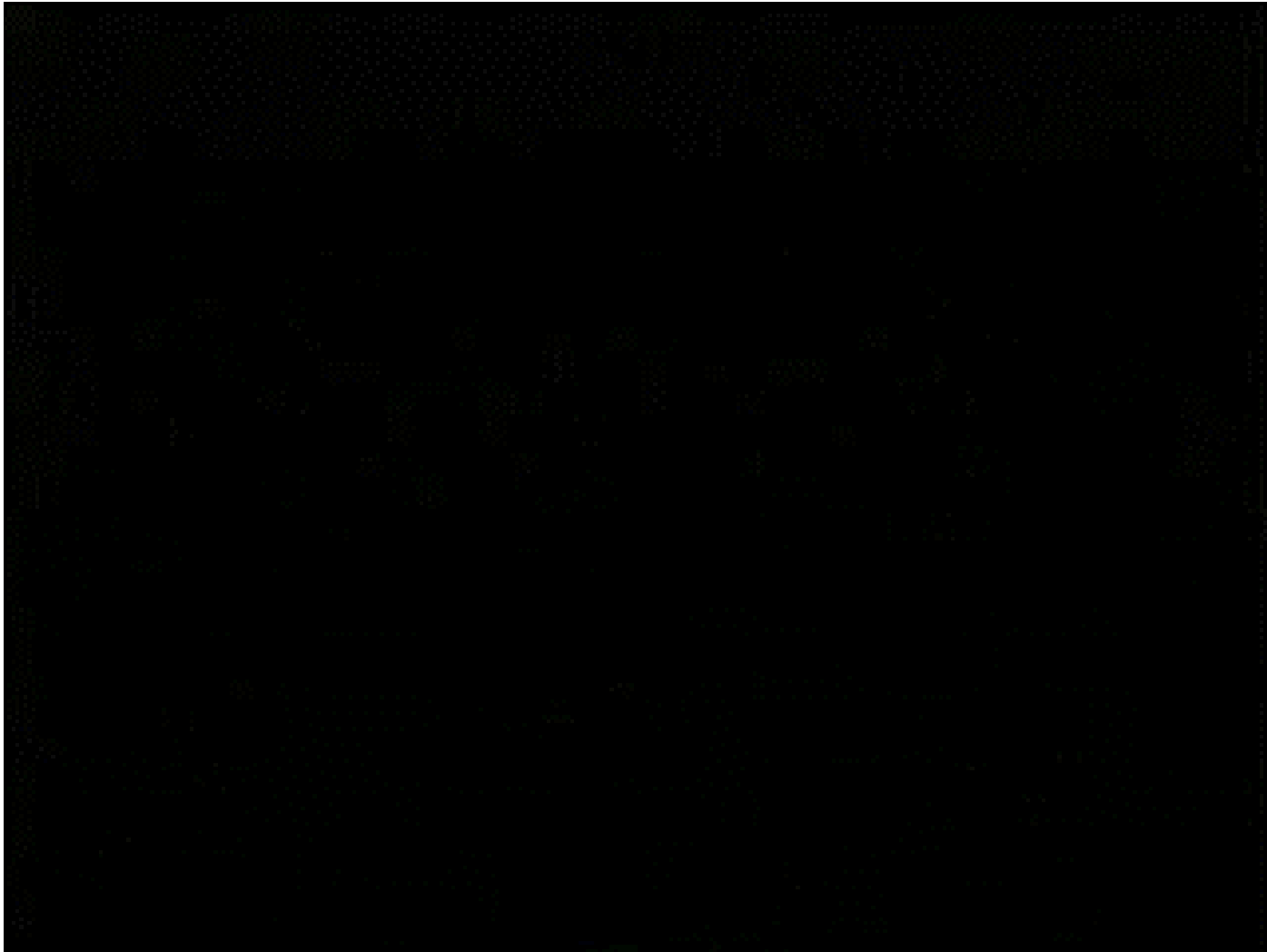
Orexin/Hypocretin and Relation to Narcolepsy

The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. **Lin et al. Cell** Aug 1999 (Minot's Lab at Stanford)

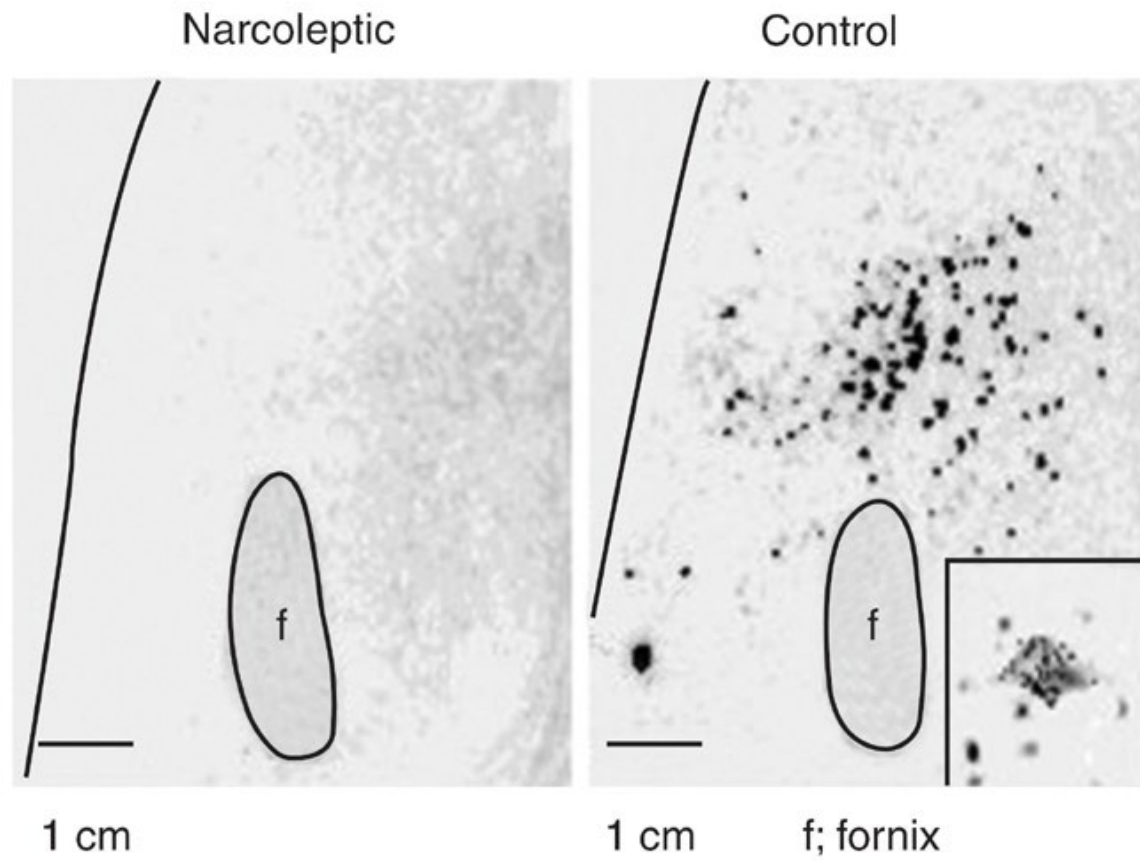
Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. **Chemelli et al. Cell** Aug 1999 (Yanagisawa's Lan UTex Southwestern)

Hypocretin (orexin) deficiency in human narcolepsy. **Nishino et al. Lancet** Jan 2000 (Minot's Lab at Stanford)

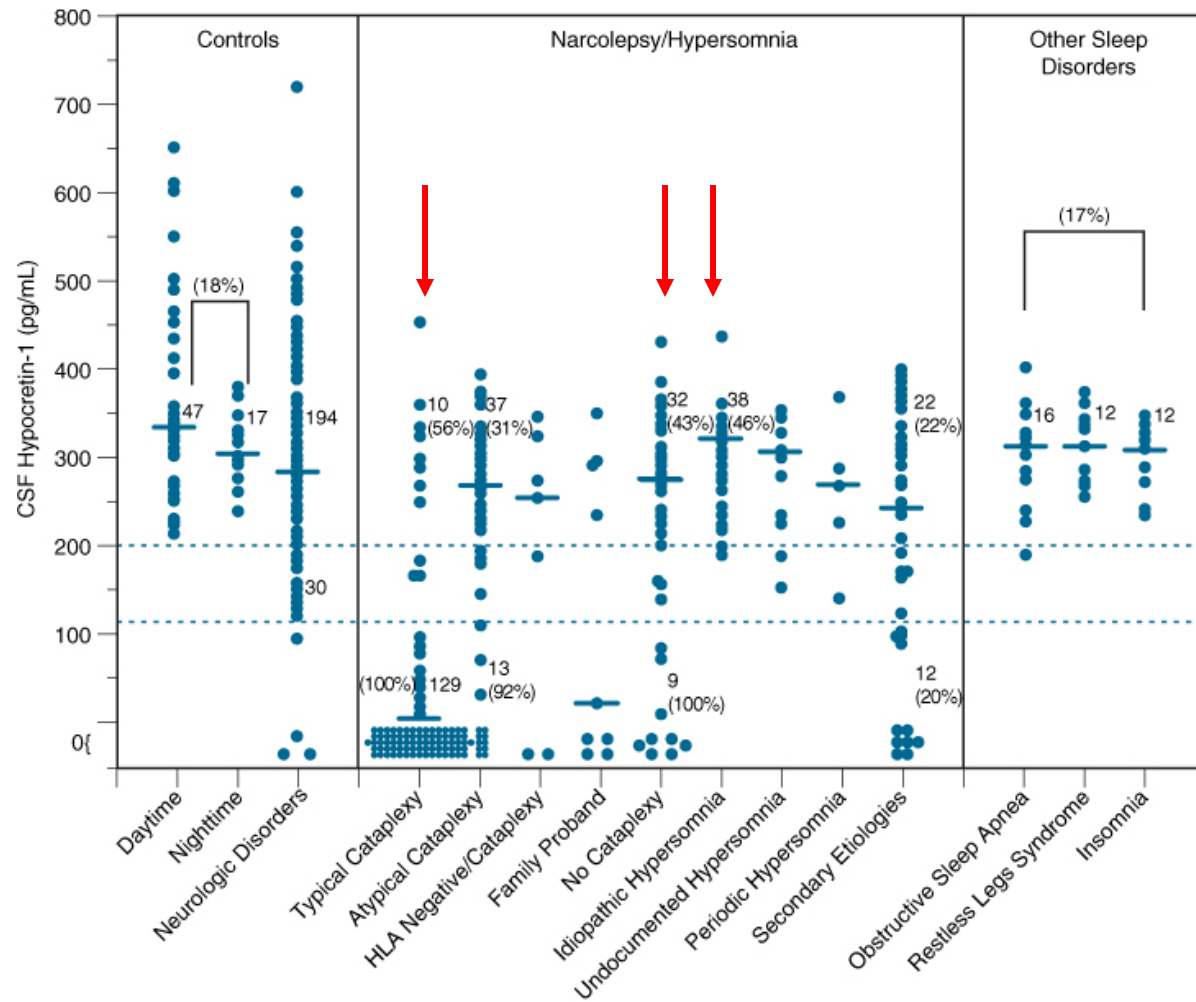
Cataplexy in Dogs with Orexin/Hcrt-2 Receptor Gene Deletion



Preprohypocretin/Orexin mRNA in Hypothalamus of Narcolepsy and Control



Orexin/Hypocretin Concentration in the CSF of Subjects with Narcolepsy and Other Diseases



Behavioral Management of Attention/Alertness Problems

Adequate sleep

Naps at least once a day

Reduce length of sedentary activity

Exercise

Food/eating reassessment

Medical Management of the Various Clinical Problems of Narcolepsy

Attention/alertness –

- A1R blocker - caffeine
- DAT blocker - modafinil, armodafinil, methylphenidate, dextroamphetamine, methamphetamine
- Inverse H3 receptor agonist - pitolisant (Wakix)
- Sodium Oxybate – (Xyrem/Xywav (low Na)/Lumryz (ER)
- Orexin receptor agonist- (coming soon)

Cataplexy –

- Antidepressants (SNRI most effective);
- Sodium Oxybate
- Orexin receptor agonist – (coming soon)

Hallucination - hypnopompic (e.g., alprazolam)

Sleep paralysis – none

Sleep fragmentation – Sodium Oxybate

PLMS - epiphenomena?

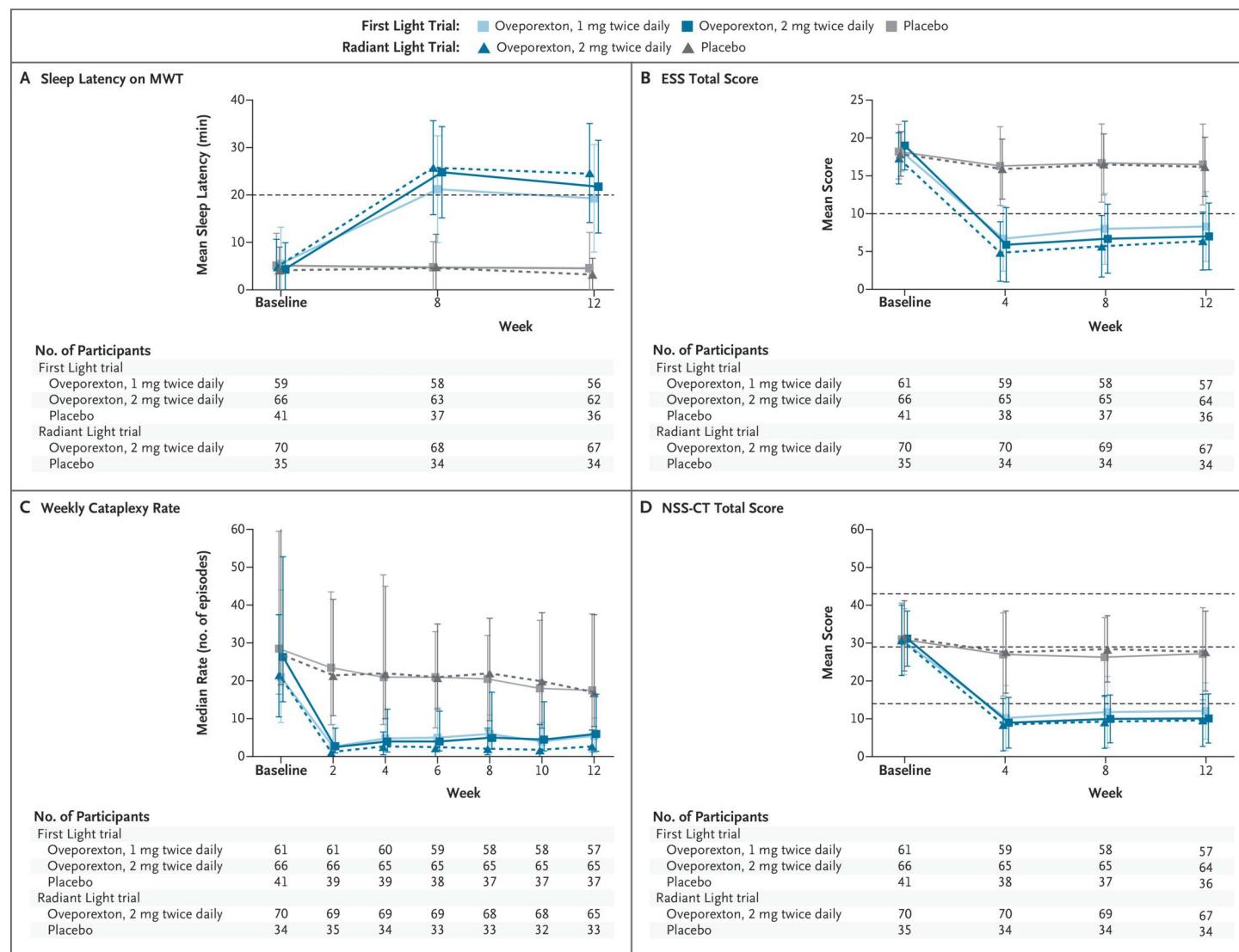
Oveporexton for Narcolepsy Type 1 — Results from Two Phase 3 Trials

Yves Dauvilliers, M.D., Emmanuel Mignot, M.D., Jakub Antczak, M.D., Isabelle Arnulf, M.D., Lucie Barateau, M.D., Erik Buntinx, M.D., Bruce Corser, M.D., Alex Iranzo, M.D., Ph.D., Ramin Khatami, M.D., Gert Jan Lammers, M.D., Katharina Lederer, M.D., Kristian Bernhard Nilsen, M.D., Ph.D., Fabio Pizza, M.D., Markus H. Schmidt, M.D., Sheila Sivam, M.D., Ph.D., Oliver Sum-Ping, M.D., Mitsutaka Taniguchi, M.D., Shuqin Zhan, M.D., Anson Abraham, Ph.D., Alice Cai, M.D., Yeting Du, Ph.D., Mark R. Etherton, M.D., Ph.D., Helene Faessel, Pharm.D, Ph.D., Samuel Hsiao, Ph.D., Harisha Kadali, M.D., Elena Koundourakis, Ph.D., Melissa Naylor, M.D., Ph.D., Rachel Neuwirth, M.S., Tina Olsson, Ph.D., Raquel Rogers, M.D., Sarah Sheikh, B.M., B.Ch., Shinichiro Tanaka, Ph.D., Philipp von Rosenstiel, M.D., Christian von Hehn, M.D., Ph.D., Yaming Hang, Ph.D., Baiyun Yao, Ph.D., Rafael del Rio Villegas, M.D., Ph.D., and Giuseppe Plazzi, M.D.

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Primary side effect: >50% complained of increased urinary frequency

Safety and efficacy of lower-sodium oxybate in adults with idiopathic hypersomnia: a phase 3, placebo-controlled, double-blind, randomised withdrawal study

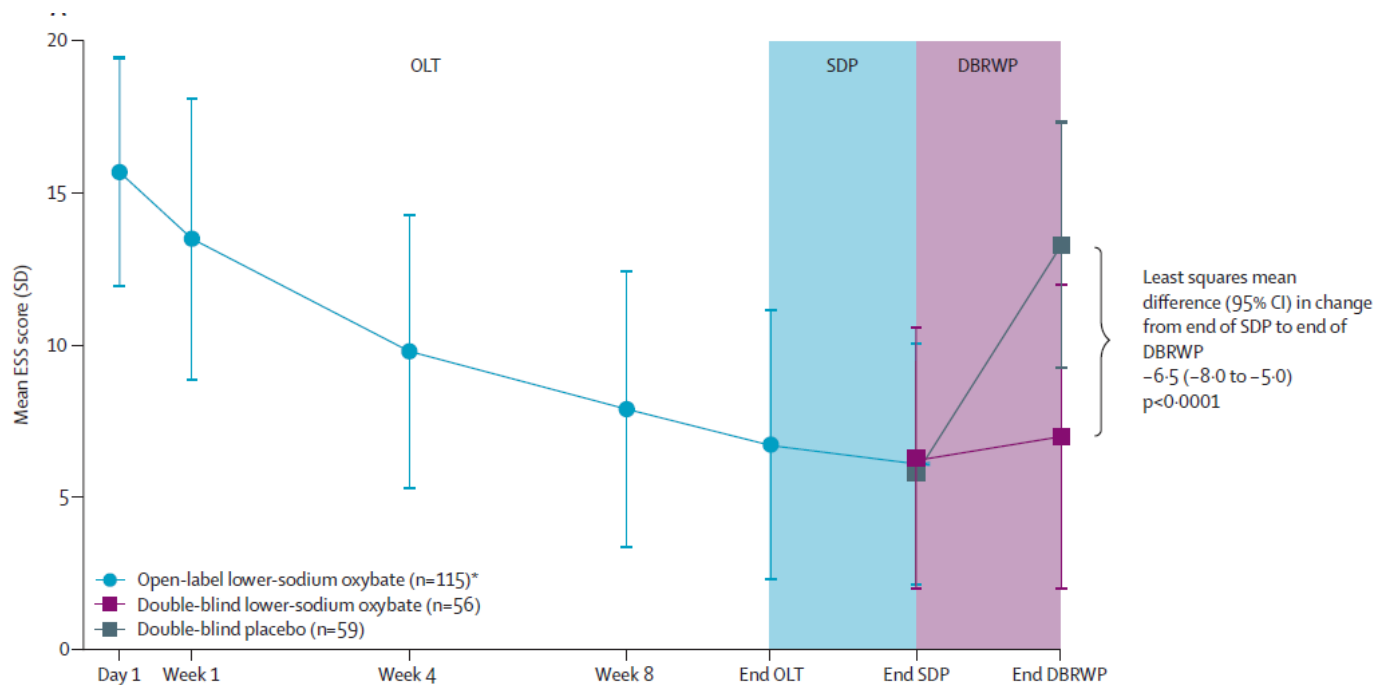
Yves Dauvilliers, Isabelle Arnulf, Nancy Foldvary-Schaefer, Anne Marie Morse, Karel Šonka, Michael J Thorpy, Emmanuel Mignot, Patricia Chandler, Rupa Parvataneni, Jed Black, Amanda Sterkel, Dan Chen, Franck Skobieranda, Richard K Bogan

The Lancet Neurology, 2022. 21: 53-65.

Methods

1. Dx IH; 7h or more sleep; ESS>10
2. NaOx- once or twice at night; prior users were enrolled
3. Outcome – change in ESS
4. Open-label (OLP) titration – 5 day
5. Stable dose period (SDP) – 2 weeks (needed to show benefits in OLP)
6. DB, Randomized withdrawal period (DBRWP) – 2weeks
7. Open-label extension (OLE)/safety -24 weeks
8. 154 (OLP) > 123(SDP) > 116 (DBRWP) > 56/57 completed (73%) >106 (OLE)

Change in ESS scores from the start of the OLT to the end of the DBRWP



Johns Hopkins Bayview Sleep Disorders Center Syndrome

