Diagnosis and Treatment of Pediatric Hypersomnia Disorders

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DISCLOSURES

- Dr. Maski has received research support from Jazz Pharmaceuticals, Inc Dr. Maski has served as a consultant to Jazz Pharmaceuticals, Alkermes and Harmony Biosciences
- I will be discussing off-label medications for narcolepsy and IH
- Royalties from UptoDate

NARCOLEPSY

NARCOLEPSY OVERVIEW

- Narcolepsy Type 1 (NT1, narcolepsy with cataplexy)
- Narcolepsy Type 2 (NT2, narcolepsy without cataplexy)

- NT1 is caused by loss of hypocretin neurons in lateral hypothalamus

- Characterized by the following:

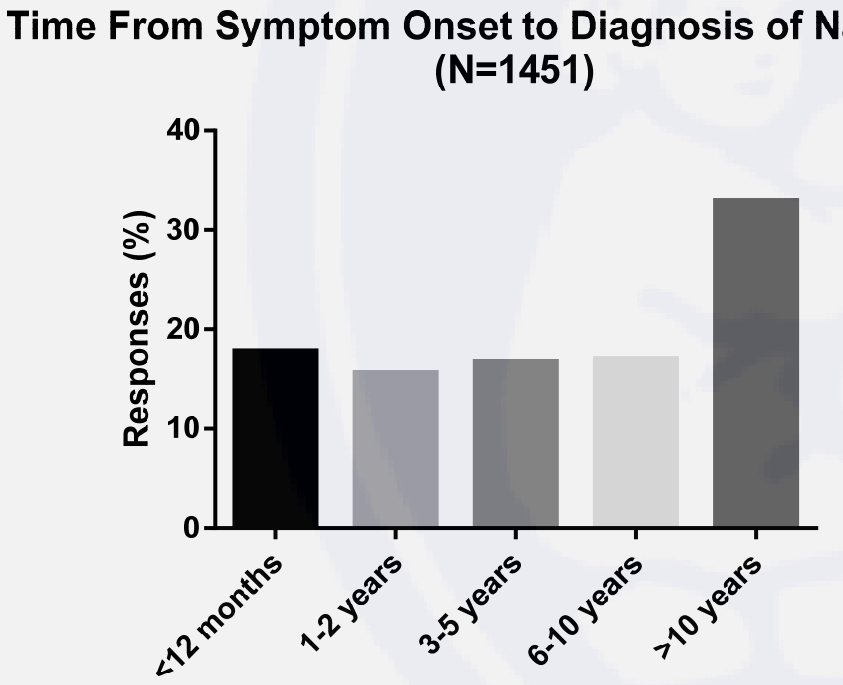
  - Sleep and wake state imbalance
    - Excessive daytime sleepiness (100%)
    - Disrupted nighttime sleep (30-90%)

  - Cataplexy (sudden episodes of loss of muscle tone typically with emotion, 50-70%)
  - Sleep paralysis (20-30%)
  - Hypnogogic and hypnopompic hallucinations (20-30%)

International Classification of Sleep Disorders, version 3; Mitler M et al. 1990; Silber M et al., 2002;Pizza F et al. 2013; Kim LJ et al. 2015; Ohayon M et al. 2013

Video

DIAGNOSTIC DELAY



- In 2013 a survey of patients with narcolepsy:
- 50% of narcolepsy patients reported it took >5 year to reach diagnosis
- Factors that contribute to delay
  - Pediatric onset of symptoms (OR=2.4)
  - No cataplexy (OR=1.8)

Maski K et al. JCSM 2017

INTERNATIONAL CLASSIFICATION OF SLEEP DISORDERS (ICSD)

Narcolepsy Type 1 (Narcolepsy with Cataplexy). A and B must be met

A. EDS for at least 3 months.

*Validated questionnaires encouraged such as Epworth Sleepiness Scale-CHADD, Pediatric Daytime Sleepiness Scale

Wang YG. Nat Sci Review 2017, Yang CN Clin Psych Neurosci 2010

B. At least <u>one</u> of the following:

- Cataplexy and a positive Multiple Sleep Latency Test (MSLT)*
- Low CSF hypocretin-1 concentrations (≤110 pg/ml or <1/3 of normal)
  - Mayo to offer clinical testing as of April 2019

Narcolepsy Type 2 (Narcolepsy without Cataplexy). A and B must be met

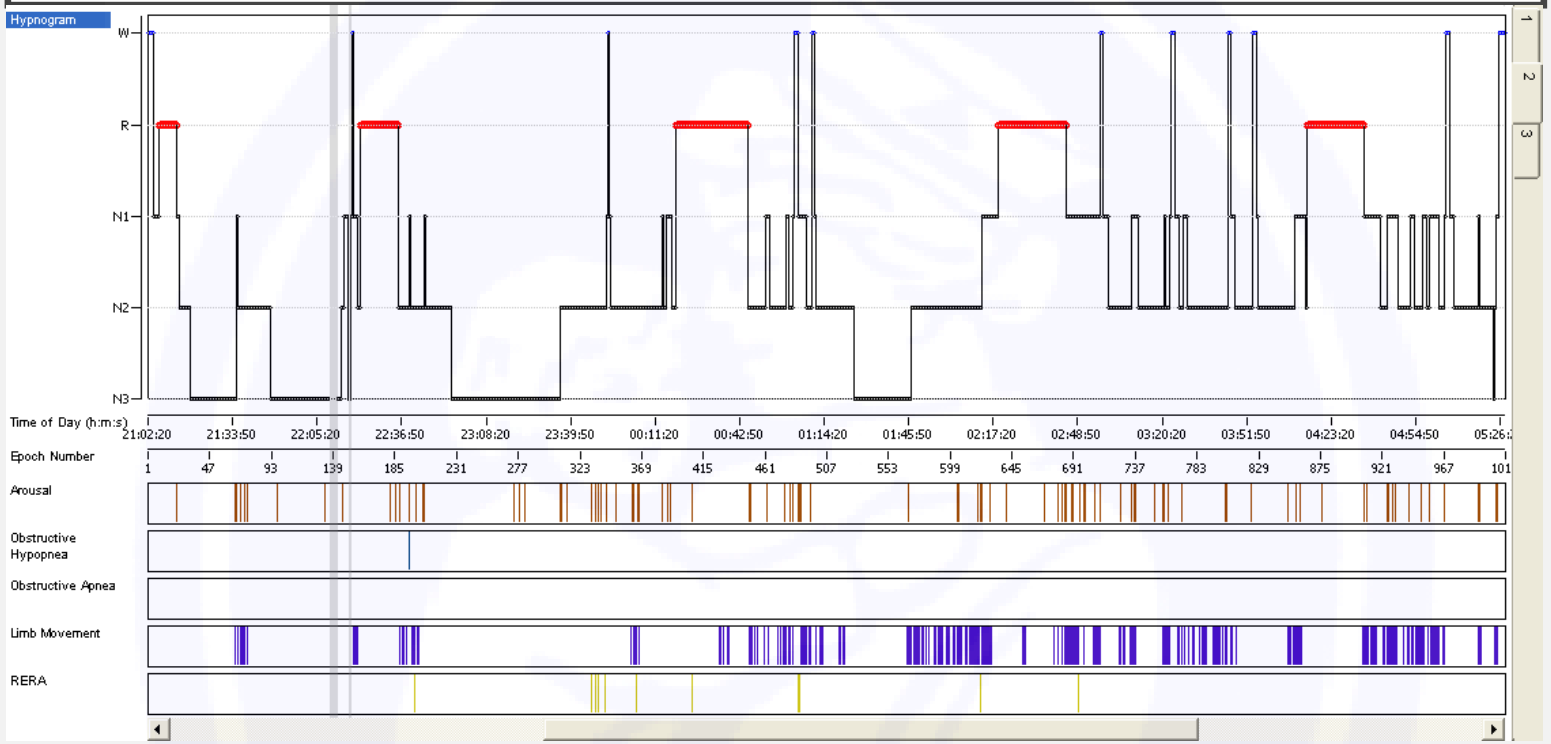
A. EDS for at least 3 months*.

B. Positive MSLT**

**<u>Positive MSLT</u> : mean sleep latency of ≤8 minutes <u>and</u> ≥2 SOREMP's.

A SOREMP on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.

NOCTURNAL POLYSOMNOGRAM

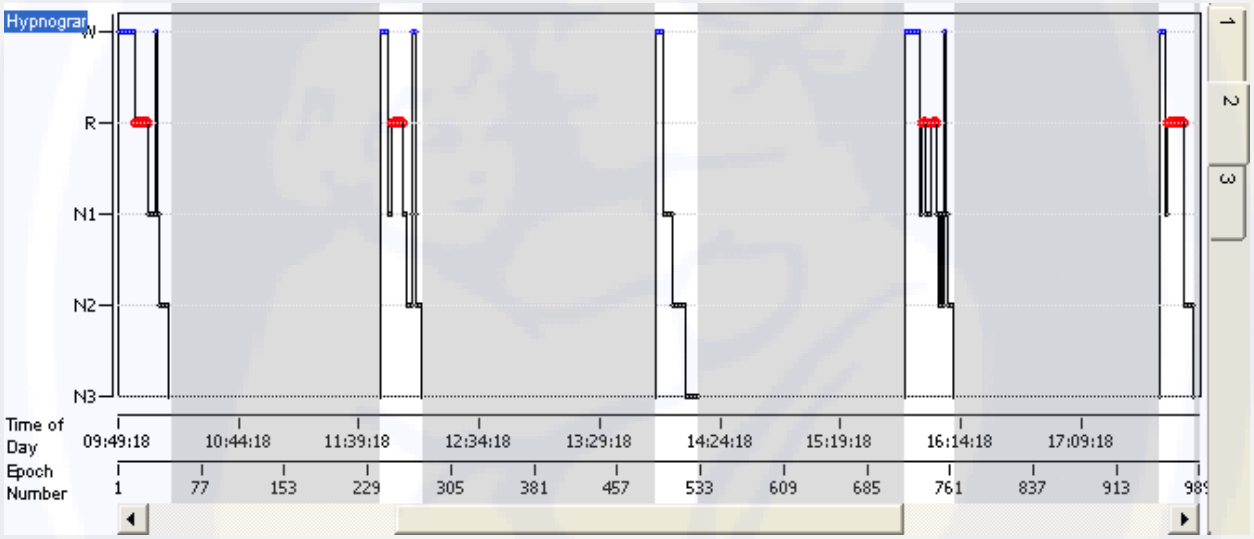


Nocturnal sleep onset REM period (REM ≤ 15 minutes from sleep onset)

- Sensitivity 47% and specificity 97%

Andlauer O JAMA Neuro 2013, Reiter J SLEEP 2015, Christensen J Sleep Med 2015, Bin Hasan J Clin Sleep Medicine 2018

Multiple Sleep Latency Test



-MSLT includes a series of four to five "opportunities". Each nap opportunity is 20 minutes long.

MEDICAL CO-MORBIDITIES

- Obesity (25-60%)
- Precocious puberty in children (16-40%)
- Obstructive sleep apnea (9-25%)
- ADHD symptoms (35%)
- Mood Disorders (depression, anxiety, OCD, social phobia; 25%)
- Hypertension in 58% of treated patients and 41% of untreated patients
  - Percentage of REM sleep associated with hypertension across both groups
- Other: peripheral neuropathy, headache, psychiatric disorders, endocrinopathies

Poli F SLEEP 2013; Sansa Sleep Med 2010, Cohen A Sleep Med 2018, Bosco A Neurology 2018

NON-PHARMACOLOGIC TREATMENTS

- One or two 15-20 min naps are often helpful (sometimes during school or work)
- Avoid sleep deprivation, phase shifts, sedating medications, heavy meals
- Movement Breaks
- Support!
  - Wake Up Narcolepsy, Hypersomnia Foundation, Narcolepsy Link, Project Sleep, Narcolepsy Network
- Anticipatory guidance (accident risk/driving safety)
  - Great variability in practitioner assessments of driving safety

Ingram DG. Sleep Breath 2019

TREATMENT OF EXCESSIVE SLEEPINESS: TRADITIONAL STIMULANTS

	Dose	Side Effects
Methylphenidate (Ritalin, Concerta, Metadate)	-10-60 mg/day IR Divided dosing BID, TID -ER (18-54 mg) -Appx 1 mg/kg/day	irritability, headaches, insomnia, GI upset, hypertension, arrhythmias, anxiety, psychosis
Mixed amphetamine salts (Adderall) FDA approved	5-60 mg/day Divided BID or ER -Appx 0.5 mg/kg/day	same, reduced appetite, weight loss, psychosis* *2x higher than MP
Lisdexamphetamine (Vyvanse)	30-70 mg/day About 1/3 potency of mixed amphetamine	Same, Hyperhidrosis, skin rash, dry mouth

*Moran LV NEJM 2019

TREATMENT OF EXCESSIVE SLEEPINESS (OFF LABEL FOR CHILDREN)

	Typical dose	Side effects
Modafinil (Provigil)	50-200 mg BID	HA, nausea, nervousness, insomnia, rash SJS, hypertension, OCP interaction
Armodafinil (Nuvigil)	50-250 mg qAM	Same
Solriamfetol (Sunosi)	75-150 mg q AM	HA (21%), Increased HR, BP, Nausea/diarrhea (11%), anxiety (5%)
Pitolisant (Wakix)	17.8 to 35.6 mg qAM	HAs, insomnia, irritability, anxiety, nausea (all <10%)
Sodium oxybate (g-hydroxybutyrate, Xyrem)	2.25-4.5 g qhs, and 3-4 hours later	OSA/hypoventilation, depression, SI, psychosis AE: Nausea, hallucinations, dizziness, OSA, weight loss/gain

TREATMENT OF CATAPLEXY

	Typical dose	Side effects
Venlafaxine (Effexor)	37.5-325 mg XR qAM (IR formulation BID)	Serotonin syndrome, SI risks, Weight gain, nausea
Fluoxetine (Prozac)	20-60 mg qAM	Same, dry mouth, sexual dysfunction
Protriptyline (Vivactyl)	5 mg TID (max 60 mg/day)	Anticholinergic effects, Cardiac arrhythmia, abnormal LFTs
Sodium oxybate (g-hydroxybutyrate; Xyrem) Off label for children	2.25-4.5 g twice nightly	REMS: OSA/hypoventilation, depression, SI, psychosis, driving safety Nausea, hallucinations, dizziness, OSA, weight loss/gain

FUTURE THERAPIES: OREXIN AGONISTS

- Orexin Receptor 2 Agonist (TAK 925) restored wakefulness, eliminated cataplexy and improved sleep/wake cycling in mouse models of narcolepsy (OX deficient)
- Oral formulation (TAK 994) in clinical trial
  - Phase 1 results (mild Aes only)
  - N=14 NT1 patients showed significantly improved objective and subjective improved sleepiness
  - N=56 sleep deprived adults showed improved wakefulness

Yukitake et al. Pharmacol Biochem Behav 2019; Abstract World Sleep Congress September 2019

IDIOPATHIC HYPERSOMNIA

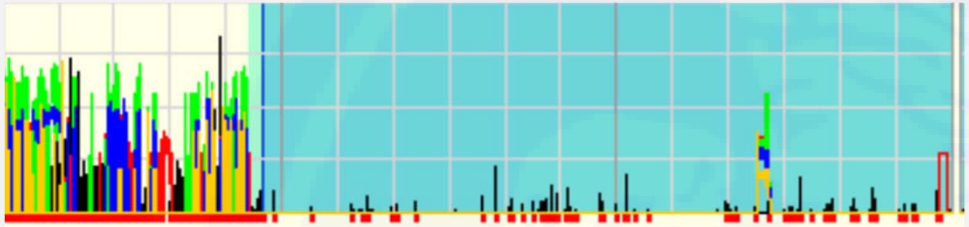
OVERVIEW

- Pathologic excessive daytime sleepiness (EDS) with or without prolonged sleep duration
  - Sleep inertia
  - "Brain Fog"
- True incidence/prevalence of IH is unknown
- Family History
  - 34-38% of IH patients report a family member with a CNS hypersomnia condition or EDS
- Pathophysiology is unknown
- Normal neurological exam. No specific neuroimaging findings identified
  - Diagnosis of exclusion
- Up to 25% of IH patients outgrow condition

Ohayon MM Ann Neurol 2013; Trotti LM Clin Neurol Neurosurg 2017; Trotti LM Sleep Med 2017

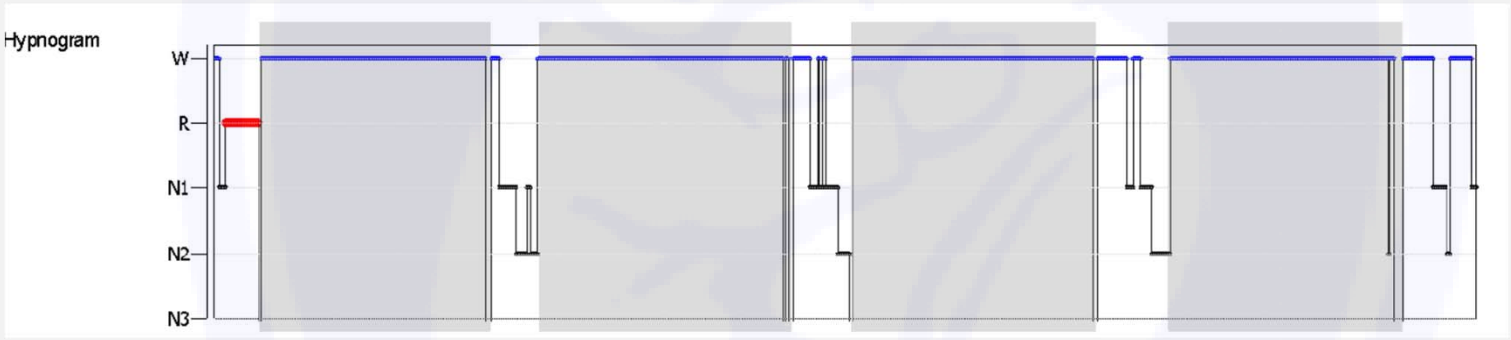
DIAGNOSTIC TESTING OPTIONS ICSD

- Actigraphy



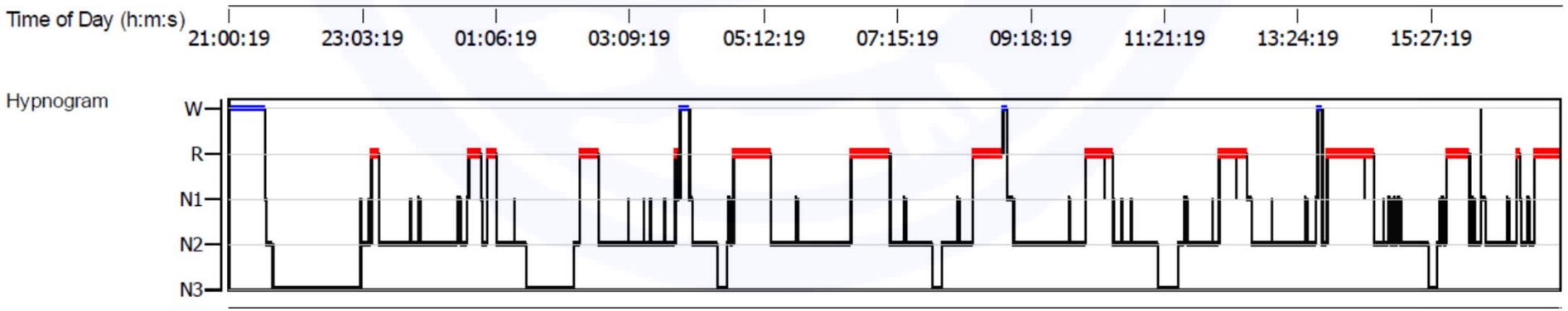
Average total sleep time ≥660 minutes over 1 week

- MSLT (multiple sleep latency test)



Mean sleep latency ≤8 minutes

- Extended Polysomnogram : Average total sleep time ≥660 minutes



Reliability of MSLT for IH patients is poor

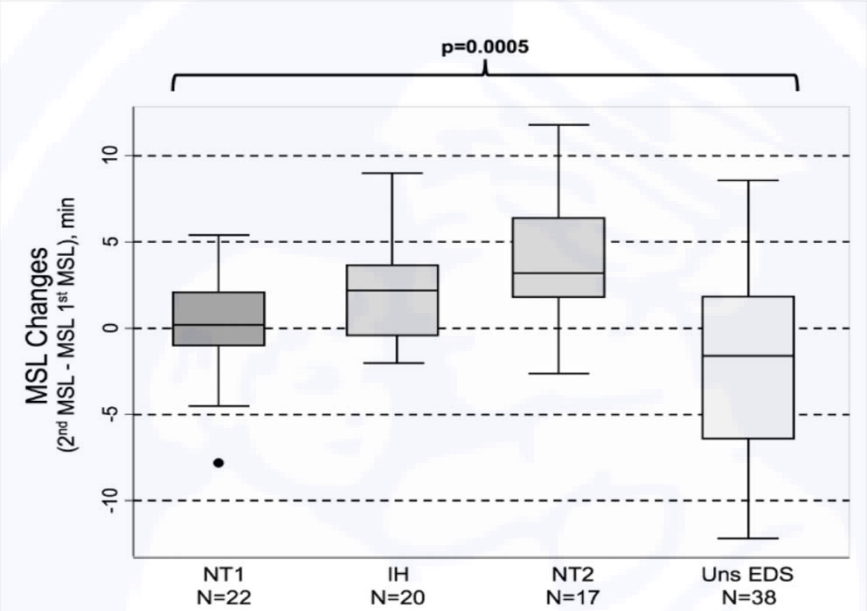


Figure 1—Changes in mean sleep latency (MSL) between the second and first MSLT in patients with narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), idiopathic hypersomnia (IH), and unspecified hypersomnolence (unspecified excessive daytime sleepiness [UnsEDS]).

- More variability between tests for NT2, IH and subjective sleepy patients than NT1 patients
  Classification consistency for IH at MSLT retesting only 25%!
- Alternative testing: 32 hour protocol of continuous PSG
  - 19 hour cut-off displayed sensitivity and specificity (92% and 81%) for IH
  - Reliability testing not conducted

Lopez R et al. SLEEP 2017; Evangelista E Ann Neurol 2018

POSSIBLE PATHOPHYSIOLOGY OF HYPERSOMNIA: GABA-A MODULATION

- Altered GABA signaling found in patients with hypersomnia patients
  - Using in vitro whole cell voltage clamp assay, CSF from hypersomnia patients showed enhanced GABA-receptor function (compared to CSF of sleep deprived healthy controls)
    - Flumazenil GABA-A receptor antagonist) reversed GABA-A signaling in 7 hypersomnia patients (significant improvement in vigilance and subjective alertness
      - Rye D et al. Sci Transl Med 2012
- Replication of study showed no difference in GABA receptor potentiation with CSF from patients with IH, NT1, and controls.
  - Dauvilliers Y et al. Ann Neurology 2016

MANAGEMENT

- Non-pharmacologic Strategies
  - Caffeine (limit to AM)
  - Ensure sufficient nocturnal sleep
  - Naps
    - Avoid Long naps as naps generally not refreshing
  - Cognitive behavior therapy (depression, management of hypersomnia)
  - Academic Support (504 plan)
  - Support!
    - Hypersomnia Foundation
  - Spontaneous remission reported in 14-32.5% of IH patients
    - Trotti LM et al. Sleep Med 2017
  - Anticipatory Guidance

TREATMENT OF EXCESSIVE SLEEPINESS IN IH:
NO FDA APPROVED MEDICATION FOR IH (OFF LABEL)

	Dose	Evidence
Methylphenidate	10-60 mg/day IR Divided dosing BID, TID -ER (18-54 mg) -Consideration of Jornay PM for sleep inertia (20 mg); no data	41% report improvement Ali et al JCSM 2009
Mixed amphetamine salts	5-60 mg/day Divided BID or ER	Pooled analysis: 33% (5/15) responded to treatment Trotti LM Sleep Med 2017
Modafinil	100-400 mg qAM or 200 mg BID	RTC data available showing decreased driving problems and improved wakefulness. Pooled analysis: 63% (124/197) report good response Phillip P SLEEP 2014; Trotti LM Sleep Med 2017

Refractory IH Treatments (off-label)

Clarithromycin (negative allosteric modulator of GABA-A rec)	500 mg BID (breakfast/lunch) Side effects: GI, abx resistance, bad taste,	RCT. • No difference in primary outcome measure (PVT) • Improved ESS (mean 4 points) • Improved QOL Trotti LM Ann Neuro 2015
Flumazenil	Compounded • Lozenges 6 mg qid • Cream 1 ml of 12 mg/ml before bedtime (or more) • Side effects: LFT elevation, dizzy, anxiety, HA, cog dysfunction, paresthesia, weight change, nausea	Observational (n=36 IH/153 total with avg use 8 months • 63% report benefit • Improved ESS (mean 5 points) Trotti LM JCSM 2016
Others: sodium oxybate, levothyroxine, pitolisant, transcranial direct current stimulation		Small cases series

KLEINE-LEVIN SYNDROME

OVERVIEW

- Rare, relapsing debilitating hypersomnia (long sleep time, avg 18 hours) lasting 2 days-5 weeks
  - Recur typically q1-3 months
- Accompanied by cognitive, behavioral, psychiatric disturbances
  - Depersonalization, derealization, aggression, regression, sensory disturbances, apathy, sexual inhibition
  - Inattentive, motor coordination, impaired working memory
- Changes in eating (hyperphagia, anorexia)
- Normal between bouts
- Typically starts in adolescence

KLEINE-LEVIN SYNDROME

Diagnosis criteria for Kleine-Levin syndrome

Kleine-Levin syndrome is defined by the presence of all the following criteria:

A. The patient experiences recurrent episodes of 2 days to several weeks duration, with severe sleepiness.

B. Episodes recur usually more than once a year and at least once every 18 months.

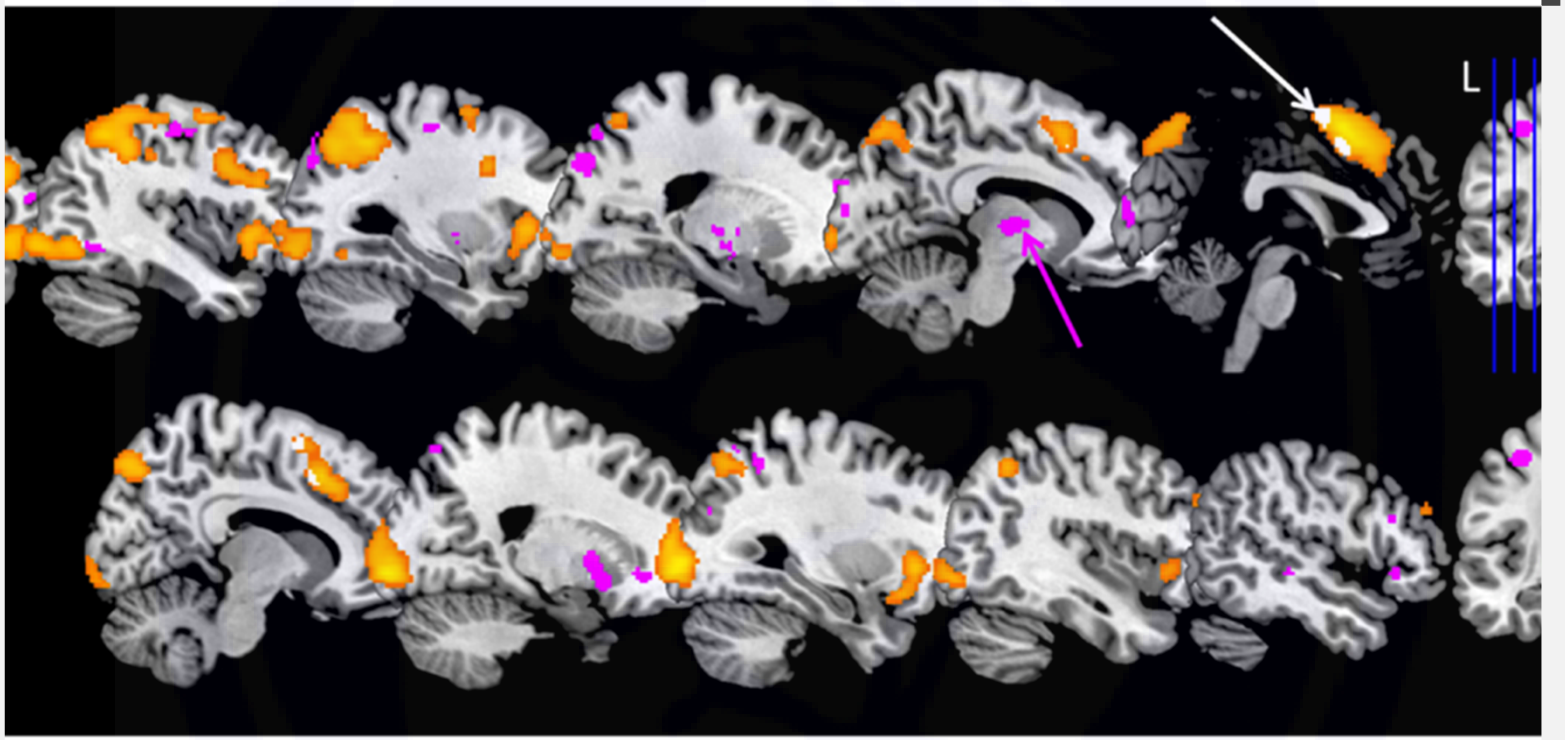
C. The patient has normal alertness, cognitive function, behavior, and mood between episodes,

D. Patients must demonstrate at least one of the following during episodes: cognitive dysfunction, altered perception (mostly derealization), eating disorder (anorexia or hyperphagia), disinhibition (such as hypersexuality)

E. The symptoms are not better explained by another sleep disorder, depression, or bipolar disorder; the effects of medications or drugs; metabolic disorders; or other neurologic, medical, or mental disorders.

From American Academy of Sleep Medicine. The International classification of sleep disorders, 3rd edition. Darien (IL): American Academy of Sleep Medicine; 2014; with permission.

NEUROIMAGING SHOWS MORE GLOBAL DYSFUNCTION



Neuroimaging studies vary
fMRI of working memory task shows:
Hyperactivation (pink): thalamus
Hypoactivation (orange): anterior cingulate, medial pre-frontal cortex (others temporal, occipital, parietal on PET)

Engström M et al SLEEP 2014; Dauvilliers Y PLos 2014

MANAGEMENT

- Avoid Triggers
  - Sleep deprivation, illness, alcohol, marijuana, head trauma
- Anticipatory Guidance
  - Allow patient to sleep
  - Return to school when back to baseline
  - Needs supervision during KLS bouts
    - Behavioral abnormalities, altered perception, automatic behaviors
  - Avoid driving/heavy machinery
  - Monitoring so patient stays hydrated/eats meals/voids
- Support
  - 504 plan
  - KLS Foundation

Arnulf I. Sleep Med Clin 2015.

KLS Drugs (off-label)	Indication	Success
Amantadine	Shorten/abort bouts of KLS	42% (may lose effect over time)
Depakote/lamictal/ Tegretol	Reduce KLS cycling/shorten bouts	20-21%
Lithium	-Reduce KLS cycling -Frequent Bouts (4-12/year)	41%
Risperdal	Severe behavioral/psychiatric problems with KLS	Case reports; not effective for KLS syndrome
Stimulants (amphetamines> methylphenidate)	Reduce sleepiness	20-71% (may make agitated, mood worse)

Arnulf, I et al. BRAIN 2005; Arnult I Lance Neurol 2012

PROGNOSIS

- After several episodes, bouts may change to be less excessive sleepiness and more behavioral/cognitive changes
- More frequent KLS bouts in childhood
- Mean disease duration 13.6 (4.3) years
- Typically ends in mid 30s

CONCLUSIONS

- Patients with hypersomnia disorders often suffer delayed diagnoses and misdiagnosis
  - Using office based tools and diagnostic protocols correctly important to reduce confounding factors
- Limitations of MSLT testing NT2 and IH
  - Consider alternative protocols for IH (actigraphy, continuous PSG)
- Supportive care and anticipatory guidance is critical for all hypersomnia conditions
- As we gain more knowledge on the underlying physiology of these disorders, more specific treatments can be offered