



5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 2

**Treatment of adult and pediatric primary sleep disorders
(Level 2)**

Management of CNS hypersomnolence disorders

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In relation to this manuscript, the author has the following conflicts of Interest to declare:

<i>Type of affiliation / financial interest</i>	<i>Name of commercial company</i>
Travel Support	UCB Pharma
Travel Support	Bioprojet
Travel Support	Allergan
Advisory Work	TEVA
Lectures	Novartis
Lectures	Bioprojet

Management of CNS hypersomnolence disorders – level 2

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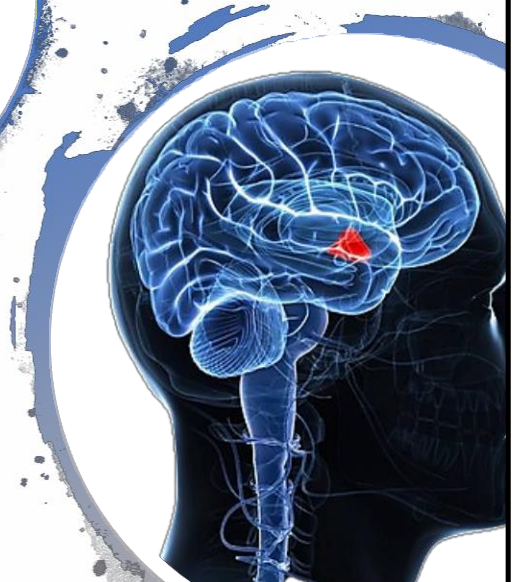
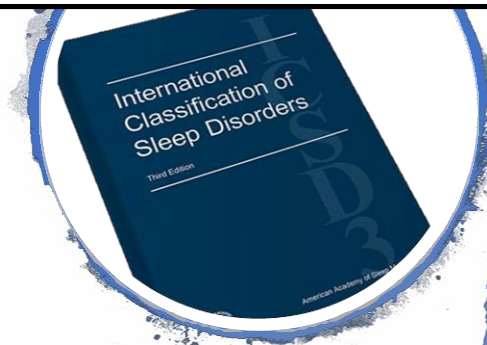
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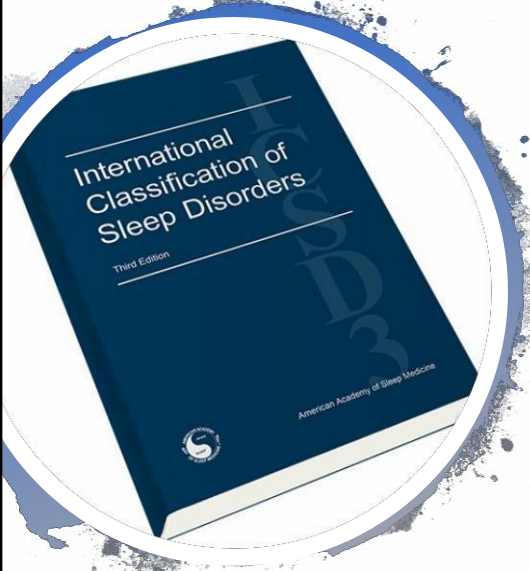
Stichting Epilepsie Instellingen Nederland



Management

Hypersomnolence?





ICSD-3

- • Narcolepsy type 1 & 2 (NT1 & NT2)
- • Idiopathic Hypersomnia (IH)
 - Kleine-Levin Syndrome (KLS)
 - Hypersomnia due to
 - Medical Disorder
 - Medication or Substance
 - Psychiatric Disorder
 - Insufficient Sleep


Hypersomnolence?

A condition in which one sleeps for an excessively long time

Excessive Daytime Sleepiness (EDS)

The inability to stay awake during the usual wake time

Periods of irresistible sleep & sleep attacks



Fatigue



Sleepiness





Fatigue

≠



Sleepiness



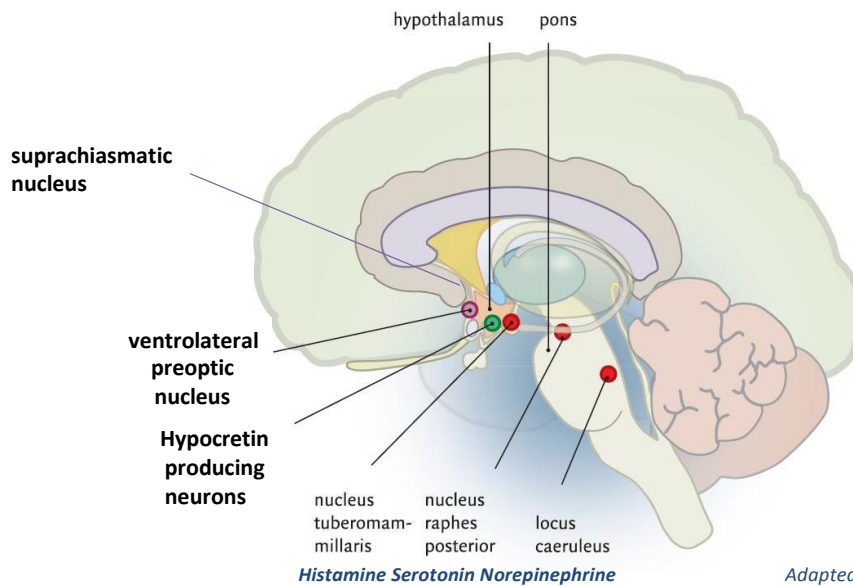
Hypersomnia
Vs.
Vigilance

Sleep and Wake Balance



Franczek et al, NTvG 2006

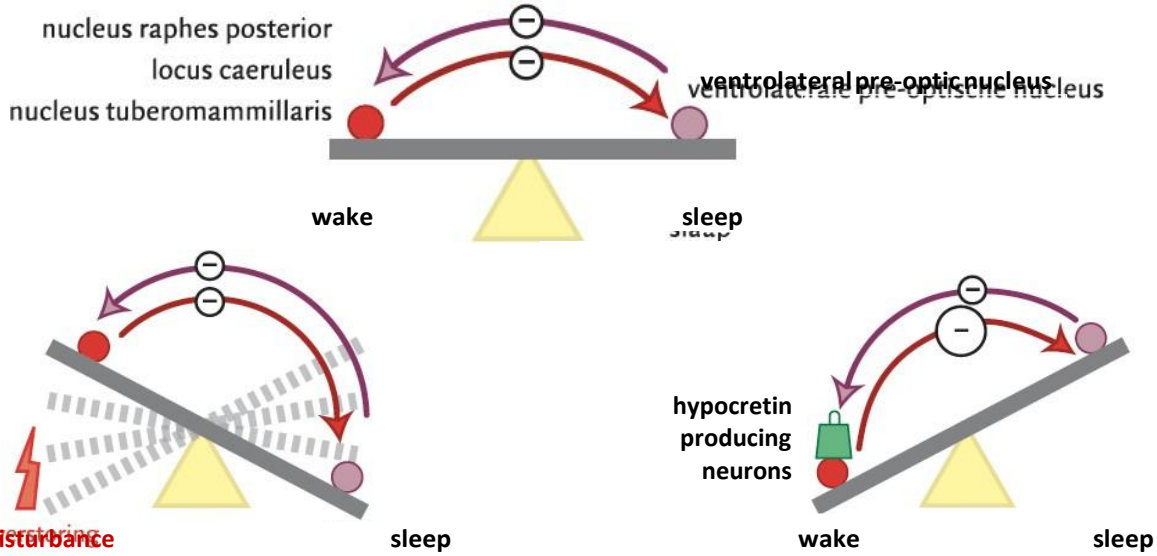
Brain nuclei important for sleep



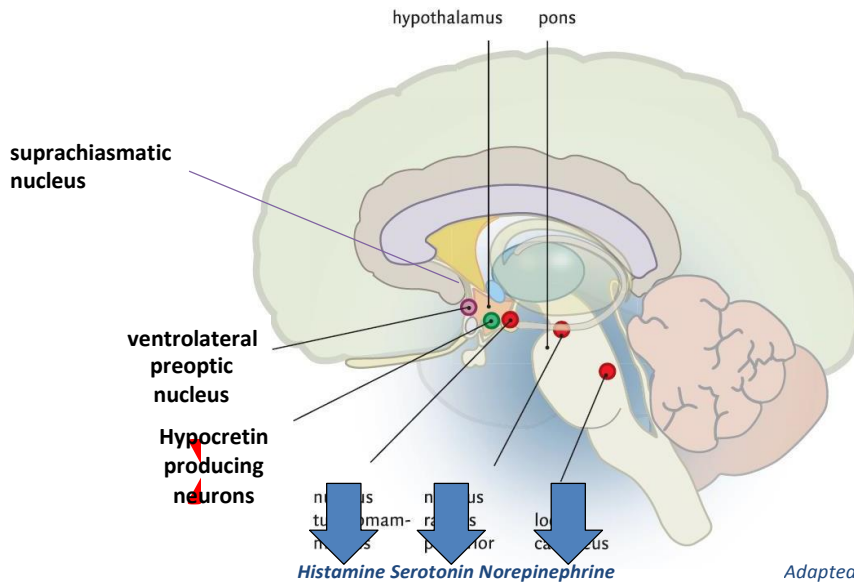
Adapted from: Franczek, et al, NTvG 2007

Adapted from Fronczek et al., NTvG 2006

Sleep flip-flop model

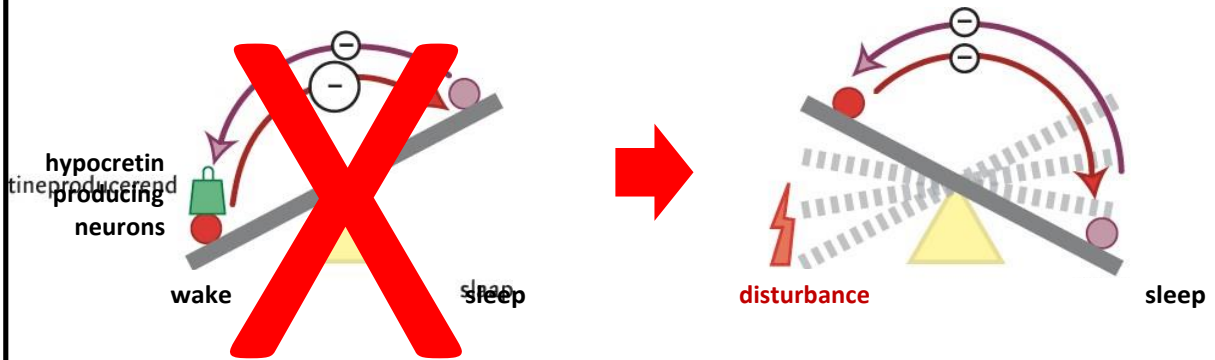


Narcolepsy type 1



Adapted from: Fronczek, et al, NTvG 2007

Narcolepsy



Adapted from Fronczek et al, NTvG 2006



ICSD-3 Criteria

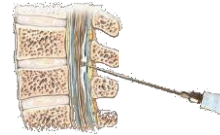
- Narcolepsy Type 1
- Narcolepsy Type 2
- Idiopathic Hypersomnia

International Classification of Sleep Disorders - third edition

ICSD-3 Criteria

Narcolepsy With Cataplexy (type 1)

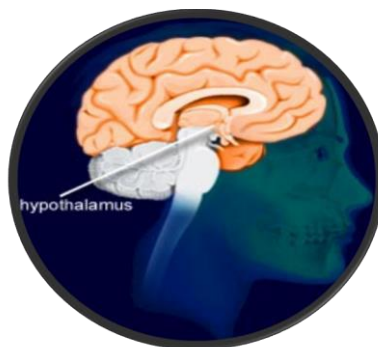
- Excessive Daytime Sleepiness
(3 months)
- Typical Cataplexy & Positive MSLT
or
- Hypocretin-1 Deficiency

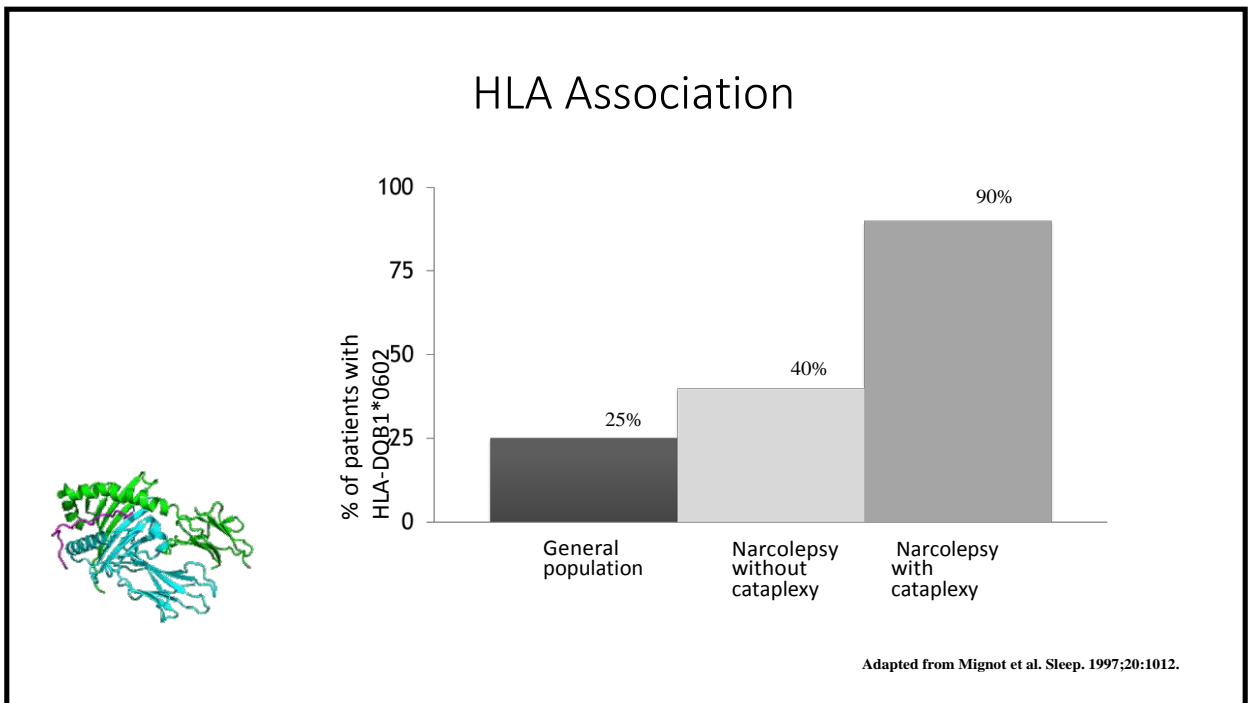
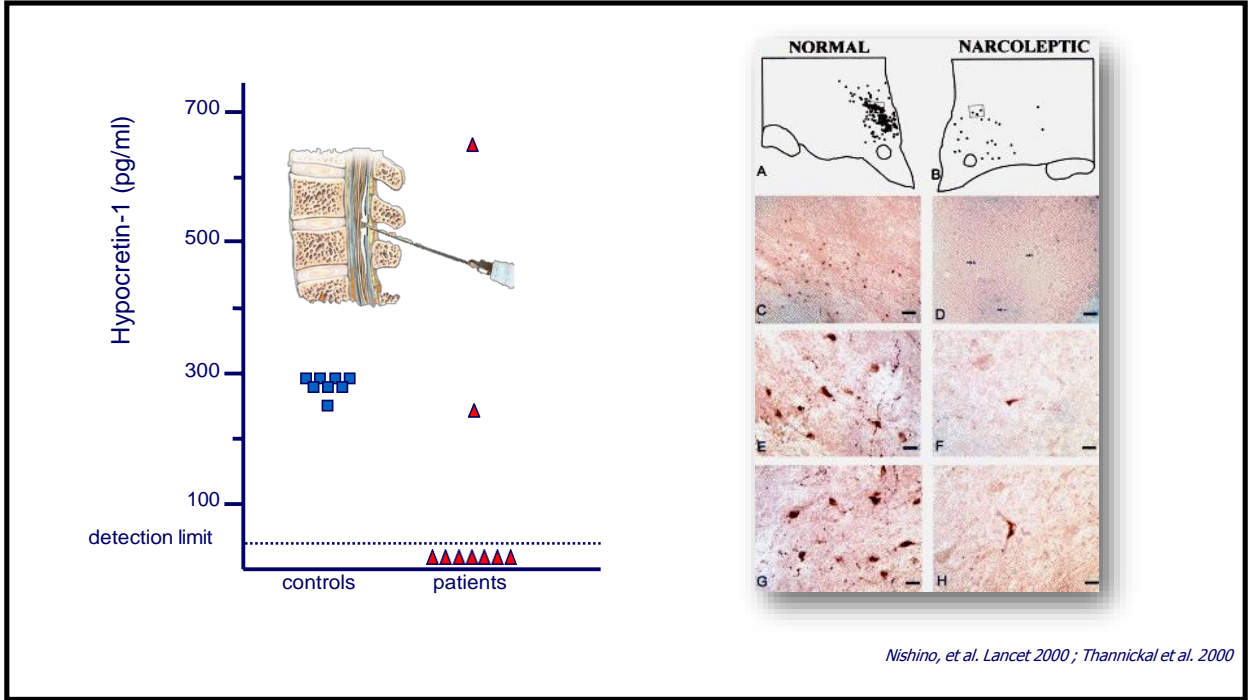


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Narcolepsy: Pathophysiology

Loss of hypocretin producing neurons
in the lateral hypothalamus

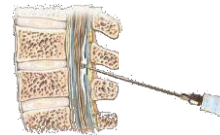




ICSD-3 Criteria

Narcolepsy With Cataplexy (type 1)

- Excessive Daytime Sleepiness
(3 months)
- **Typical Cataplexy** & Positive MSLT
or
- Hypocretin-1 Deficiency



International Classification of Sleep Disorders - third edition

Typical Cataplexy?



ICSD-3 Criteria

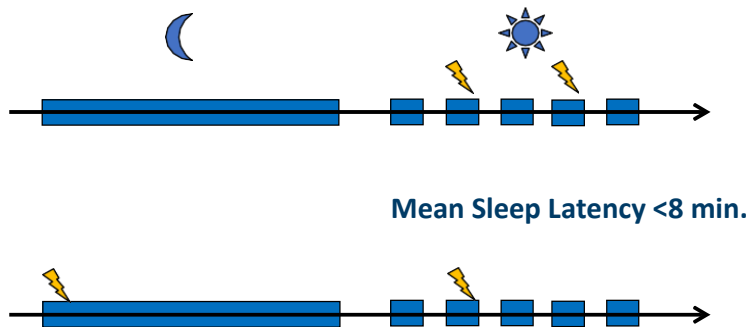
Narcolepsy without Cataplexy (type 2)

- Excessive Daytime Sleepiness (3 months)
- Positive MSLT



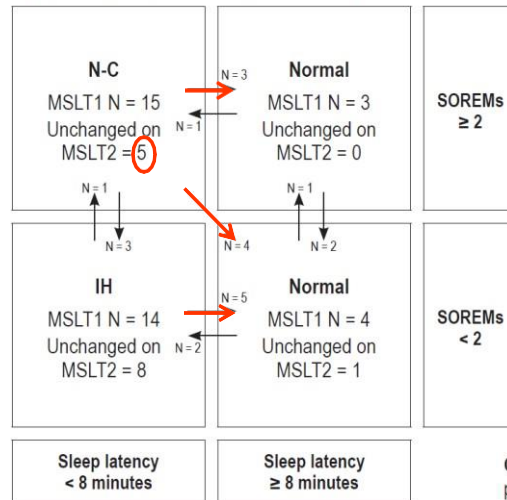
International Classification of Sleep Disorders - third edition

Positive MSLT?



MSLT test-retest

Figure 2—MSLT-based diagnosis on repeat MSLT



Conclusions: The multiple sleep latency test demonstrates poor test-retest reliability in a clinical population of patients with central nervous system hypersomnia evaluated in a tertiary referral center. Alternative diagnostic tools are needed.

ICSD-3 Criteria

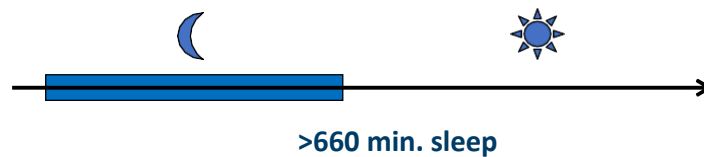
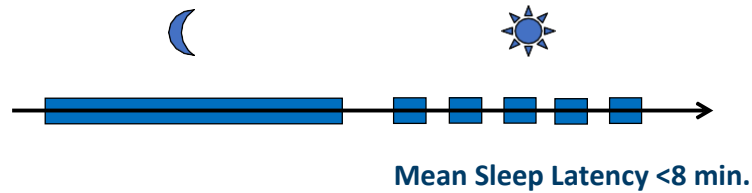


Idiopathic Hypersomnia

- Excessive Daytime Sleepiness (3 months)
Positive MSLT (<8 min.) or
- Positive PSG (>660 min. sleep in 24hrs)
 - **No** cataplexy
 - <2 SOREM's
- Insufficient sleep has been ruled out (actigraphy)

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Positive MSLT?



ICSD-3 Criteria

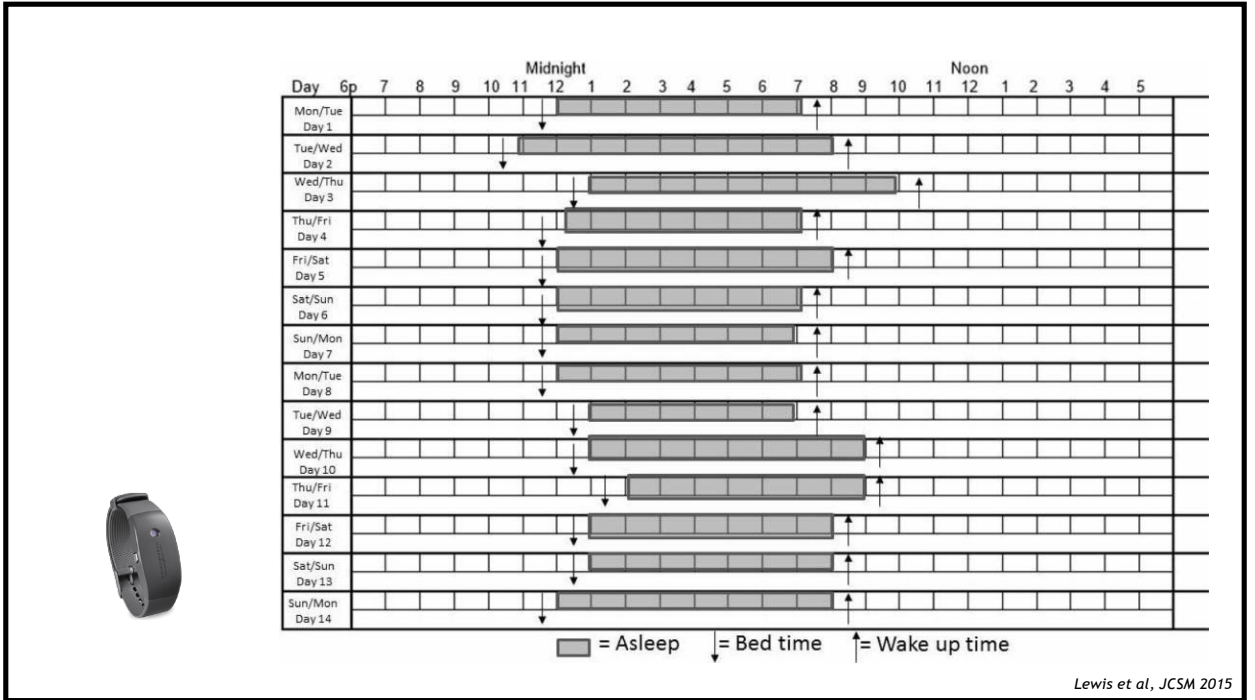


Idiopathic Hypersomnia

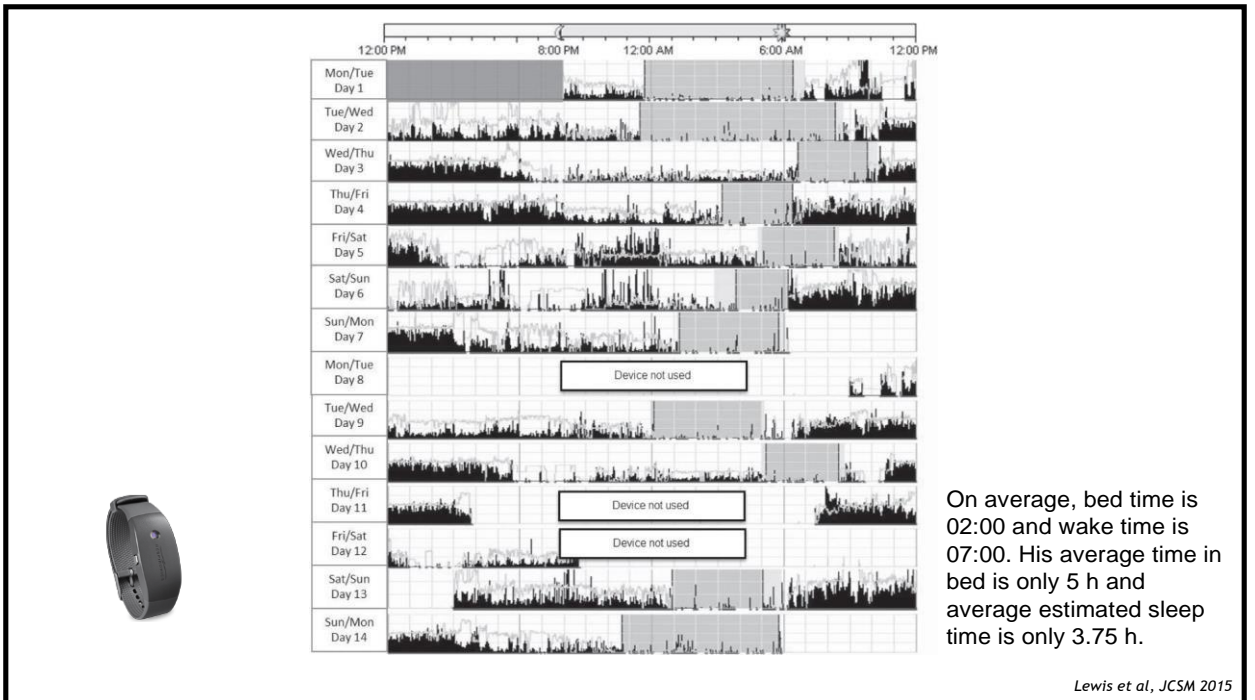
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 - <2 SOREM's
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International Classification of Sleep Disorders - third edition



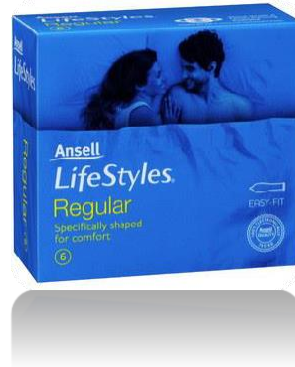
Lewis et al., JCSM 2015



Lewis et al., JCSM 2015

Lifestyle

- Regular schedule
- Planned naps



Stimulants

Stimulating drugs

- Methylphenidate (Ritalin), 60 mg/day
- Modafinil, 400 mg/day



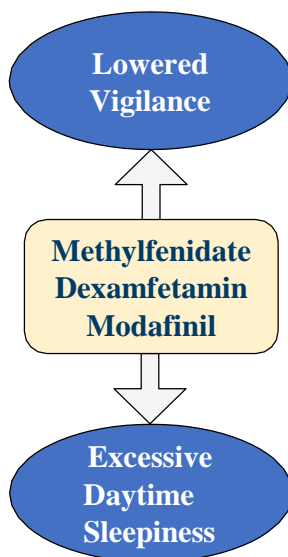
Cataplexy

Anti-cataplectic

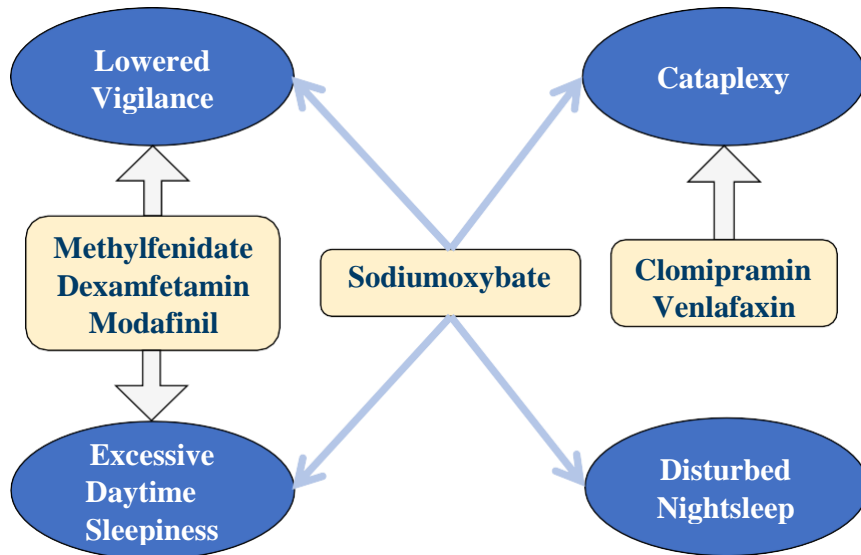
- Tricyclic antidepressants/SSRI's
- Gammahydroxybutyricacid (Xyrem)
4.5-9.0 grams/night



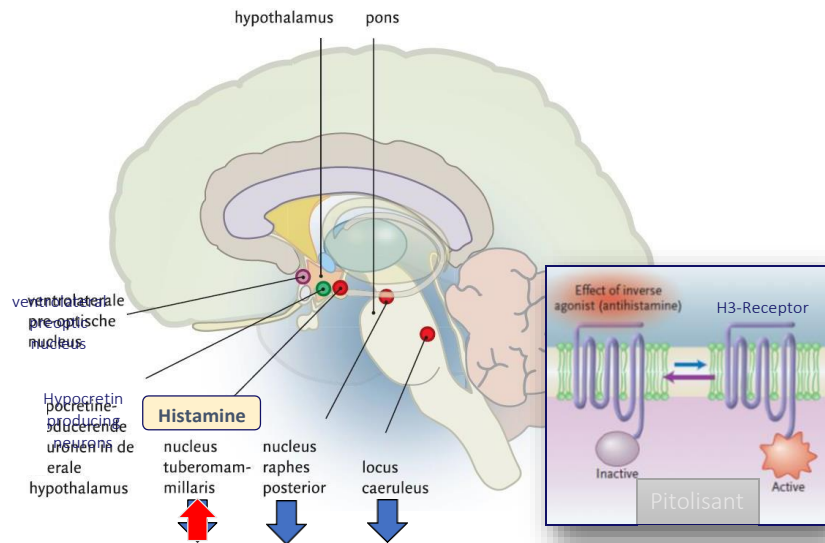
Idiopathic Hypersomnia: drugs



Narcolepsy Treatment: Drugs



Narcolepsy



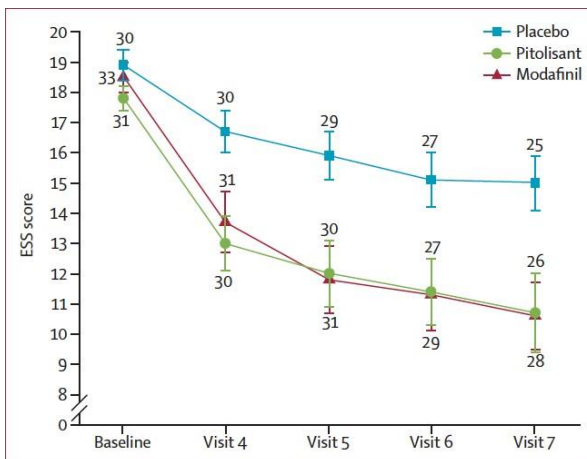
Adapted from: Espada et al. NMG 2012

Pitolisant – Clinical Data

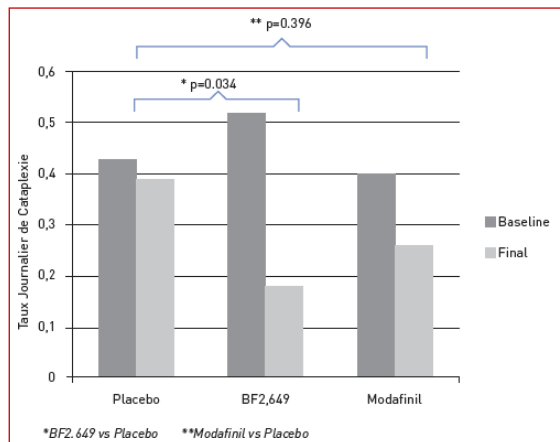
- Harmony I
- Harmony CTP
- Harmony III
- Liability Study



Epworth Sleepiness Scale



Cataplexy Rate / Day



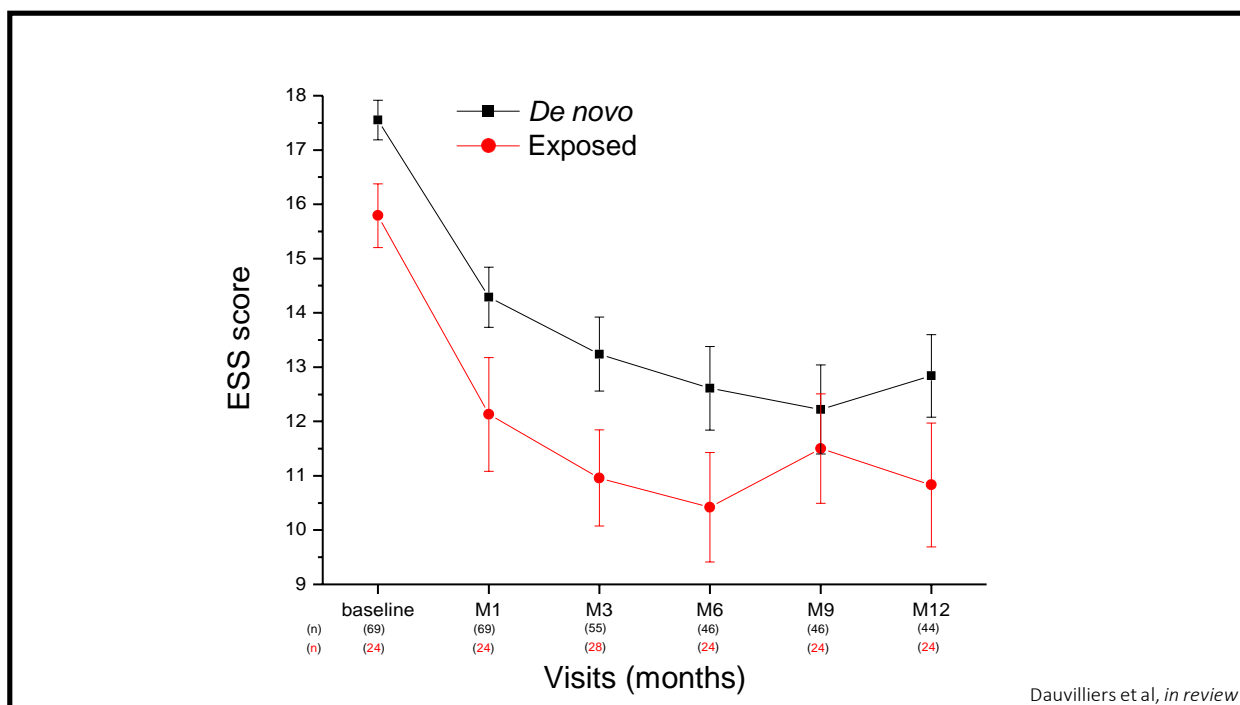
	Pitolisant group (n=54)	Placebo group (n=51)	p value
Adverse events	19 (35%)	16 (31%)	0.528
Headache	5 (9%)	5 (10%)	..
Somnolence	1 (2%)	3 (6%)	..
Irritability	3 (6%)	1 (2%)	..
Anxiety	3 (6%)	0	..
Nausea	3 (6%)	0	..
Apathy	1 (2%)	2 (4%)	..
Dizziness	0	2 (4%)	..
Treatment-related adverse events	15 (28%)	6 (12%)	0.048
Severe adverse events	1 (2%)	0	..
Amphetamine-like withdrawal syndrome	0	1 (2%)	0.305

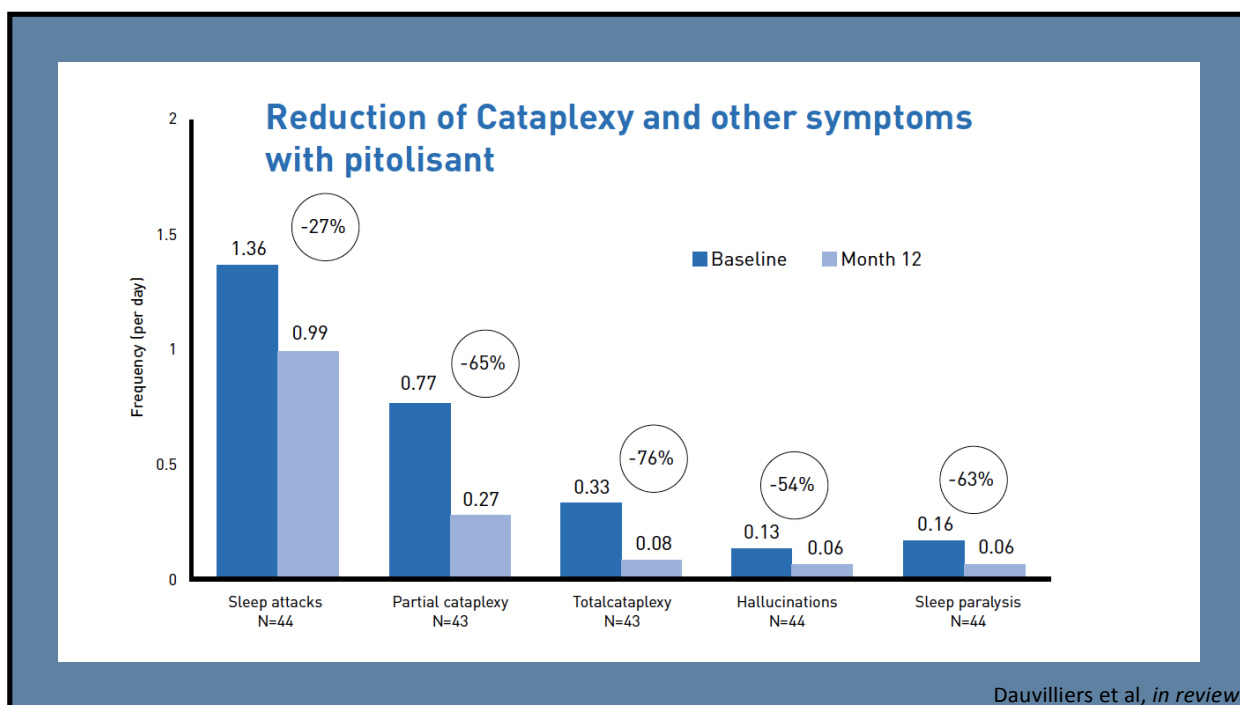
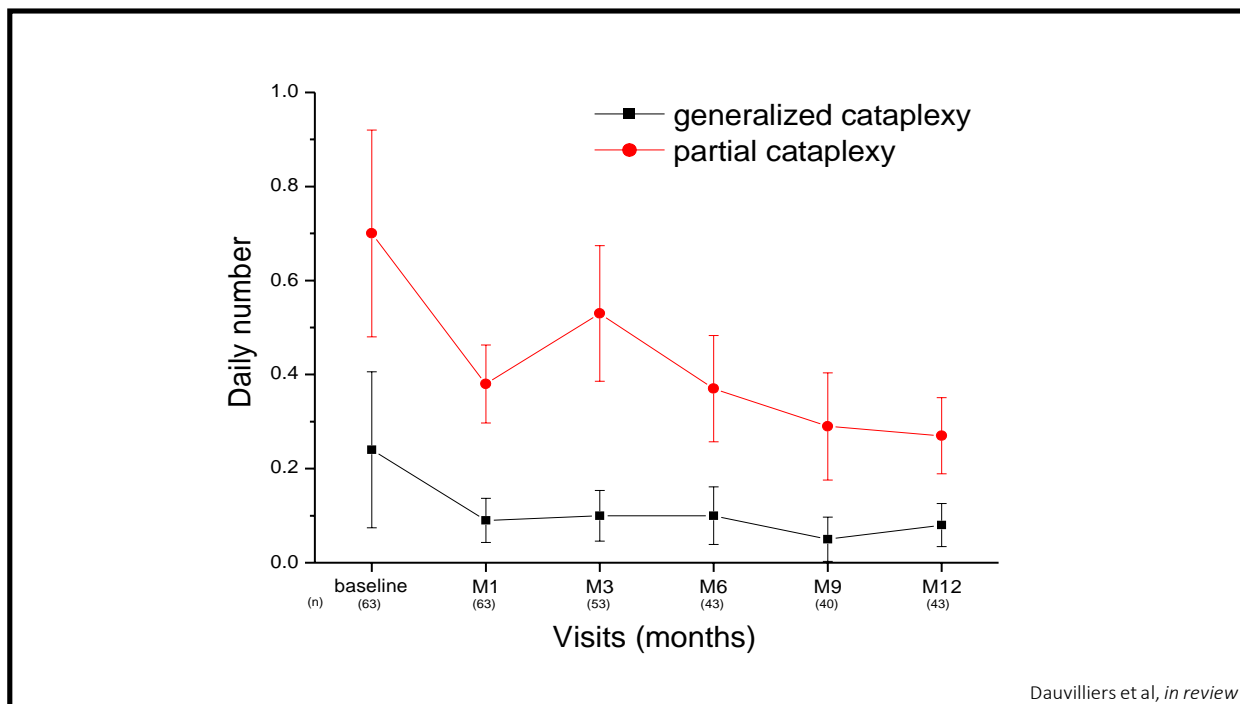
Data are number of patients (%). p values are from χ^2 tests.

Table 3: Adverse events



Szakacs et al, Lancet Neurol 2017



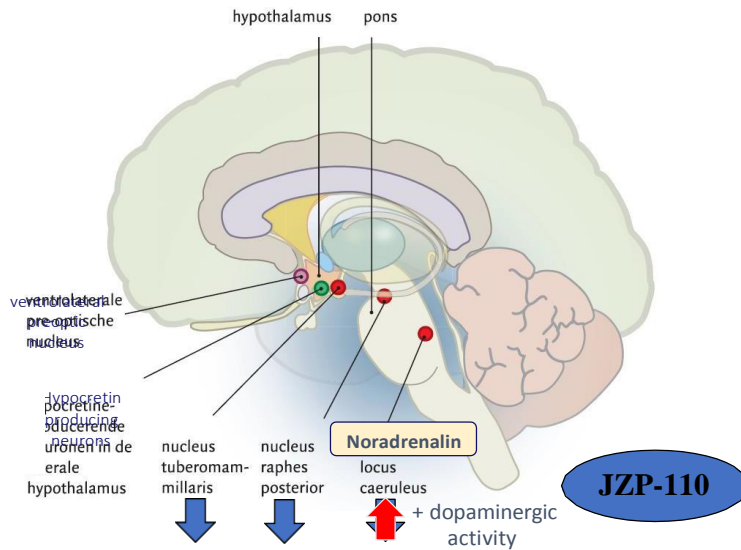


Pitolisant (Wakix): Narcolepsy (with and without cataplexy)



2016

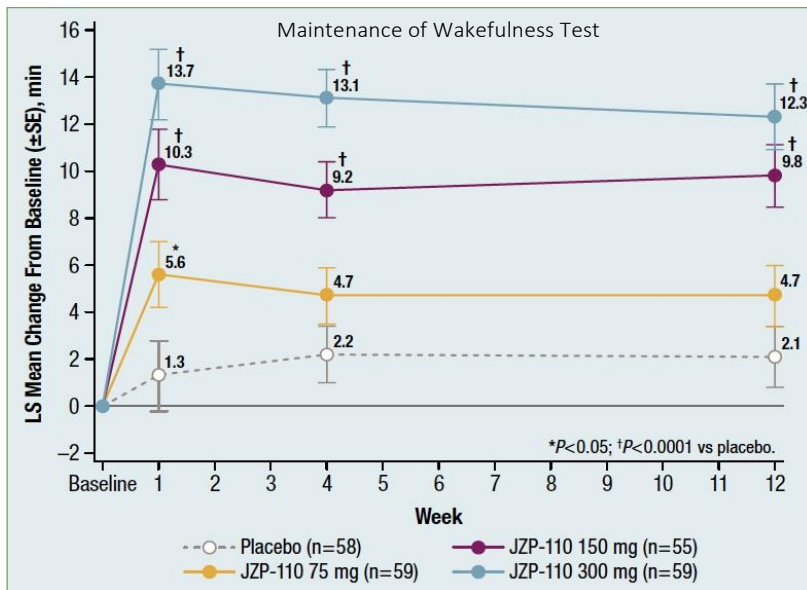
Narcolepsy



Adapted from: Franczek, et al, NTVG 2007

Solriamfetol

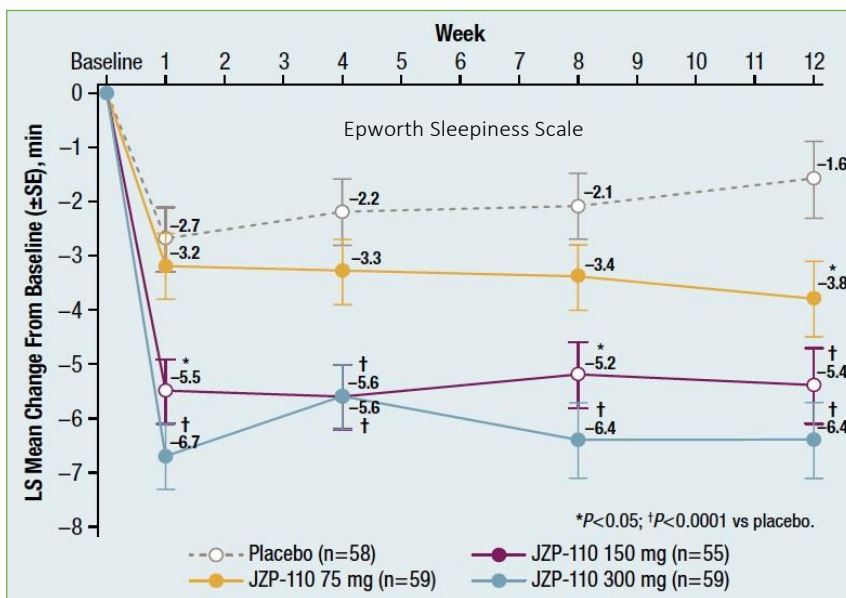
JZP-110



Thorpy et al, 2019

Solriamfetol

JZP-110



Thorpy et al, 2019

Solriamfetol (Sunosi): Excessive daytime sleepiness in narcolepsy and sleep apnea



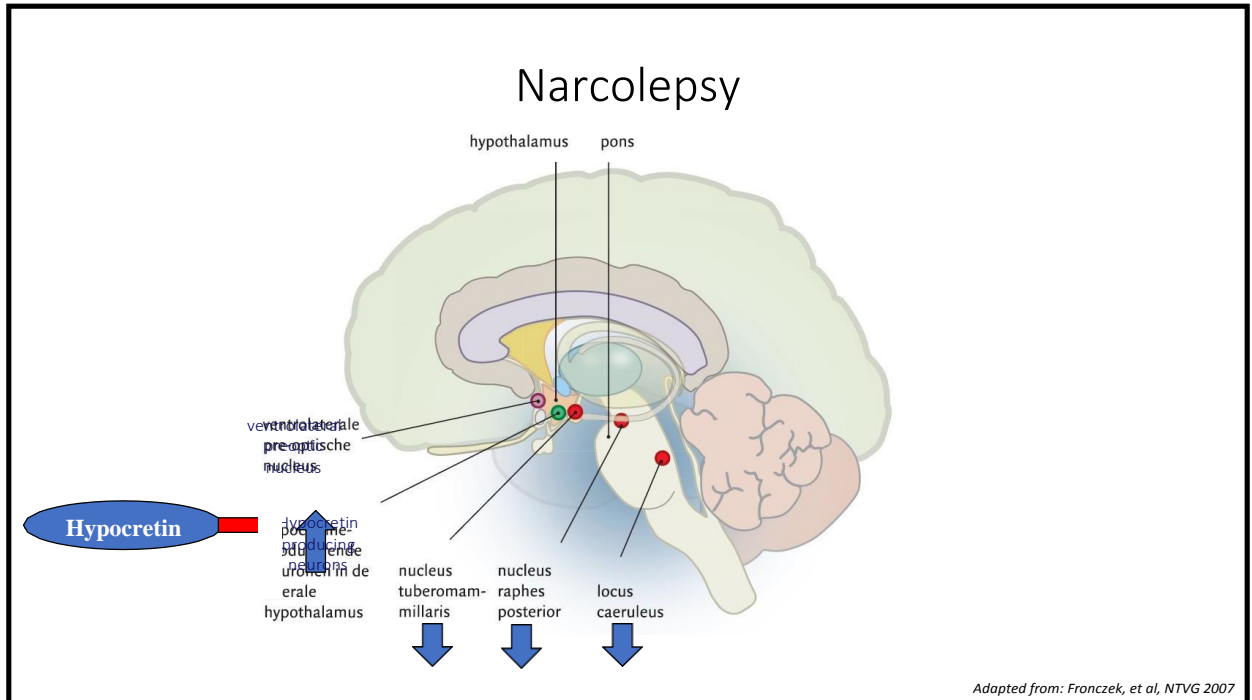
Sodium Oxybate – renewed?



Sodium oxybate delivered via micropump technology



Sodium oxybate with 90% less sodium



Nonpeptide orexin type-2 receptor agonist ameliorates narcolepsy-cataplexy symptoms in mouse models

Yoko Irukayama-Tomobe^{a,1}, Yasuhiro Ogawa^{a,1}, Hiromu Tominaga^{a,1}, Yukiko Ishikawa^a, Naoto Hosokawa^a, Shinobu Ambai^a, Yuki Kawabe^a, Shuntaro Uchida^a, Ryo Nakajima^a, Tsuyoshi Saitoh^a, Takeshi Kanda^a, Kaspar Vogt^a, Takeshi Sakurai^a, Hiroshi Nagase^a, and Masashi Yanagisawa^{a,2}

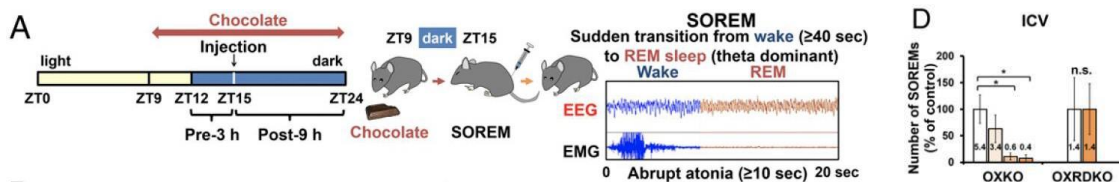
^aInternational Institute for Integrative Sleep Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan

Contributed by Masashi Yanagisawa, March 22, 2017 (sent for review January 13, 2017; reviewed by Thomas S. Kilduff and Thomas E. Scammell)

Narcolepsy-cataplexy is a debilitating disorder of sleep/wakefulness caused by a loss of orexin-producing neurons in the lateroposterior hypothalamus. Genetic or pharmacologic orexin replacement ameliorates symptoms in mouse models of narcolepsy-cataplexy. We have recently discovered a potent, nonpeptide OX2R-selective agonist, YNT-185. This study validates the pharmacological activity of this compound in OX2R-transfected cells and in OX2R-expressing neurons in brain slice preparations. Intraperitoneal, and intracerebroventricular, administration of YNT-185 suppressed cataplexy-like episodes in orexin knockout and orexin neuron-ablated mice, but not in orexin receptor-deficient mice. Peripherally administered YNT-

methylphenidate and modafinil), sedative (sodium oxybate), and tricyclic antidepressants. However, the use of these medications is often limited by adverse side effects such as headache, nausea, anxiety, irritability, and insomnia.

Murine models of narcolepsy-cataplexy include OXKO mice (2), orexin receptor-deficient (*Hcrtr1*^{-/-};*Hcrtr2*^{-/-}, abbreviated as OXRDKO) mice, and the orexin/ataxin-3 transgenic mice (in which orexin neurons are genetically and postnatally ablated) (12). Tabuchi et al. created another narcolepsy mouse model, which expressed diphtheria toxin A in orexin neurons under control of the Tet-off system, leading to conditional ablation of





Typical Cataplexy?





Typical Cataplexy?

