Narcolepsy in Pediatrics

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Child Neurology and Sleep Medicine

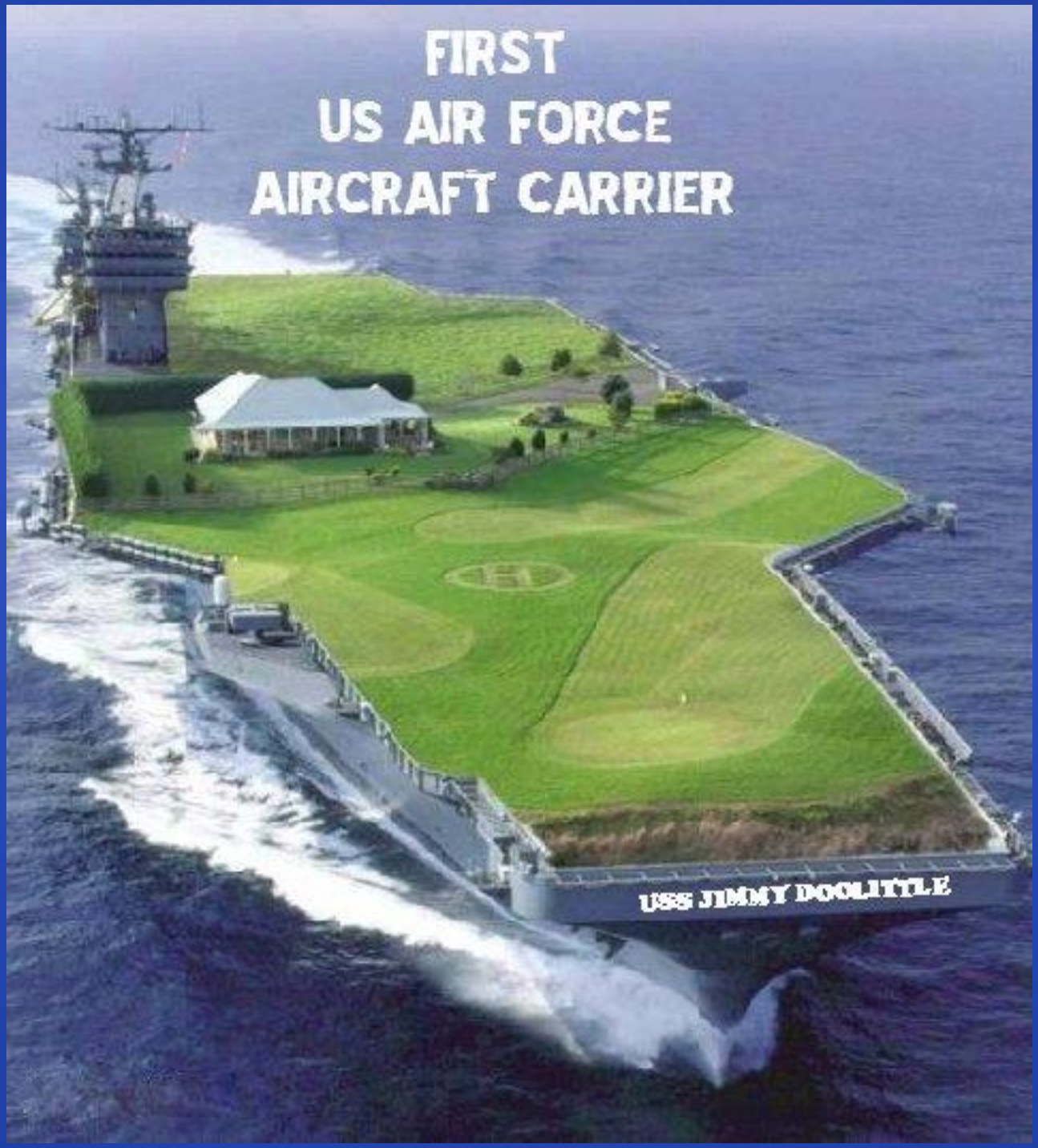
Conflict

Research/Speaker JAZZ Pharmaceuticals

Pediatric study of Sodium Oxybate in Children with Narcolepsy

I WILL discuss use of sodium oxybate in children

- Treatment of dyssomnias and parasomnias in childhood.
- Kotagal S.
- Curr Treat Options Neurol. 2012 Dec;14(6):630-49. doi: 10.1007/s11940-012-0199-0.
- PMID: 23011807


FIRST
US AIR FORCE
AIRCRAFT CARRIER
USS JIMMY DOOLITTLE

Case

- 15 year old high school student
- Great student, until high school, when became increasingly fatigued, tired, sleepy.
- Most severe is sleepiness- she will fall asleep multiple days a week at school, often multiple times a day.
- Not systemically ill.
- Grades slipping, moody, and increasing concern by parents that something is seriously wrong.

Case

- Medical Hx-unremarkable. No fevers, weight loss- in fact she has had 15 pound weight gain over past 6 months.
- Mood- frustrated, and admits to being down a lot secondary to grades, and how hard it is to stay awake.
- ROS? What do you want to know?
- No other HEADSS stuff.
- What is sleep story for her?

Case

- Sleep Hx
  - Teenager who usually naps after school, unless has practice.
  - If she does, comes home afterward- then naps 1-2 hours.
  - Naps- help sometimes, but only for short time.
  - Often stays up late, or will fall asleep early, only to wake on and off through the night. (sleep time-? 7 hours).
  - Sleep is frustrating- cannot sleep when she wants, falls asleep (it seems) most days.
  - She snores sometimes, it is not loud, no pauses/gasping episodes. (Does not wake household).
  - When she wakes up, no real relief, (or brief) – she feels she could simply go back to sleep.

Case

- Medical Hx
  - Boring- healthy teenager in general.
  - No history of concussion, trauma.
  - She has no surgical history
  - Has seen cardiology for near-syncope event that occurred at volleyball practice. Completely normal evaluation.
- Social Hx
  - Lives with parents, younger sibling at home. Likes school, has friends, and denies any acute new stressors.
- Family Hx
  - No history of similar phenotype in family members. Well, mom is really sleepy, but she is always running kids, working at school, getting dinner ready. Of course she is sleepy!
  - No hx of epilepsy, cardiac disease.

Exam

- Normal Vital Signs, though weight gain as noted.
- SHEENT- unremarkable, with no apparent obstruction.
- The rest of exam– NORMAL.

- What is her problem? What differential diagnosis?

Hypersomnia

- Systemic Illness- Thyroid, cancer, Anemia, CFS, Hypoglycemia, Lupus…
- Drugs
- Depression/Mood Disorder
- Sleep Diagnoses?
  - OSA, Inadequate Sleep(Delayed Sleep Phase Syndrome), Insomnia, Narcolepsy

ICSD-3 Hypersomnias

- Narcolepsy type 1(Narcolepsy with Cataplexy)
- Narcolepsy type 2(Narcolepsy without Cataplexy)
- Idiopathic hypersomnia
- Kleine-Levin syndrome
- Hypersomnia due to a medical disorder
- Hypersomnia due to a medication or substance
- Hypersomnia associated with a psychiatric disorder
- Insufficient sleep syndrome

More Hx

- Detailed Hx---the sleepiness is remarkable to her and family, this is just not normal.
- If she is not “engaged”, she can fall asleep in minutes just about anywhere.
- What is your sleep like?

Hypersomnia

Sleep at night is often easy to achieve, but can be fragmented or even like I am not sure I am asleep. Regardless of how long I DO sleep, I am very sleepy all day. I wake pretty much ready to go to sleep again, right now.

If I am sitting in the car, in front of TV, in class, and I do NOT do something to sort of, keep myself busy, I can fall asleep in a few minutes.

I don't - if I am under the watchful eye of a stern teacher, since I know I will get busted. But if they do not care, and I do not care, I am falling asleep.

Hypersomnia

- Despite sleep time, naps, etc.
- CAN have scenarios where patients are able to combat it.
- Not the same as fatigue/energy- actually have a powerful tendency to fall asleep.
- Often missed/misinterpreted: where it occurs, teacher (apathy), mood, normal to nap?, ADHD, mask with behavior- or medicines.
- Worsens over time.
- SCORE this with Epworth Sleepiness Scale

Pediatric Epworth

Table 1: Modified Epworth Sleepiness Scale

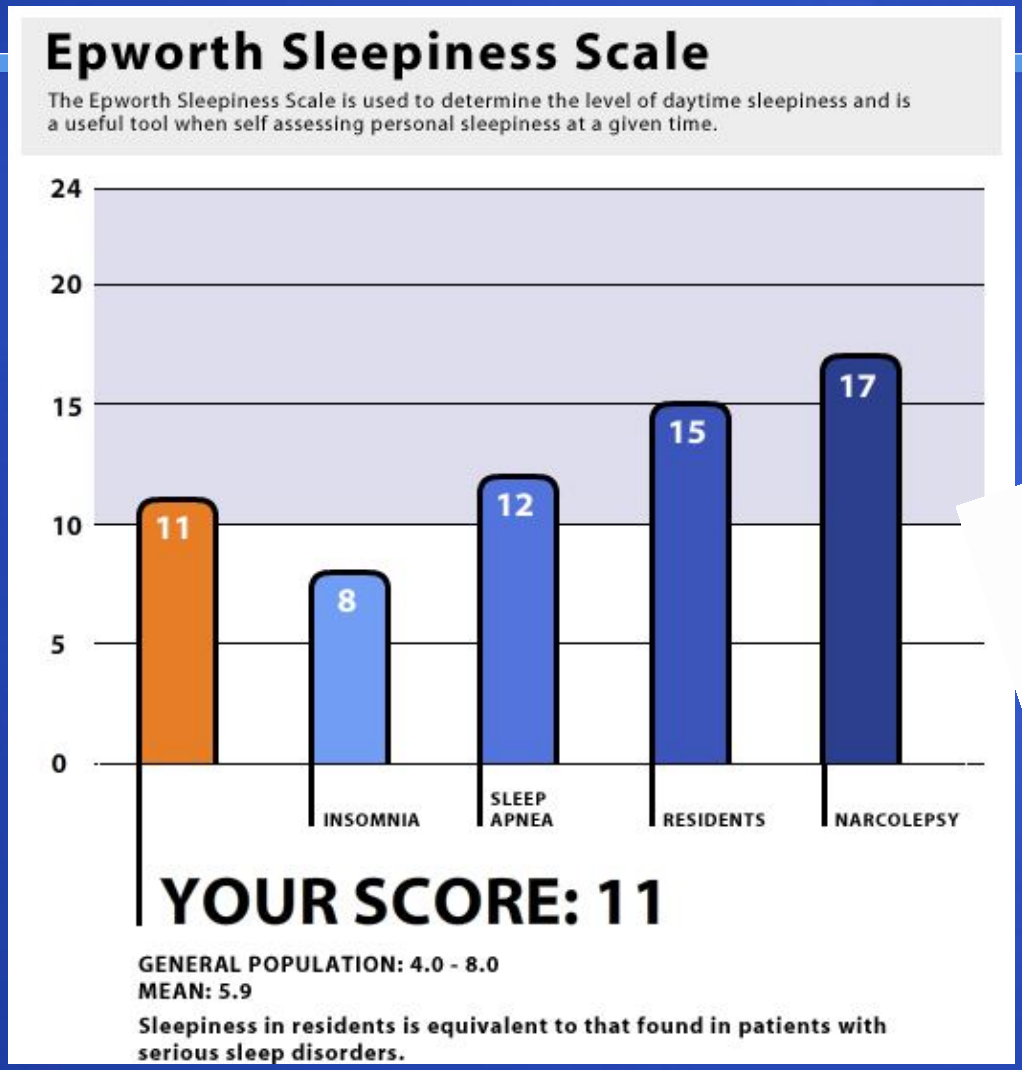
Situation	Chance of Dozing
Sitting and reading	
Watching TV	
In the classroom	
As a car passenger for an hour without a break	
Lying down to rest in the afternoon	
Sitting and talking to someone	
Sitting quietly after lunch	
During a short break from an activity that requires alertness (e.g. playing a game, during a test, climbing something)	

Scoring: 0-3 with 0=unlikely, 1-slight, 2- moderate, 3- high

Scoring

- “normal” less than 10.
- Average(adults) 6
  - OSA 8-12 typical
- Differences in grade-schooler, adolescent, adult.
- Narcolepsy- often 15 or higher.
- Remember to have child/parent team fill this out.

Scoring-10 is cut off…



Our patient—Epworth Sleepiness Scale-- 16

History

- Do you dream?
- Do you ever have dreams that are, weird? Or very realistic? Or, have you ever had an episode prior to falling asleep when you saw, heard, felt something- only to realize it was not real?
- Have you ever acted on a dream. Gone to check on sibling, or make sure a parent checked the house.
- What is this like?
- Ever have dreams with really powerful emotion tied to them?

HH/Vivid Dreams

- Dream content is vivid and realistic.
- Often not shared with parents- it is weird, scary.(feel things, figures, shadows, hear steps, monster or demon).
- At wake/sleep transition- ever hear, see unusual things?
- Dreams may lead to misperception(thought I did my chores, called my friend, intruder was in our home).
- Often, (not always) disturbing content, and usually very strong emotional reaction to dreams.
- “Have you ever woken from a dream and started to act on content of your dream?”

Hypnagogic Hallucinations and Vivid Dreams

Dreamer on beach with son
Intruder in home
Wake ready for school
Shadows, or your sister

Stuck

- Have you ever had an episode where you woke from sleep, and you could not get up, move, turn?
- Have you ever felt like this as you fell asleep?
- In or coming out of a dream?
- Ever experience this, and found someone touching you "releases" the paralysis?
- Ever see, feel, hear things during this?

Paralysis

- May not be sure they are awake or asleep.
- Seconds to minutes, then often fall back asleep and wake just fine.
- Can be very frightening- often accompanied by visual or auditory hallucination.
- So, they may not share this- unless you ask.
- Touch may release paralysis.

  “the witch riding you”

In Mexico, it's believed that sleep paralysis is in fact the spirit of a dead person getting on the person and impeding movement, calling this "se me subió el muerto" (the dead person got on me).

In Iceland folk culture sleep paralysis is generally called having a "Mara". Mara is an old Icelandic word for a mare but has taken on the meaning for a sort of a devil .

In African American culture, isolated sleep paralysis is commonly referred to as "the devil riding your back"

Cataplexy

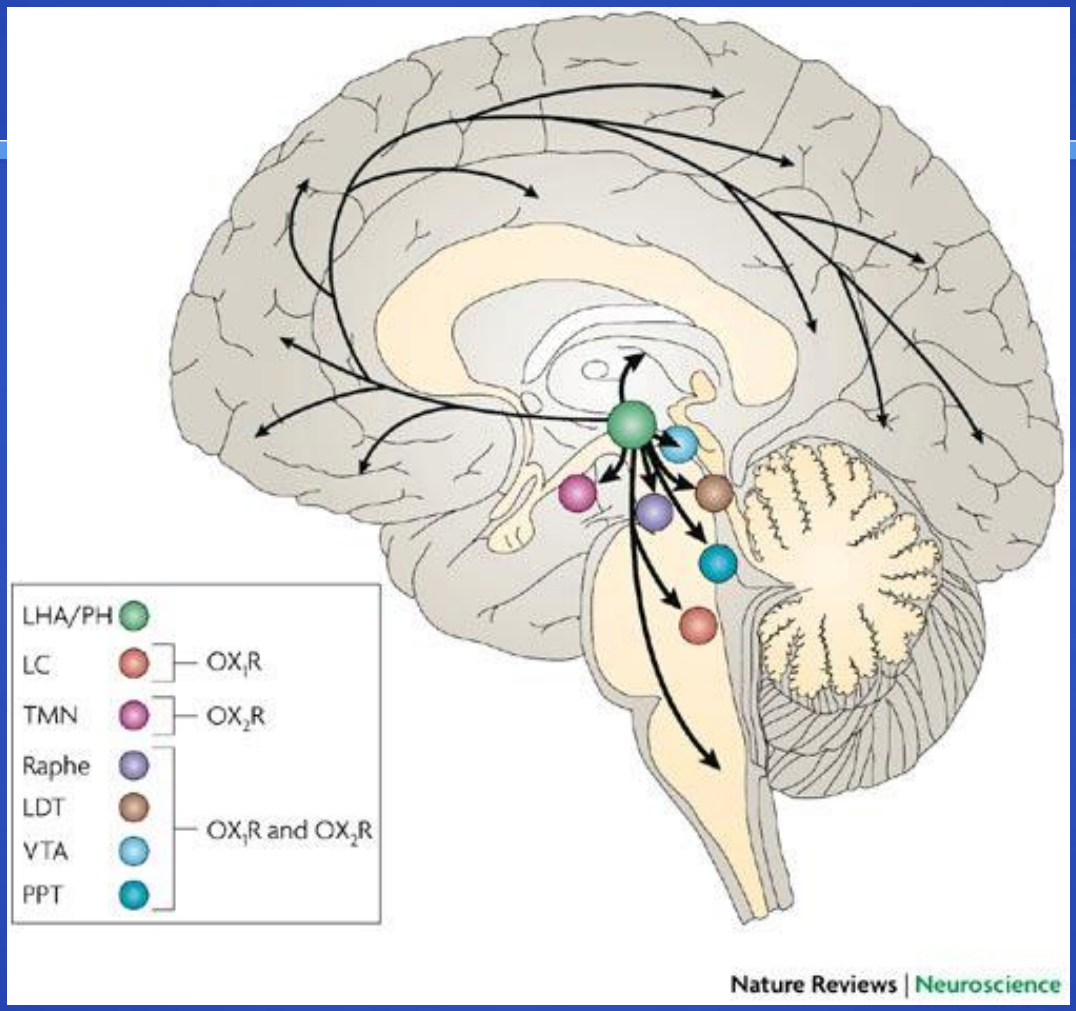
- NOT usually, “laugh and I fall down”.
- IS usually triggered by emotion: laughter, anger, surprise, startle. ANY emotion!
- *Preserved consciousness- must ask patient*.
- Fragmentary; head nod, jaw slack, stuttering/halting or “drunken” speech, drop object, lean, “weak in knees”, short of breath, chest discomfort, just looks dazed briefly when laughs.
- Seconds, to minutes and then recover.
- Usually symmetric, descending.
- Often misinterpreted(near-syncope, atonic seizure, or “normal-laugh so hard I almost fall”, he/she often sags, leans, sits when laugh, conversion disorder?

Examples

- Football out on playground
- Stolen phone
- Angry at brother
- Dad and I wrestling, fight back
- Zone outs, weird way kids can look

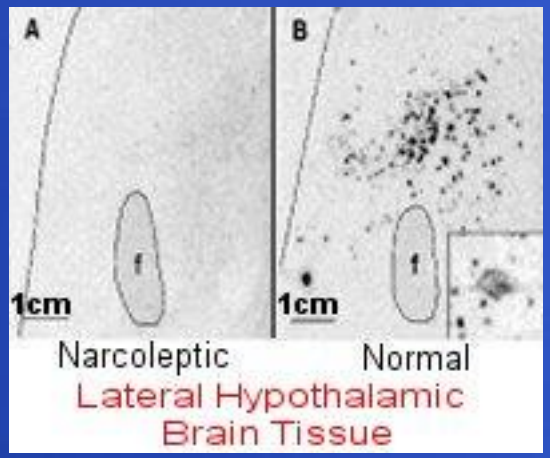
Narcolepsy

- Classic tetrad (fragmented/disturbed nocturnal sleep?)
- Sleep state instability- wake/sleep/REM.(Very sleepy during day, but often fragmented and disturbed sleep at night).
- Not a rare disorder, 1 in 2,000.
- Peak incidence- symptoms most often reported to have onset between 7-25, but diagnosis often takes years. Peak diagnosis teens, and 30s.
- HLA DQB1*0602, Genetics, Japan and Israel.
- Autoimmune theory- susceptible patients with some trigger that attacks/destroys cells in hypothalamus that produce hypocretins.
- These neuropeptides(hypocretin 1 and 2) are critical in maintaining wakefulness, but also affect metabolism.

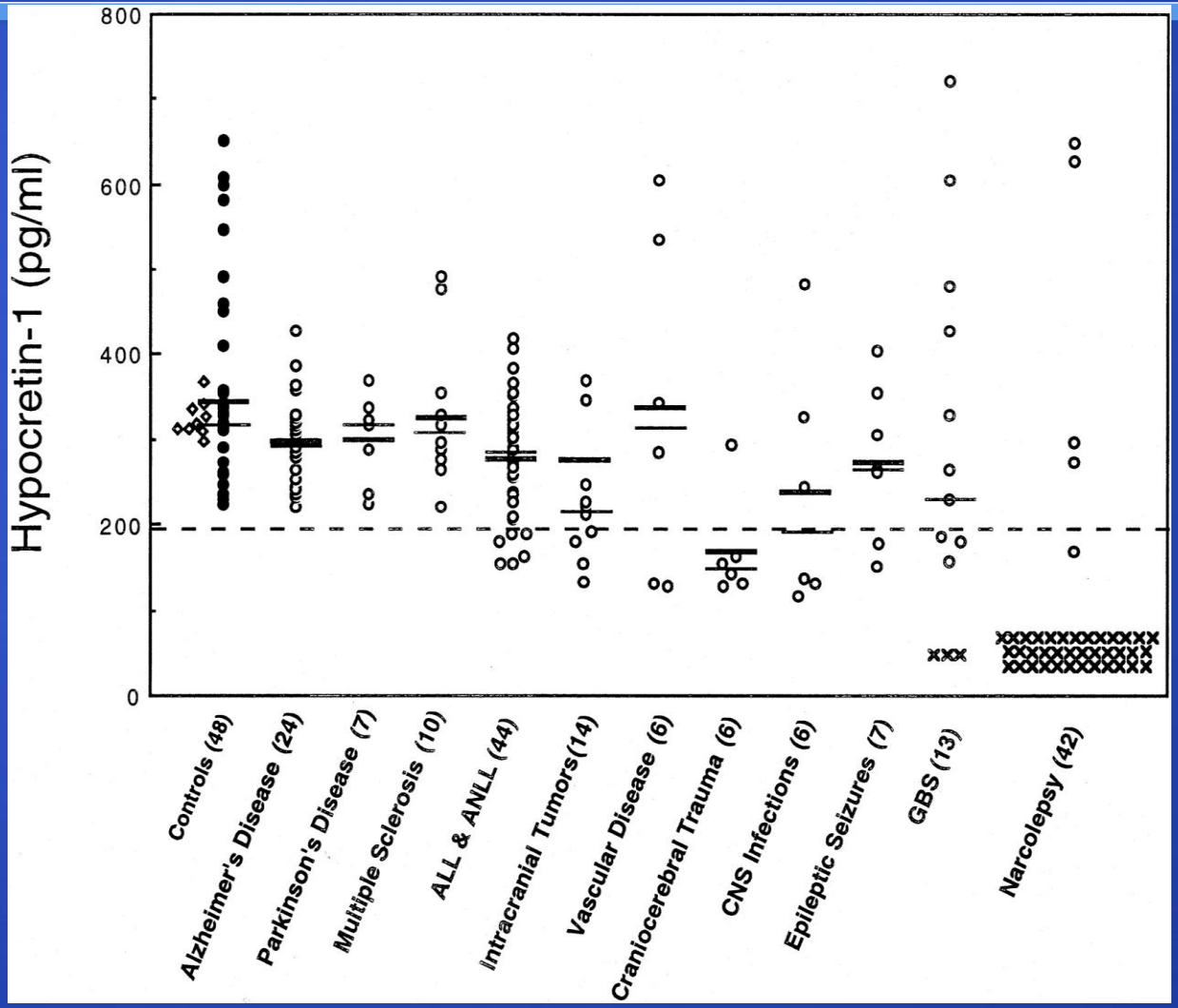

LHA/PH
LC
TMN
Raphe
LDT
VTA
PPT
OX1R
OX2R
OX1R and OX2R
Nature Reviews | Neuroscience

Hypocretin

- Hypocretin

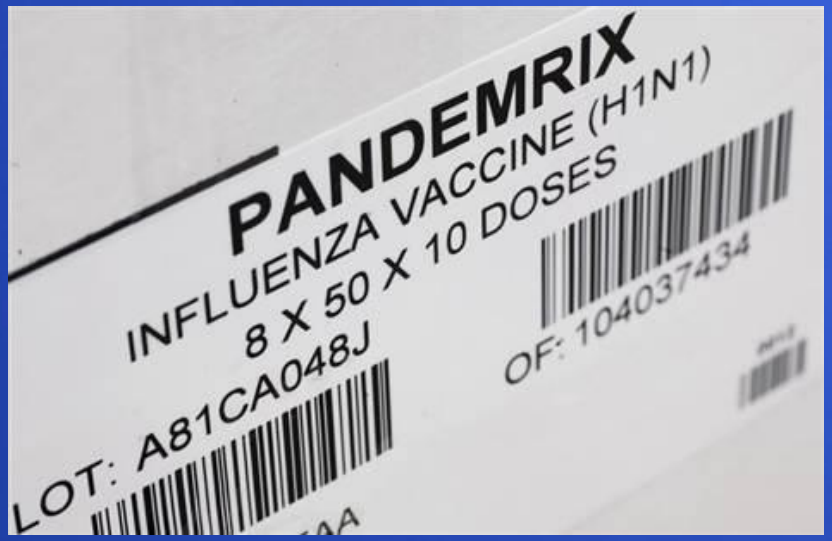


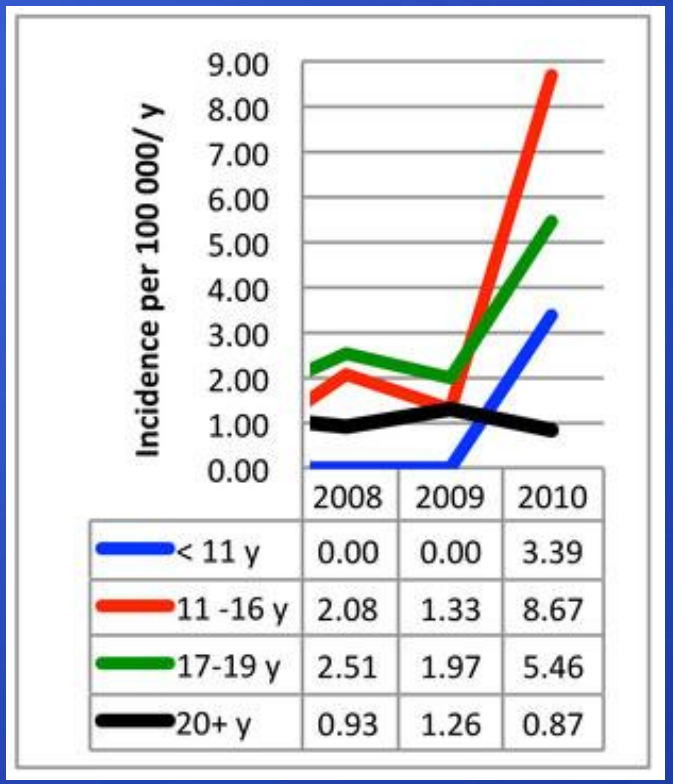
? No cataplexy



Autoimmune

- Increased Incidence and Clinical Picture of Childhood Narcolepsy following the 2009 H1N1 Pandemrix vaccination.





	2008	2009	2010
< 11 y	0.00	0.00	3.39
11 -16 y	2.08	1.33	8.67
17-19 y	2.51	1.97	5.46
20+ y	0.93	1.26	0.87

Diagnosis-Type 1

- **Criteria A and B must be met:**
- A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for ≥3 months.*
- B. The presence of one or both of the following:
- Cataplexy (as defined under Essential Features) and a mean sleep latency of ≤8 minutes and ≥2 sleep-onset REM periods (SOREMPs) on an MSLT performed according to standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.†
- CSF hypocretin-1 concentration, measured by immunoreactivity, is either ≤110 pg/mL or <1/3 of mean values obtained in normal subjects with the same standardized assay.

Type 2

- **Criteria A-E must be met:**
- A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for ≥3 months.
- B. A mean sleep latency of ≤8 minutes and ≥2 sleep-onset REM periods (SOREMPs) are found on an MSLT performed according to standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.
- C. Cataplexy is absent.*
- D. Either CSF hypocretin-1 concentration has not been measured or CSF hypocretin-1 concentration measured by immunoreactivity is either

  >110 pg/mL or >1/3 of mean values obtained in normal subjects with the same standardized assay.†

  E. The hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, obstructive sleep apnea, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal.

DSM-5

- DSM-5 criteria require EDS in association with any one of the following: (1) cataplexy; (2) CSF hypocretin deficiency; (3) REM sleep latency within 15minutes on nocturnal polysomnography (PSG); or (4) mean sleep latency 8 minutes on multiple sleep latency testing (MSLT) with 2 sleep-onset REM-sleep periods (SOREMPs).
- Cataplexy considered diagnostic of disorder

Sleep Testing

- Formal testing is recommended for all children suspected of having narcolepsy(with or without cataplexy).
- Overnight Polysomnogram- rule out OSA primarily.
- Two weeks of diary is ideal, need to know sleep is routine and set for patient.
- MSLT following day.
- Critical to review medicines, and if possible, have patient off any that can invalidate MSLT.
  - Stimulants, SSRI, SNRI

MSLT

- Multiple Sleep Latency Test
  - Series of 5 nap opportunities separated by 2 hours.
  - No napping in between.
  - Patient monitored for sleep onset, staging, and REM.
  - IF sleep attained- allow 15 minutes to see if patient goes into REM sleep.
  - Goal for the patient is to TRY to sleep, not to avoid it.
    - THIS can be really difficult for kids, repeat ?
  - Scored as latency to sleep for each nap, and whether REM occurs.

Scores

- Normal mean latency considered greater than 10 minutes.
- Less than 8 minutes considered pathologic sleepiness.
- Sleep-onset REM(SOREMP)- 2 or more diagnostic.
- *So- Mean less than 8 minutes, 2 SOREMPS=supports diagnosis of narcolepsy.*
- *SOREMP within 15 minutes on PSG counts as one.*
- Under 8 years of age- no clear-cut standard established.
- In prepubertal children relative hyperalert.
- ? What value is correct for kids?

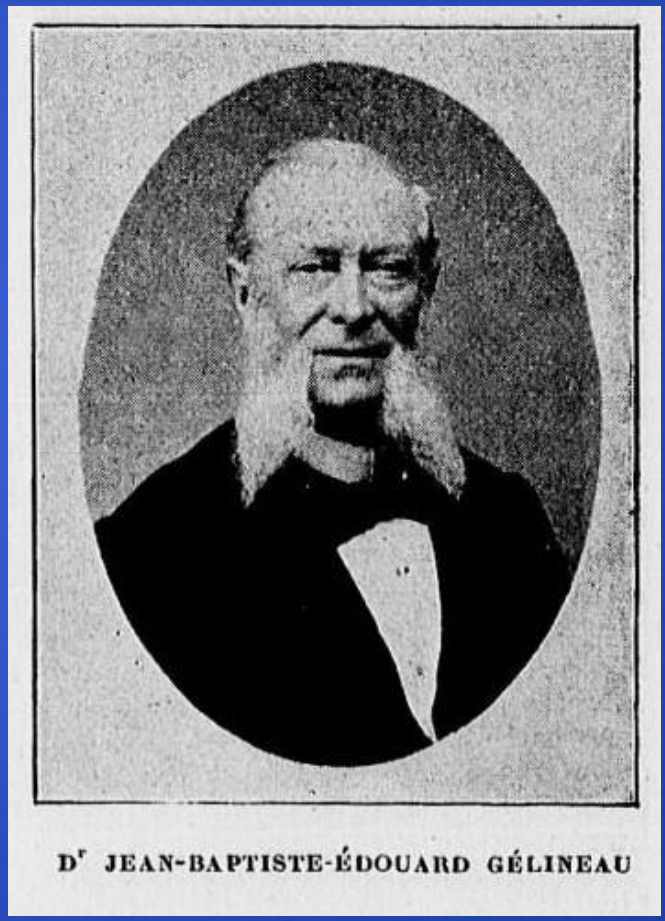
Pitfalls

- Sensitivity-last nap, motivation
- Recent sleep history(sleep-deprived, circadian shifts)
- Medicines- ADHD, Mood
  - Stimulants
  - SSRI- REM suppressants
- Can easily lead to false negative, false positive.

Our patient's test

- PSG- mild decrease in efficiency with increased arousals noted, and onset of REM at 10 minutes of sleep.
- No OSA
- MSLT- Mean Latency 6 minutes
- SOREMPs 2/5 naps

Narcolepsy



Dr JEAN-BAPTISTE-ÉDOUARD GÉLINEAU

Narcolepsy Treatment

- *Nonpharmacologic*
- Education/Advocacy-there is no cure, it is progressive.
- Planned naps
  Maintaining regular sleep-wake schedules
- Regular physical exercise
- Safety- school/home/work/Driving?
- Counselor- overlap with mood, and often misdiagnosis
- Vocational guidance

Narcolepsy Treatment

- *Pharmacologic Measures*
- *Daytime sleepiness*
  Sodium Oxybate
- Modafinil, Armodafinil
  Methylphenidate
  Dextroamphetamine mixtures
- *Cataplexy*
  Sodium oxybate , TCAs, SSRI/SNRI
- Specific treatment for associated sleep phenomenon

How I do this

- Education
  - Google can be your friend, narcolepsy network, office materials
- Sleep Schedules, work, sports, etc.
  - You will suffer more than I will if chaos rules your day, and night.
- Medicines- how I discuss with patients and families

Drugs

- Sodium Oxybate- NOT FDA approved in kids yet. Routinely used by me, and peds sleep docs.
- Most potent medication and IN ADULTS considered the standard of care for disease.
- ONLY FDA approved medication to treat both hypersomnia, and cataplexy.
- I discuss "the good, the bad, the ugly" with every family
- First line, or not. Driven by symptoms and patient, family desires, fears, and ability to comply

Drugs

- Modafinil- my preference if do not consider sodium oxybate initially. Start low, go slow.
- Ritalin-use every and all preparations. Long-acting, once a day to start. Low, slow.
- Dextroamphetamine-see above.

Side effects

- Modafinil- GI, Headaches
- Stimulants- Appetite suppression, mood, “zombie”, or not so nice.
- Sodium Oxybate- Nausea, parasomnias, enuresis, mood, what else do you take, SSADH, salt, and mostly can you do this successfully?

Summary

- Sleepiness is common, narcolepsy is uncommon, but not THAT uncommon.
- History- in sleepy patient: what do they mean?
- In narcolepsy, patients often do not share the odd details of what they are experiencing.
  - HH, vivid/realistic dreams, ability to sleep very quickly if NOT engaged, paralysis, cataplexy.
- Ask about cardinal features- but do not ask, "Do you fall down when you laugh", or you will miss it.
- Use the Epworth Sleepiness Scale- easy, quick, sensitive.
- Look for weight gain, watch for presumed mood/adhd diagnosis.
- "Near-syncope, vaso-vagal spells AND sleepy patient.
- IF ESS is abnormal(> 10), if story is there, send them to sleep doc.

Summary

- Narcolepsy is often mis-diagnosed.
- It is a brain disorder primarily caused by loss of hypocretin-producing cells in the lateral hypothalamus.
- Symptoms are progressive, but often under-recognized, mislabeled, or hidden.
- It affects all aspects of a child's life, and mood disorders are commonly seen in these patients.
- Testing for narcolepsy is done with PSG followed by MSLT, but must be careful to avoid pitfalls.
- It is lifelong, but treatable.
- Treatment is directed toward normal daytime functioning/alertness, and eliminating untoward symptoms.