CHEST Congress 2019 | Thailand Bangkok | 10-12 April

Narcolepsy and Hypersomnia

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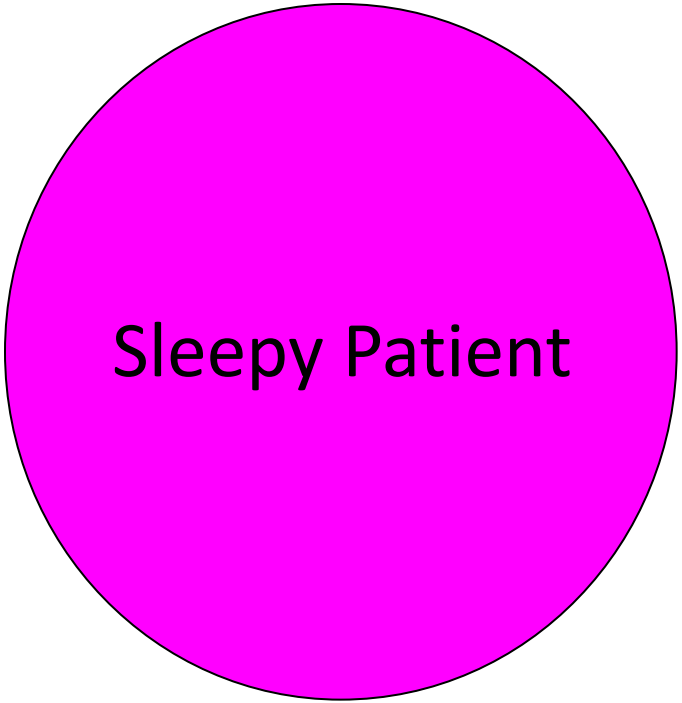
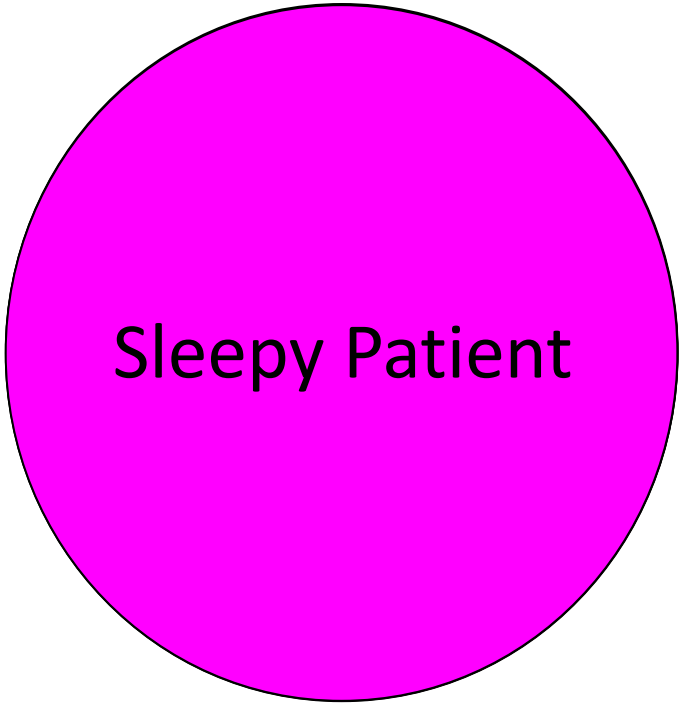
With thanks to Neil Freedman, MD and David Rye, MD, PhD

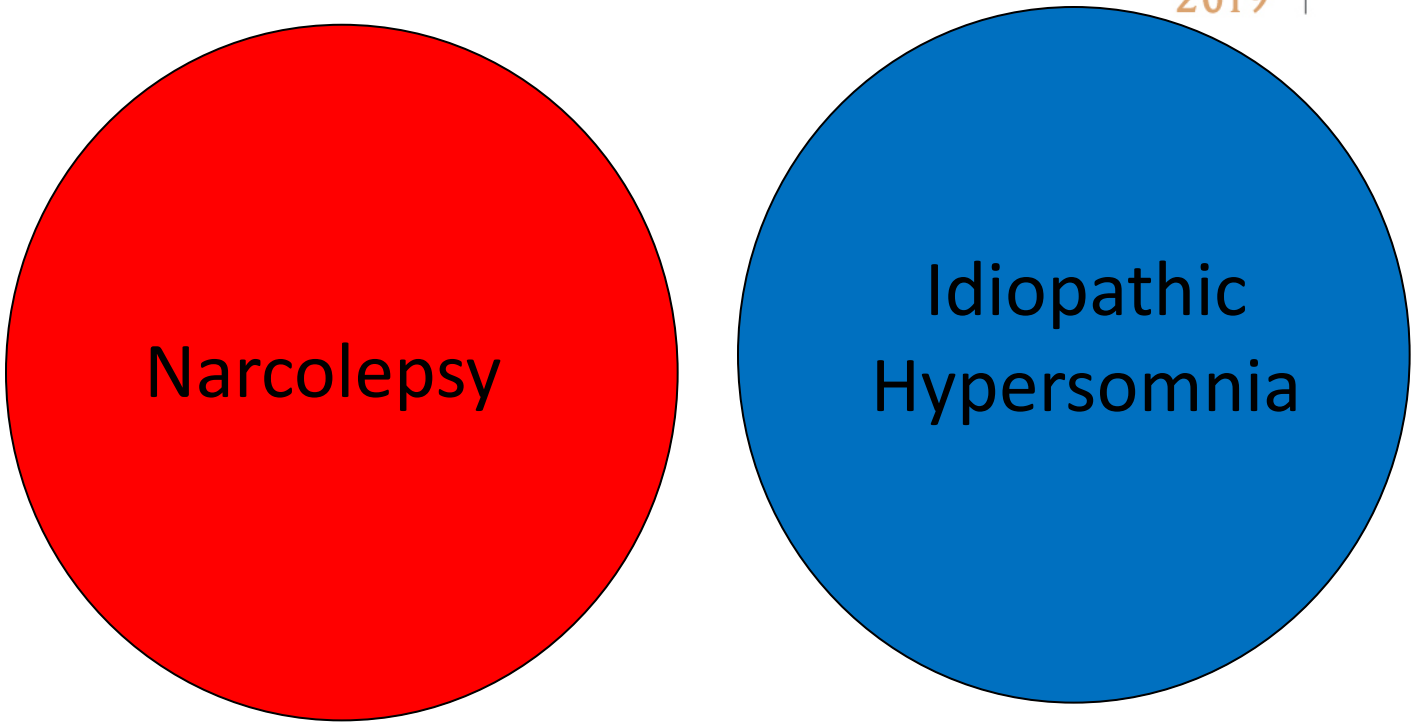
Once Upon a Time…..



As the Story Progressed…



And it Got Worse….



Kinda sorta sleepy

Tired with a blotchy rash

Extremely fatigued but not really "tired"

Falling asleep driving, but not while watching TV

Sleeping between 10 - 10.5 hours / day

Arthritis patients who have no energy

Thailand

Bangkok | 10-12 April

2019

Red-heads who can't stay awake

Tired lounge singers

Lack of energy & precisely 64% N2 sleep

Ex-NFL linemen with sleep inertia

Looks sleepy, but not really, unless you listen to the spouse

Only tired after eating pizza with GERD

Dog owners sleepier than their pets

Apnea with 2+ MSLT REMs

30-50 arousals from sleep per hour

Left-handed sleepy shift-workers

Listless men married to energetic

Octogenarians with diurnal sleep attacks

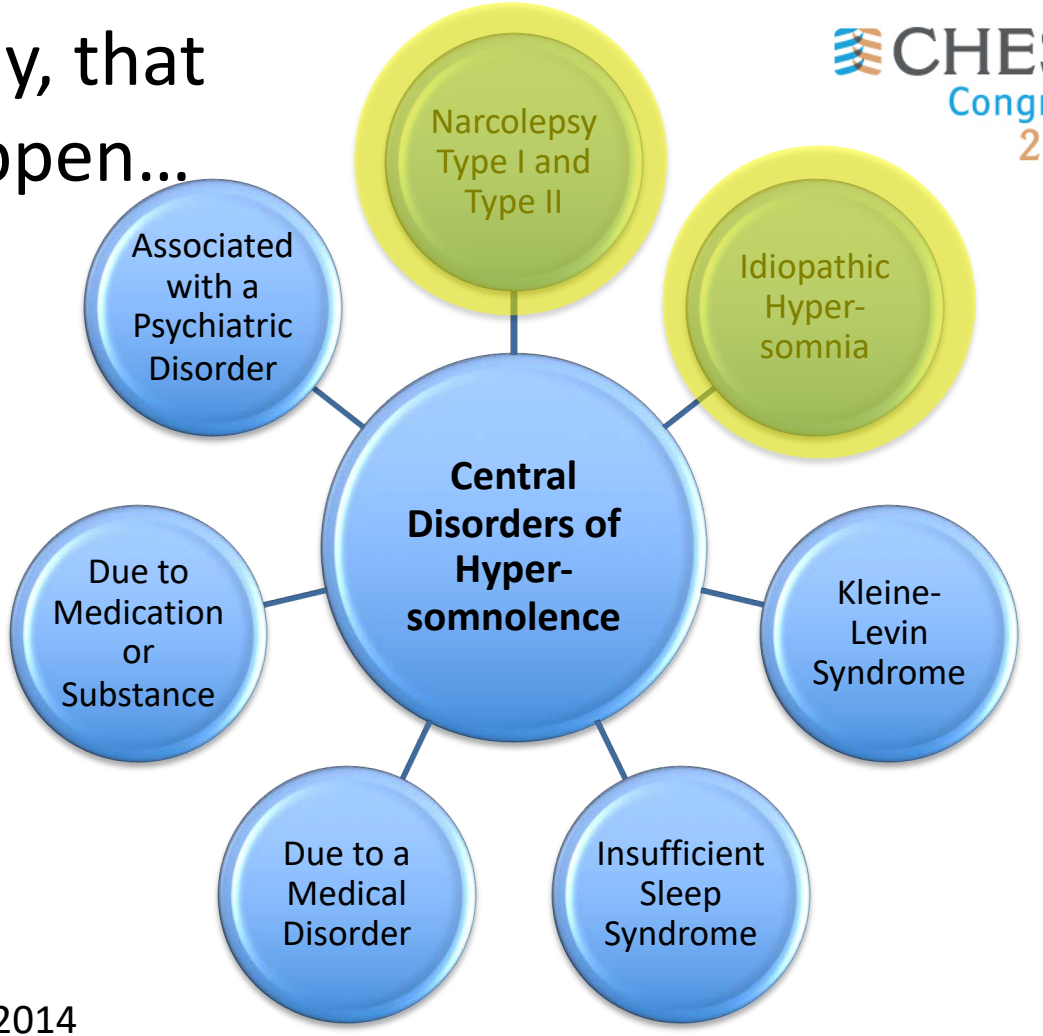
Sleepy sleep doctors

Basic cable reality show stars with

Residents of Nebraska who can't

"Two and a half men" starts with comorbid sleep drunkenness

Fortunately, that didn't happen…



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Case

- A 21 year old woman presents with long standing daytime sleepiness.
- She also reports intermittent lower extremity weakness that may be associated with laughter, though you are not able to reproduce it in clinic
- She regularly sleeps 8-9 hours per night and has no symptoms of OSAS, or insomnia
- Medications: None
- Exam: Normal
- An overnight PSG demonstrates:
  - TST 8.5 hours
  - REM latency of 70 minutes
  - No abnormalities are observed
- A multiple sleep latency test (MSLT) performed the following day demonstrates :
  - Mean sleep latency (MSL) of 6.5 minutes and 1 sleep onset REM period during the first nap

Question:

What other test would be most helpful to help confirm a diagnosis of narcolepsy?

A. HLA DQB1*0602
B. MRI of the brain
C. CSF hypocretin 1 (Orexin A) level
D. Maintenance of wakefulness test (MWT)

Question:

What other test would be most helpful to help confirm a diagnosis of narcolepsy?

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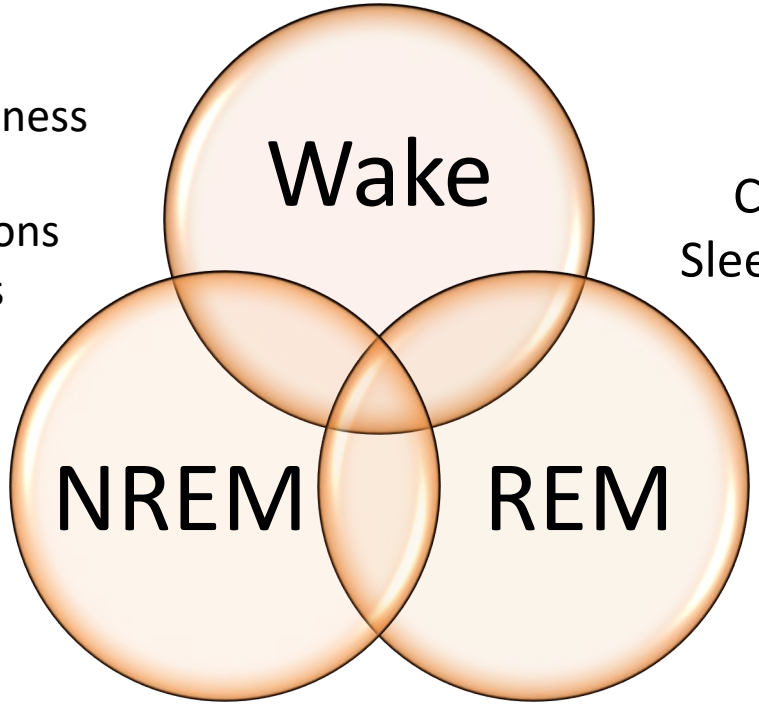
Narcolepsy

- Hallmark symptoms of Type 1 narcolepsy:
  - Excessive daytime sleepiness
  - Cataplexy (average time to onset from sleepiness ~ 4 years)
  - Hallucinations upon falling sleep or awakening from sleep (hypnagogic hallucinations)
  - Brief episodes of total paralysis upon falling asleep or awakening from sleep (sleep paralysis)
  - Disrupted sleep
- EDS is the most common initial symptom, occurring alone in ½ of patients

- >60% of patients present with only 1 hallmark symptom
- <10% of patients present with all 4 hallmark symptoms

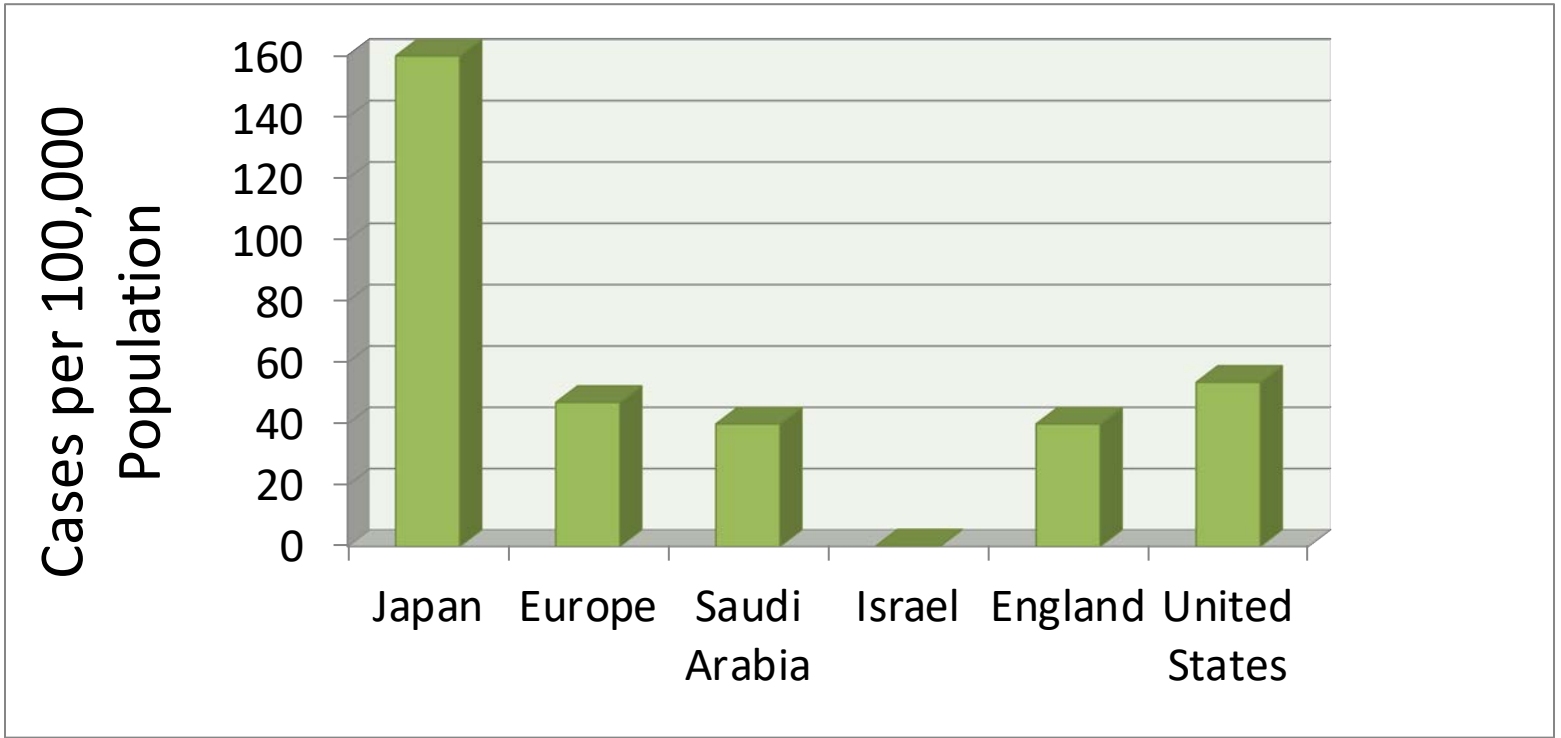
Many Symptoms of Narcolepsy Stem from the Loss of Sleep-Wake Boundaries

Excessive Daytime Sleepiness
Disrupted Sleep
Hypnagogic Hallucinations
Automatic Behaviors

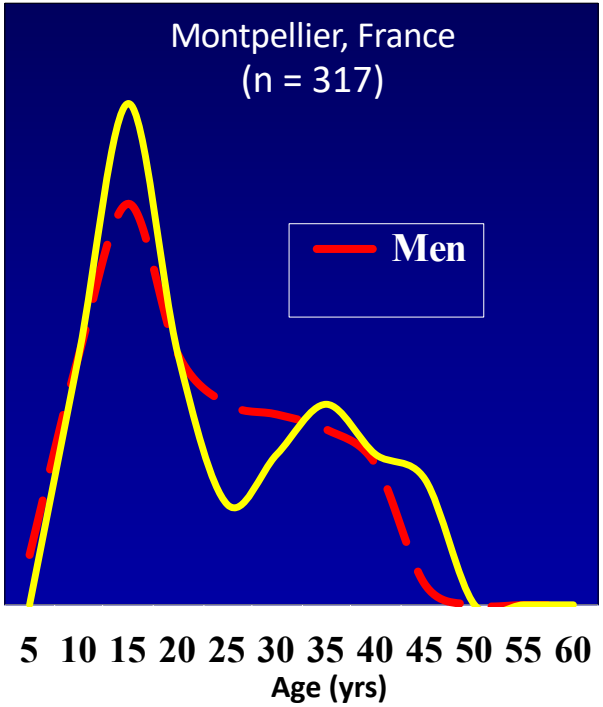


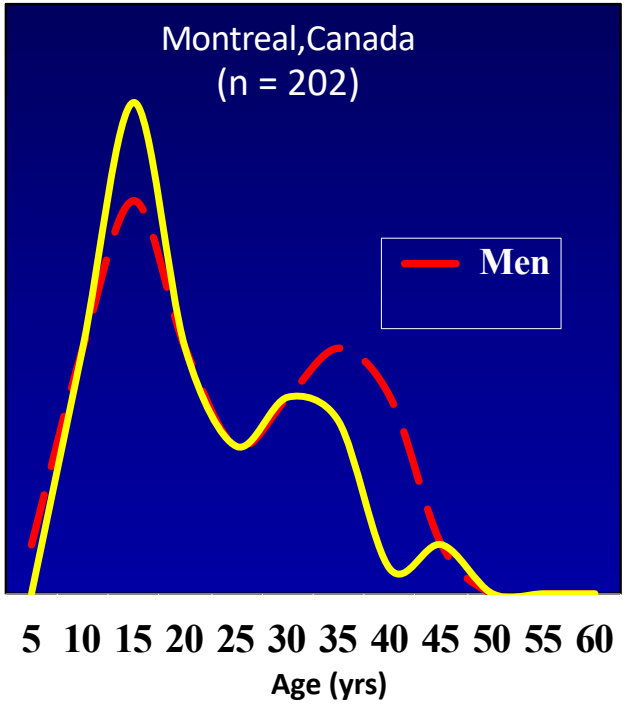
Cataplexy
Sleep Paralysis

Narcolepsy Prevalence Varies among Populations



Symptom Onset is Biphasic





Dauvilliers, Y et al. Neurology 2001;57:2029-33

Excessive Daytime Sleepiness

- Universal and most disabling symptom
- Typically the first symptom
- Transiently improved by nighttime sleep and daytime naps
  - As opposed to idiopathic hypersomnia
- May occur suddenly (sleep attacks)
- Despite EDS, the total sleep time per 24 hour period is similar to healthy adults

Cataplexy

- Sudden loss of bilateral muscle tone (partial or generaliz
- Full consciousness maintained during episode
  - Reflexes absent during episode
- Almost always associated with:
  - HLA DQB1-0602 + CSF hypocretin-1 deficiency
- Typically presents years (mean 1 to 5 yrs) after the onset of daytime sleepiness
- Typically triggered by emotion (not always)
  - Laughter most common
- Present in 60% to 90% of narcoleptics
- Virtually pathognomonic for narcolepsy

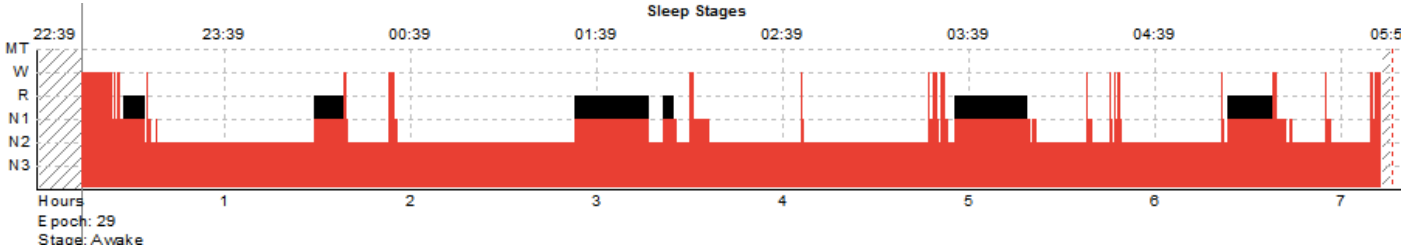
- Duration = Seconds to minutes
- Recovery is immediate and complete

Clinical Features are inadequate by themselves to diagnose Type 1 narcolepsy

Symptom	Sensitive	Specific
CATAPLEXY	NO	YES
SLEEP PARALYSIS	NO	NO
HYPNAGOGIC/HYPNOPOMPIC HALLUCINATIONS	NO	NO
SLEEPINESS	YES	NO
DISRUPTED SLEEP	YES	NO

Diagnostic Criteria for Narcolepsy Type 1

- Daily sleepiness for ≥ 3 months
- The presence of one of the following:
  - Cataplexy AND a MSL ≤ 8 minutes with ≥ 2 SOREMP on the MSLT
    - A SOREMP (within 15 minutes of sleep onset) on the preceding night's PSG may replace one of the SOREMPs on the MSLT



  - CSF hypocretin-1 concentration ≤ 110 pg/mL, or < 1/3 of mean values obtained in normal subjects

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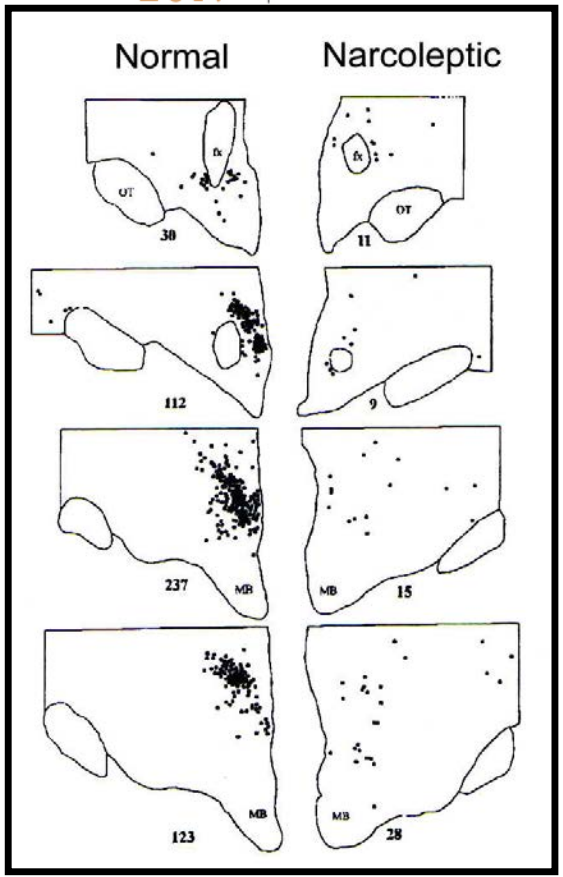
Reduced Number of Hypocretin Neurons in Narcolepsy with Cataplexy

- Specific loss of HCRT cells in the posterior and lateral hypothalamus
  - No significant difference in the number of melanin-concentrating hormone (MCH) neurons
- Presence of gliosis in HCRT cell region most consistent with a degenerative process
  - No clear evidence for immune activation



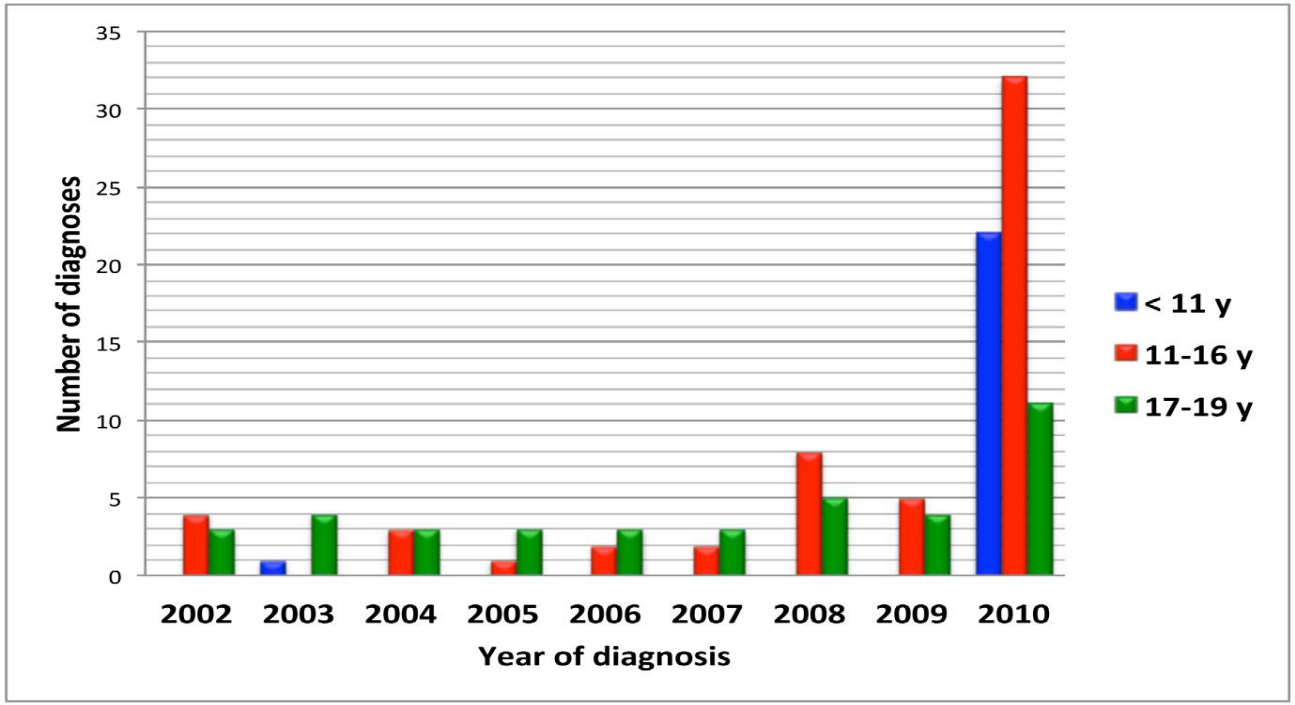
Thannickal, TC et al. Neuron 2000;27:469-74
Thannickal, TC et al. Sleep 2009;32:993-98

Mechanism of Disease and Hypocretin Deficiency Not Clear

- Possibly genetic
  - DQB1*0602 haplotype in 90% of narcolepsy 1
    - Only 25% of affected monozygotic twins concordant
    - Most familial cases (-) for HLA DQB1*0602

- Possibly autoimmune
  - Onset greatest in the spring / winter related viral infection
  - Association with polymorphisms in T cell receptor alpha genes

What causes hypocretin cell loss?



What causes hypocretin cell loss – molecular mimicry and H1N1?

Increased Incidence and Clinical Picture of Childhood Narcolepsy following the 2009 H1N1 Pandemic Vaccination Campaign in Finland

Markku Partinen et al. PLOS One (2011)

Narcolepsy Onset Is Seasonal and Increased following the 2009 H1N1 Pandemic in China

Fang Han et al. Annals of Neurology (2011)

CNS HCRT-1 Deficiency is Highly Specific for HLA+ Narcolepsy Type 1

- Sensitivity = 87%
- Specificity = 99%
- PPV and NPV = 96%
- Normal levels in other sleep disorders
  - OSA, RLS, insomnia, idiopathic hypersomnia
- May be useful diagnostically for atypical presentations, non-diagnostic MSLT, children and patients on antidepressants

Mignot, E. et al. Archives of Neurology 2002;59:1553-62

Diagnostic Criteria for Narcolepsy Type 2

- Daily periods of sleepiness for ≥ 3 months
- A MSL ≤ 8 minutes with ≥ 2 SOREMP on the MSLT
  - A SOREMP (within 15 minutes of sleep onset) on the preceding night's PSG may replace one of the SOREMPs on the MSLT
  - Polysomnographically indistinguishable for Narcolepsy Type I
- Cataplexy is absent
- CSF hypocretin-1 concentration, > 110 pg/mL, or > 1/3 of mean values obtained in normal subjects, or not measured
- The hypersomnolence and or MSLT findings are not better explained by other causes

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Narcolepsy Type 2

- Less prevalent than narcolepsy with cataplexy
  - 15% to 25% of diagnosed narcoleptics
- Association with HLA DQB1*0602 less than with narcolepsy type 1:
  - 45% vs 90%
- CSF hypocretin 1 levels normal
  - Underlying pathophysiology of most patients with narcolepsy type 2 not known; ? A manifestation of several underlying pathologies?
- Other:
  - If cataplexy develops later or CSF hypocretin 1 levels are found to be deficient at a later date, reclassify as narcolepsy type 1

Narcolepsy Treatment

- Goal of therapy is to treat symptoms
  - Sleepiness
  - Cataplexy, if present
- Stimulant therapy typically improves, but does not resolve daytime sleepiness in many/most patients with narcolepsy

Treatment of Type 1 Narcolepsy

Behavioral Strategies

- Short, regularly scheduled naps
- Consistent sleep / wake schedule
- Exercise for at least 20 minutes per day at least 4 or 5 hours before bedtime
  - Regular exercise for prevention of obesity important in children with narcolepsy
- Avoid alcohol, caffeine and nicotine for several hours before bedtime

Mullington and Broughton. *Sleep*. 1993;16:444-456.
Rogers et al. *Sleep*. 2001;24:385-391.
National Institute of Neurological Disorders and Stroke. Narcolepsy Fact Sheet. Available at: http://www.ninds.nih.gov/disorders/narcolepsy/detail_narcolepsy.htm. Accessed July 17, 2007.

Treatment of Type 1 Narcolepsy

Pharmacologic Interventions

- **Excessive Daytime Sleepiness**
  - Modafinil (Provigil®) and Armodafinil (Nuvigil®)*
  - Amphetamine /dextroamphetamine (Adderall®)/ methamphetamine (Desoxyn®)*
  - Methylphenidate* (Ritalin®; Concerta®)
  - Sodium oxybate* (Xyrem®)
  - Selegiline (Emsam®)
- **Cataplexy**
  - Sodium oxybate*
  - Selegiline
  - Serotonin-norepinephrine reuptake inhibitors (SNRIs)
  - Tricyclic antidepressants (TCAs)
  - Selective serotonin reuptake inhibitors (SSRIs)

*** Approved by the US FDA for the treatment of narcolepsy.**

Billiard et al. *Eur J Neurol*. 2006;13:1035-1048.
Littner et al. *Sleep*. 2001;24:451-466.

Modafinil

- Recommended as a standard by AASM for the treatment of daytime sleepiness
  - Supported by 14 studies
- Dosing: 100 to 400 mg daily
- Split-day dosing may be better for late day symptoms
- Half life = 15 hours
- May interact with birth control pills
  - Induces several cytochrome P450 enzymes
  - Need to recommend alternative birth control methods during treatment
- Pregnancy class C
- Should be taken without food

- Headache (10-26%)
- Nervousness/anxiety (3-20%)
- Nausea (5-11%)
- Dry mouth (3-7%)
- Insomnia (3-6%)
- HTN risk low
  - 1 study of OSA increased BP by 4%
- Stevens Johnson

Armodafinil

- Enantiomer of modafinil with longer half life
- FDA approved for the treatment of narcolepsy
- Dosing 150 to 250 mg once daily
- Data limited to 2 RCTs
  - Improved MWT, ESS and CGIC vs placebo
  - MWT increased 1.3 to 2.6 minutes vs placebo
- Side effects similar to modafinil
  - Headache most common (16 to 28%)
  - Dose related

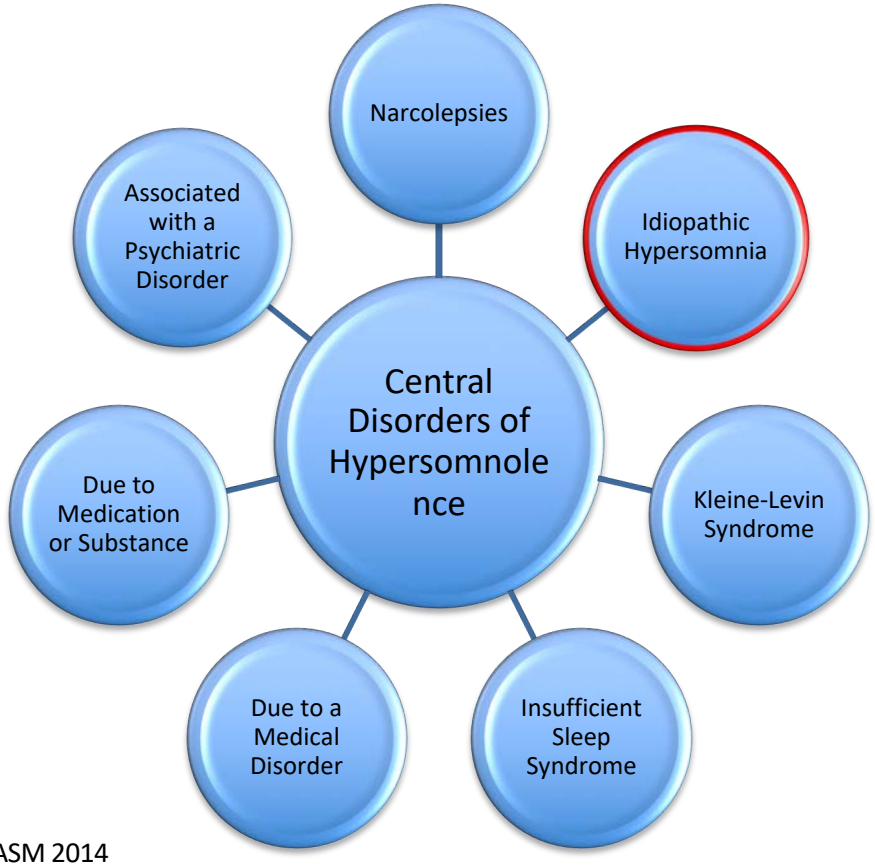
Sodium Oxybate

- Recommended as a standard for EDS/Cataplexy
- Mechanism: GABA-B and own receptors
  - Actual mechanism in narcolepsy not known
- Schedule III
- Divided dosing 4.5 to 9 grams/night
  - One dose at bedtime, another 3-4 hours later
- Important:
  - Improvements are dose dependent
  - Tolerance typically does not develop
  - No significant adverse events upon abrupt discontinuation
  - No withdrawal or rebound cataplexy
- Pregnancy category C
- Contraindications:
  - Succinic semialdehyde dehydrogenase deficiency
  - Sedative hypnotics, ETOH, CNS depressants
- Adverse Effects: (dose related)
  - Most common: Dizziness (12-34%), nausea (6-34%) and headache (23%)
  - Other: Enuresis, vomiting, anorexia, backpain, edema, acute confusional state, falls, elevated LFTs, weight loss
- Very low risk of abuse, misuse and dependence

Treatments for Cataplexy

Agent/Class	Daily Dose Range	AASM Recommendation
Sodium Oxybate	4.5 to 9 grams	Standard
Tricyclics	Various	Guideline
SSRIs	Various	Guideline
Venlafaxine	75 – 375 mg	Guideline
Reboxetine	?	Guideline
Selegiline	5 -10 mg	Option

Morgenthaler, TI et al. Sleep 2007;30(12):1705-1711
Wise, MS et al. Sleep 2007;30(12):1712-1727



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Diagnostic Criteria for Idiopathic Hypersomnia

- Daily periods of sleepiness for ≥ 3 months
- Cataplexy is absent
- The MSLT demonstrates < 2 SOREMPs or no SOREMPs if the REM latency on the preceding PSG was ≤ 15 minutes
- The presence of at least one of the following:
  - The MLST demonstrates a MSL of ≤ 8 minutes or
  - Total 24 hour sleep time is > 660 minutes on 24 hour PSG monitoring or by wrist actigraphy in association with a sleep log (averaged over at least 7 days without sleep restriction)
- The hypersomnolence and or MSLT findings are not better explained by other causes (including insufficient sleep syndrome)

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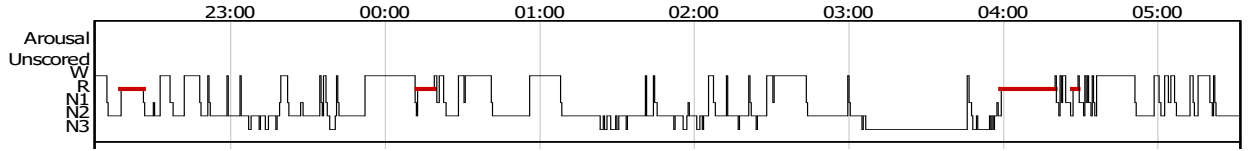
Idiopathic Hypersomnia

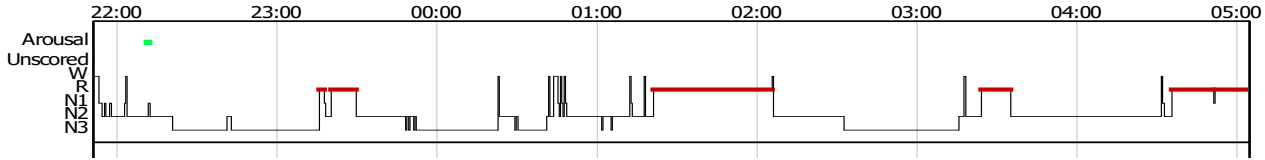
- Previously classified into “with and without long sleep time” – no longer
- Prevalence unknown
- Prolonged and severe sleep inertia common
- Unrefreshing naps and nighttime sleep periods
- A high sleep efficiency (> 90%) on the PSG is common
- No association with HLA DQB1*0602 or other HLA
- Normal CSF hypocretin 1 levels
- Family history in minority (34%)
- Spontaneous resolution described, but uncommon (14-25%)

PSG of Narcolepsy vs IH

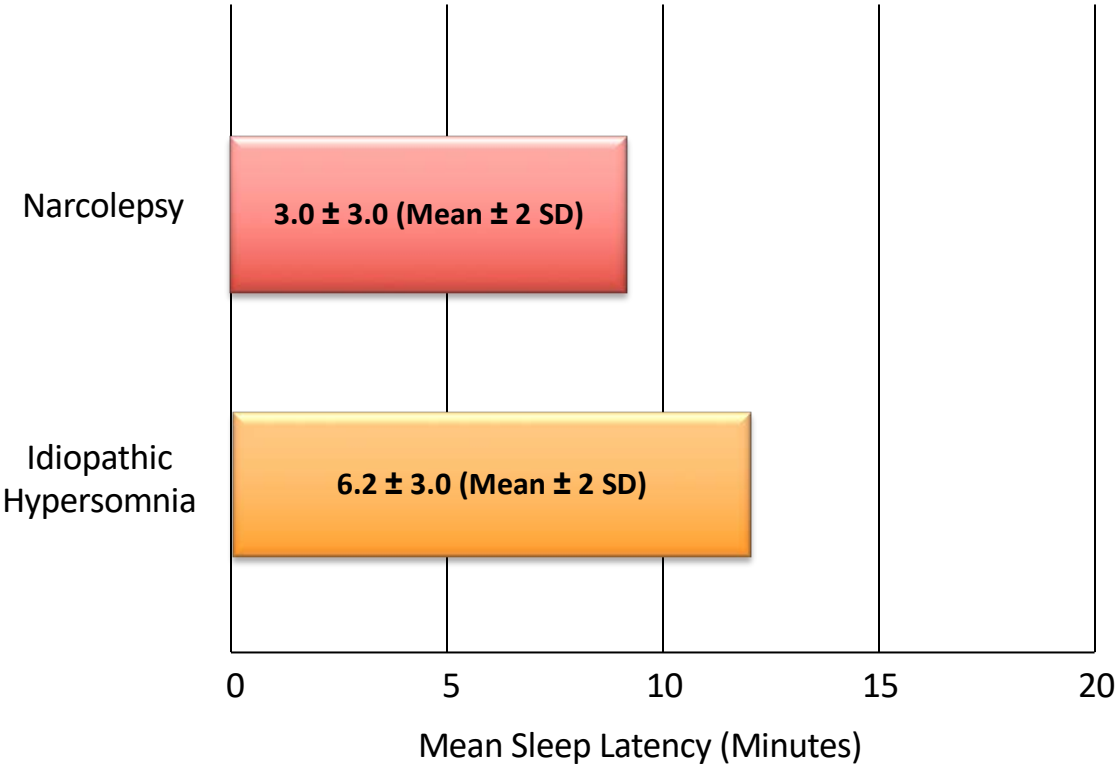
Narcolepsy Type I



Idiopathic Hypersomnia



MSLT:MSL Greater in IH than Narcolepsy

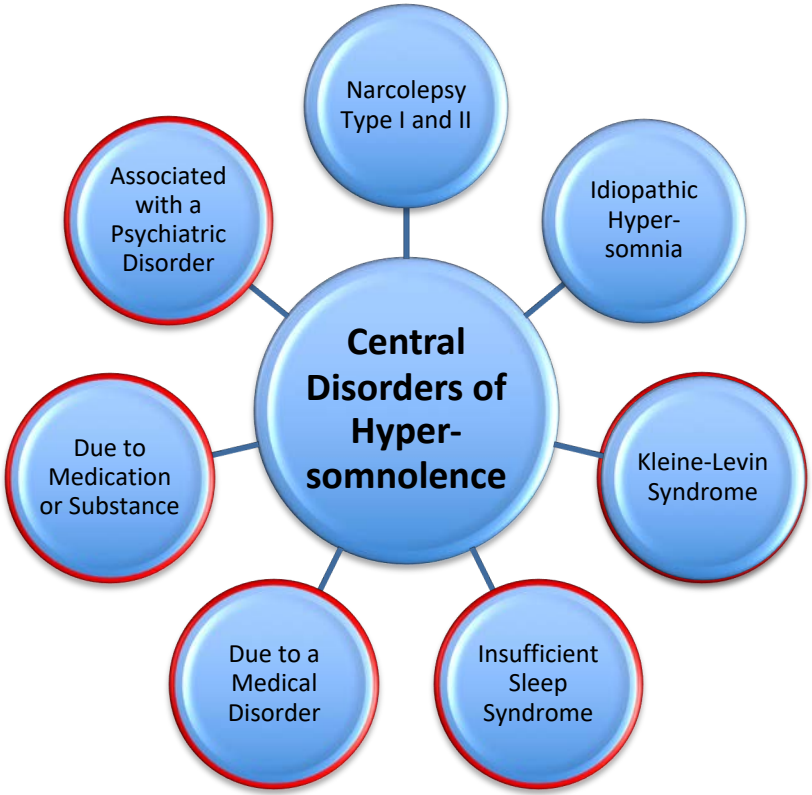


Idiopathic Hypersomnia: Treatment

- Treatment approach similar to EDS with narcolepsy
- No FDA approved drugs for IH
- Modafinil, armodafinil
- Amphetamines and methylphenidate

- Possible role for clarithromycin or flumazenil

Morganthaler, TI et al. Sleep 2007;30:1705-1711
Mayer G et al. J Sleep Res 2015;24:74



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Question

- Which one of the following statements is TRUE?
  - A) Narcolepsy Type II is a disease whose pathophysiology has been well-characterized
  - B) The number of sleep-onset REM periods (SoREMPs) can be used to distinguish Narcolepsy Type I from Narcolepsy Type II
  - C) Patients with Idiopathic Hypersomnia tend to be sleepier (and more refractory to therapy) than patients with Narcolepsy Type I or Narcolepsy Type II
  - D) There are no stimulant therapies that have been deemed to be safe in pregnancy

Question

- Which one of the following statements is TRUE?
  - A) Narcolepsy Type II is a disease whose pathophysiology has been well-characterized
  - B) The number of sleep-onset REM periods (SoREMPs) can be used to distinguish Narcolepsy Type I from Narcolepsy Type II
  - C) Patients with Idiopathic Hypersomnia tend to be sleepier (and more refractory to therapy) than patients with Narcolepsy Type I or Narcolepsy Type II
  - D) There are no stimulant therapies that have been deemed to be safe in pregnancy

	Type 1 Narcolepsy	Idiopathic Hypersomnia
Prevalence	1: 2,000	Unknown – rare (?) (1:400) ?
Age of Onset	Pre-pubertal Teens Twenties	Pre-Pubertal Teens Twenties Adulthood
Course	Modestly Progressive Plateaus in 30s	More likely progressive
Remissions	NONE	RARE (15%)
Heritability	Minimal (4 x risk to 1^0 relative)	Modest (~ 1/3 rd of subjects with 1^0 relative)
Treatments	Wake promoting agents (e.g., psychostimulants; modafinil; Xyrem®)	Wake promoting agents, possible role for sleep "lytics" (e.g., **$GABA_A$ receptor** antagonists) ?

	Type 1 Narcolepsy	Idiopathic Hypersomnia
Excessive Daytime Sleepiness	Imperative	Not as imperative
Daytime Sleep Duration	Minutes	Hours
Daytime Naps	With REM-sleep (dreams)	ABSENT REM-sleep
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	LABORIOUS

	Type 1 Narcolepsy	Type 2 Narcolepsy	Idiopathic Hypersomnia
Excessive Daytime Sleepiness	3 months	3 months	3 months
Cataplexy	YES (60-95%)	NO	NO
MSL < 8 minutes	YES	YES	YES (40%) / NO (60%)
≥ 2 SOREMPs	YES	YES	NO ≤ 1 SOREMP
CSF Hypocretin < 110 pg/ml	YES	NO	NO
660’ of total sleep time (PSG + MSLT)	NO (normal)	Some (?)	YES
660’ average total Sleep time 1 week	NO (normal)	N/A (?)	YES

Thank you for your kind attention!