Why Are They So Sleepy?

Narcolepsy and Central Nervous System Disorders Causing Excessive Daytime Sleepiness

Maggie Lavender MSN, APRN FNP-C
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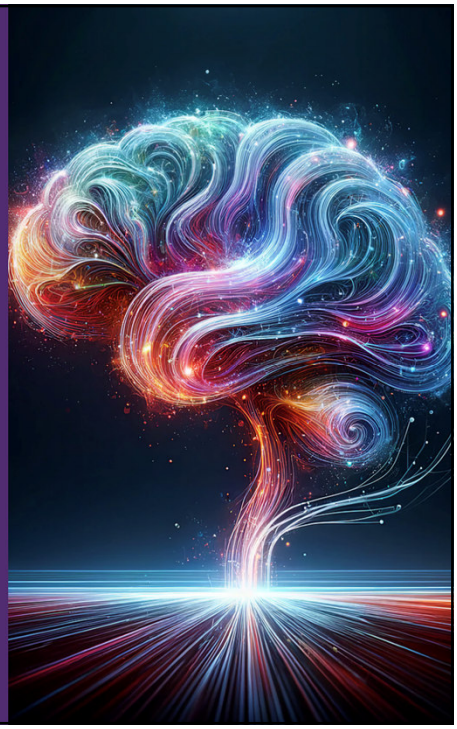

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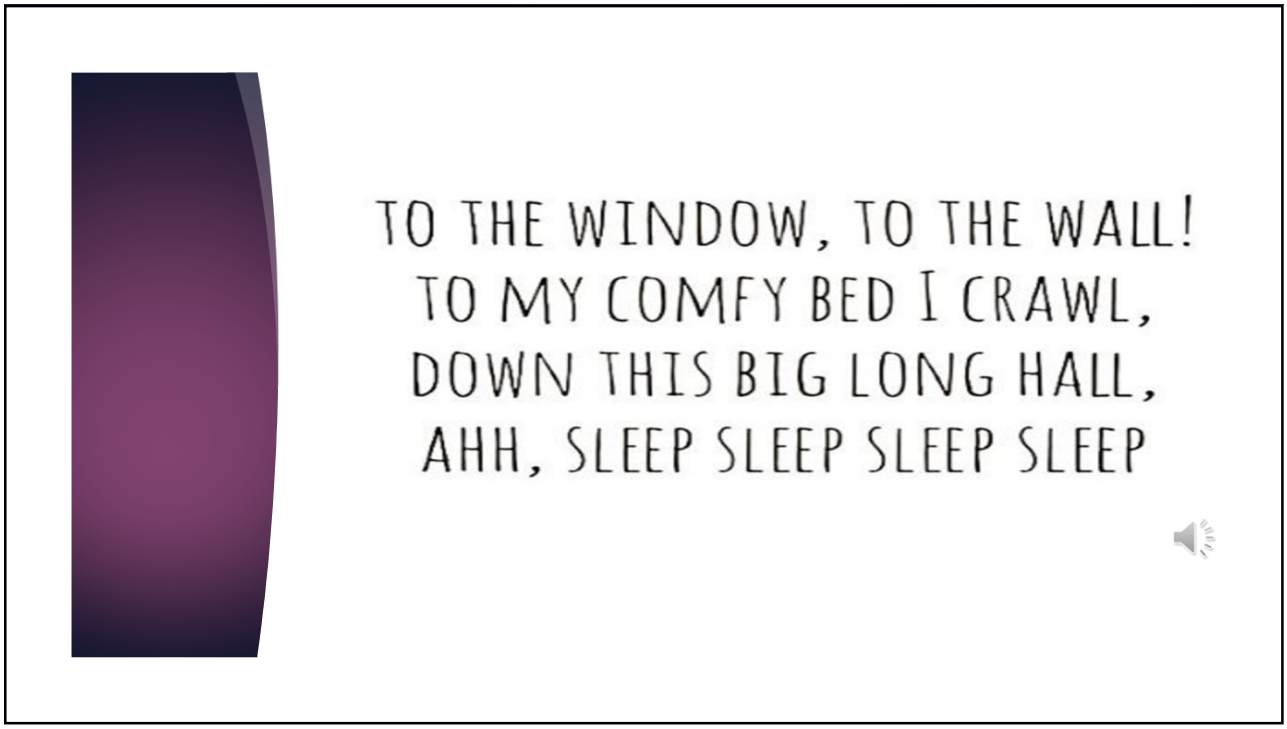

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Disclosures

- President and Founder of SMAPP Foundation
- Speaker Honorarium for Avadel/Alkermes Pharmaceuticals, Axsome Therapeutics
- Consultant and Advisory Board Member for Avadel/Alkermes Pharmaceuticals, Harmony Biosciences, Jazz Pharmaceuticals and Axsome Therapeutics, Takeda Pharmaceuticals
- Board Member of PWN4PWN

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Objectives

- Understand the circadian process of sleep wake control as well as the neurotransmitter pathways in the brain that control sleep vs. wake cycles.
- Understand different characteristics of sleep stages.
- Understand the most common central hypersomnia sleep disorders, their distinguishing symptoms and the changes to the neurotransmitter pathways.
- Understand the difference in presentation and diagnostic criteria for narcolepsy vs. idiopathic hypersomnia.
- Understand available treatment modalities for narcolepsy and idiopathic hypersomnia and the future treament landscape.

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How does the brain control sleep vs wake?

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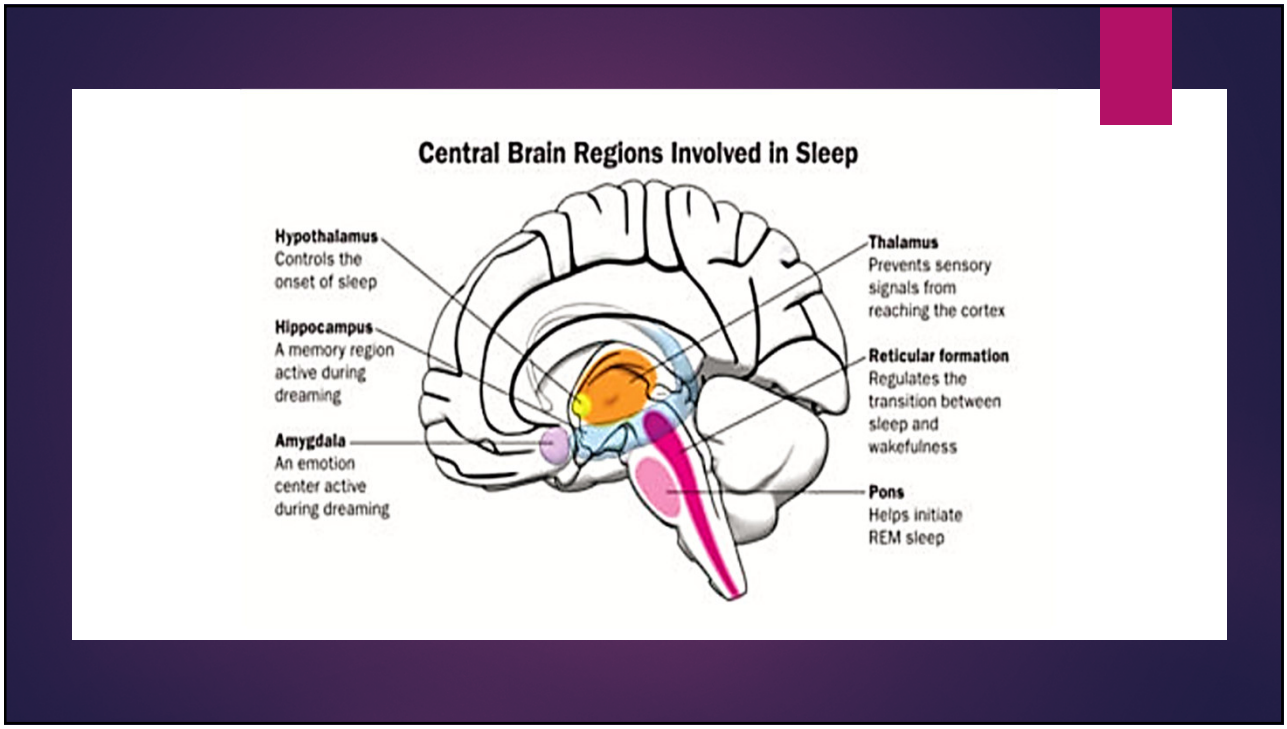
Central Brain Regions Involved in Sleep
Hypothalamus
Controls the onset of sleep
Hippocampus
A memory region active during dreaming
Amygdala
An emotion center active during dreaming
Thalamus
Prevents sensory signals from reaching the cortex
Reticular formation
Regulates the transition between sleep and wakefulness
Pons
Helps initiate REM sleep

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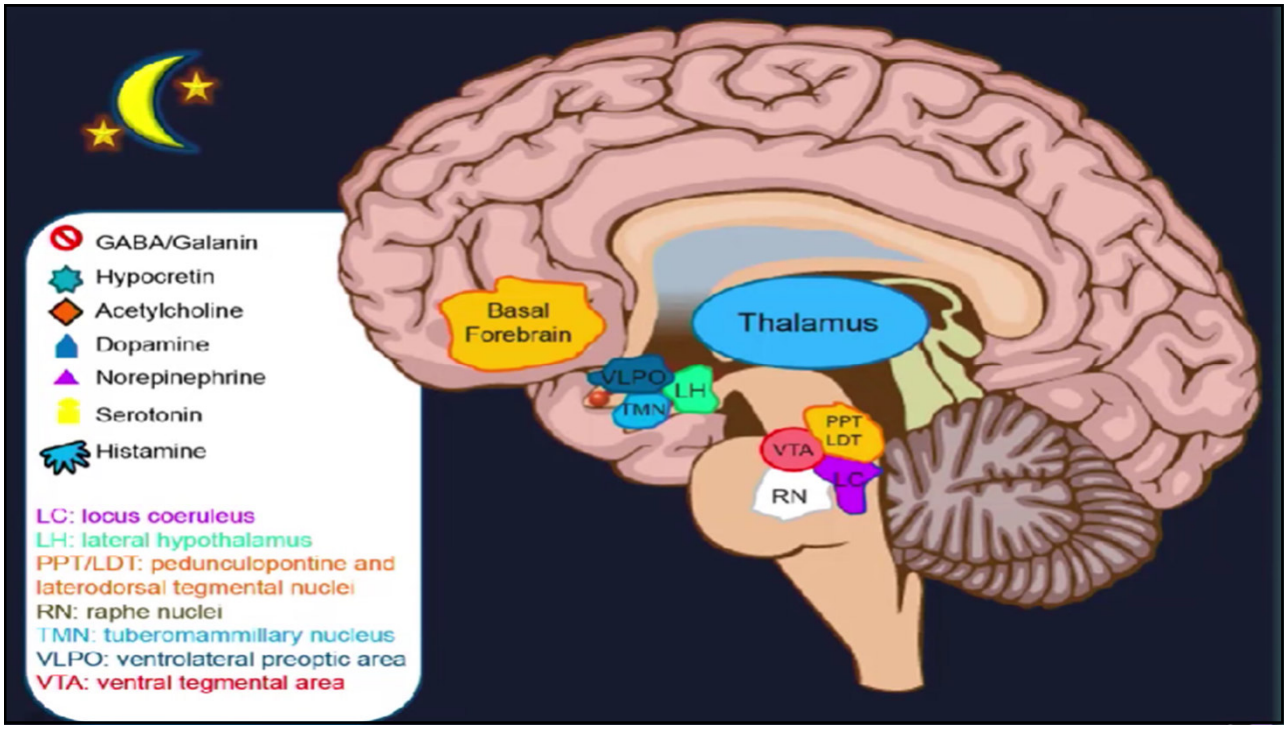
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Dopamine
Norepinephrine
Serotonin
Histamine
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LH: lateral hypothalamus
PPT/LDT: pedunculopontine and laterodorsal tegmental nuclei
RN: raphe nuclei
TMN: tuberomammillary nucleus
VLPO: ventrolateral preoptic area
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Basal Forebrain
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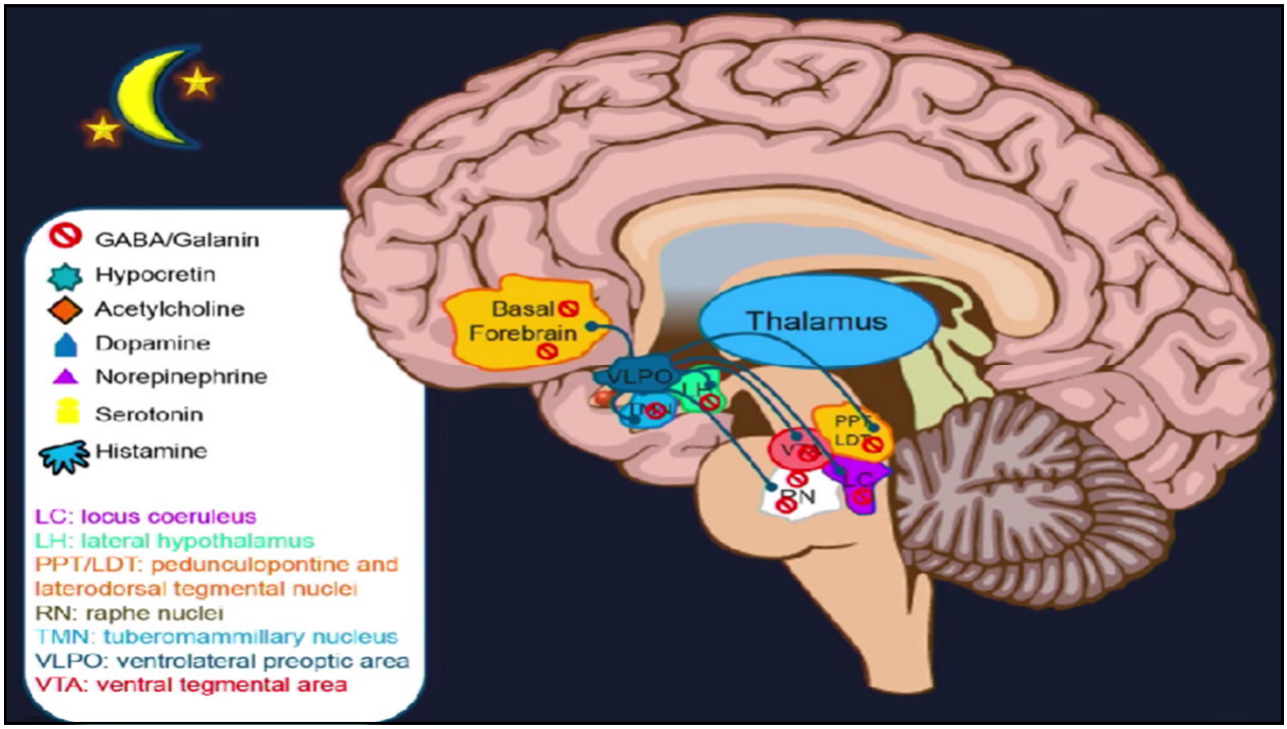
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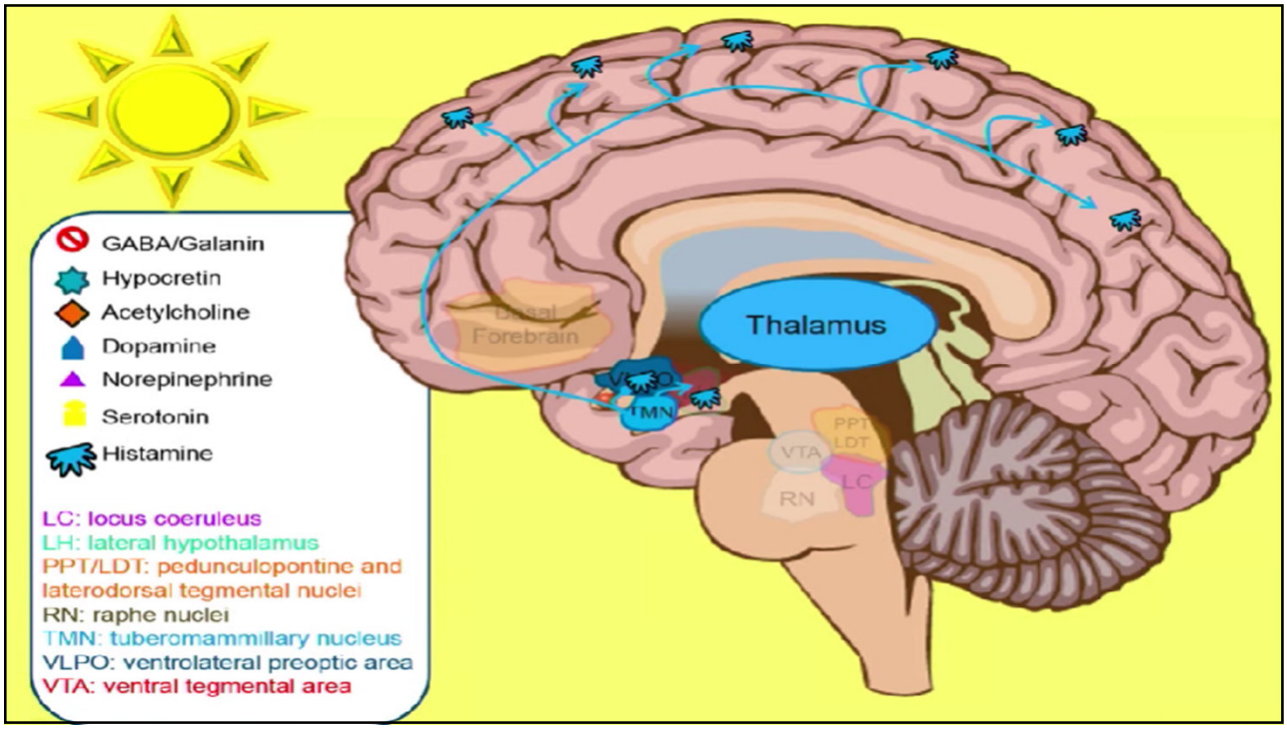
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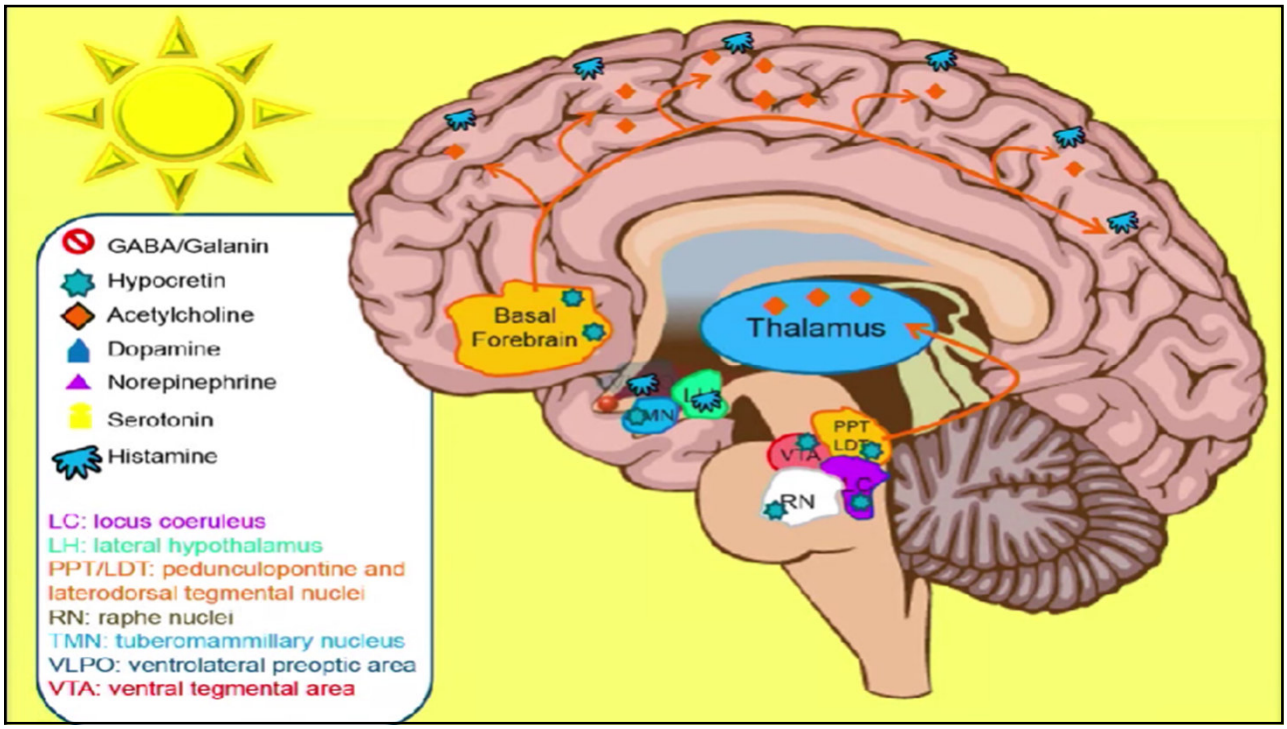
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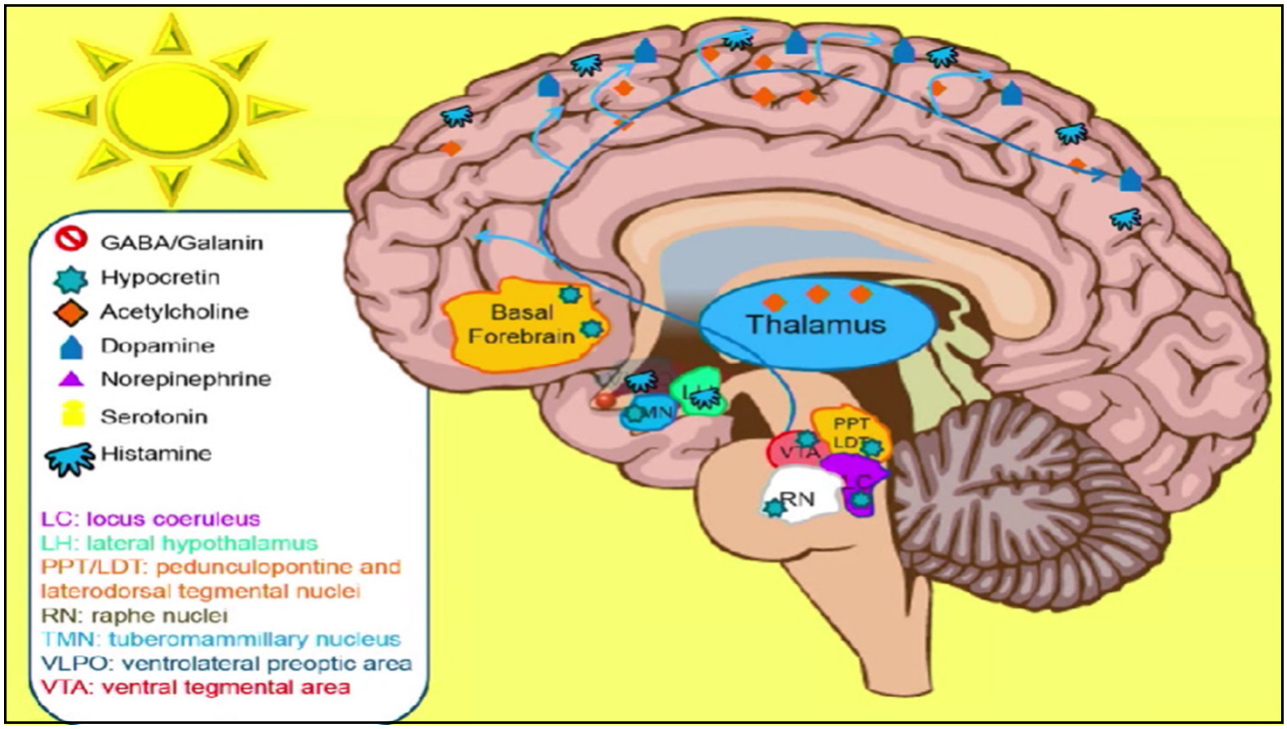
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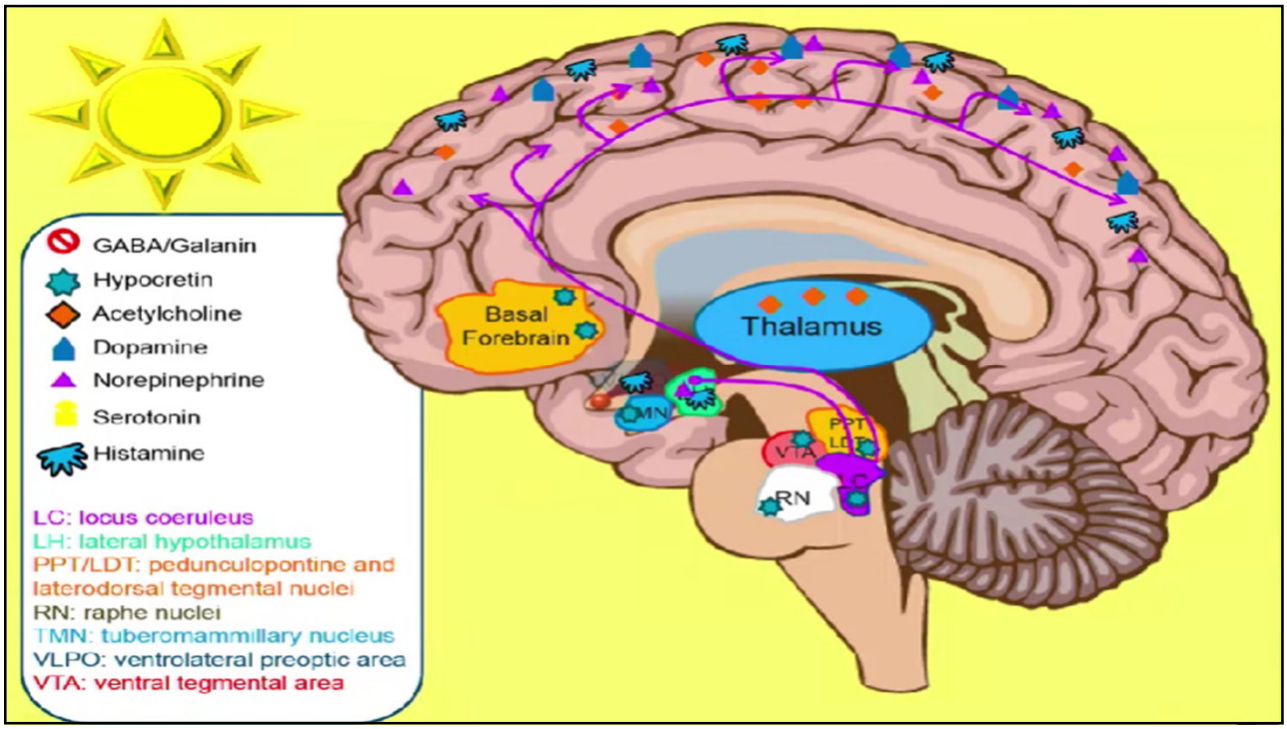
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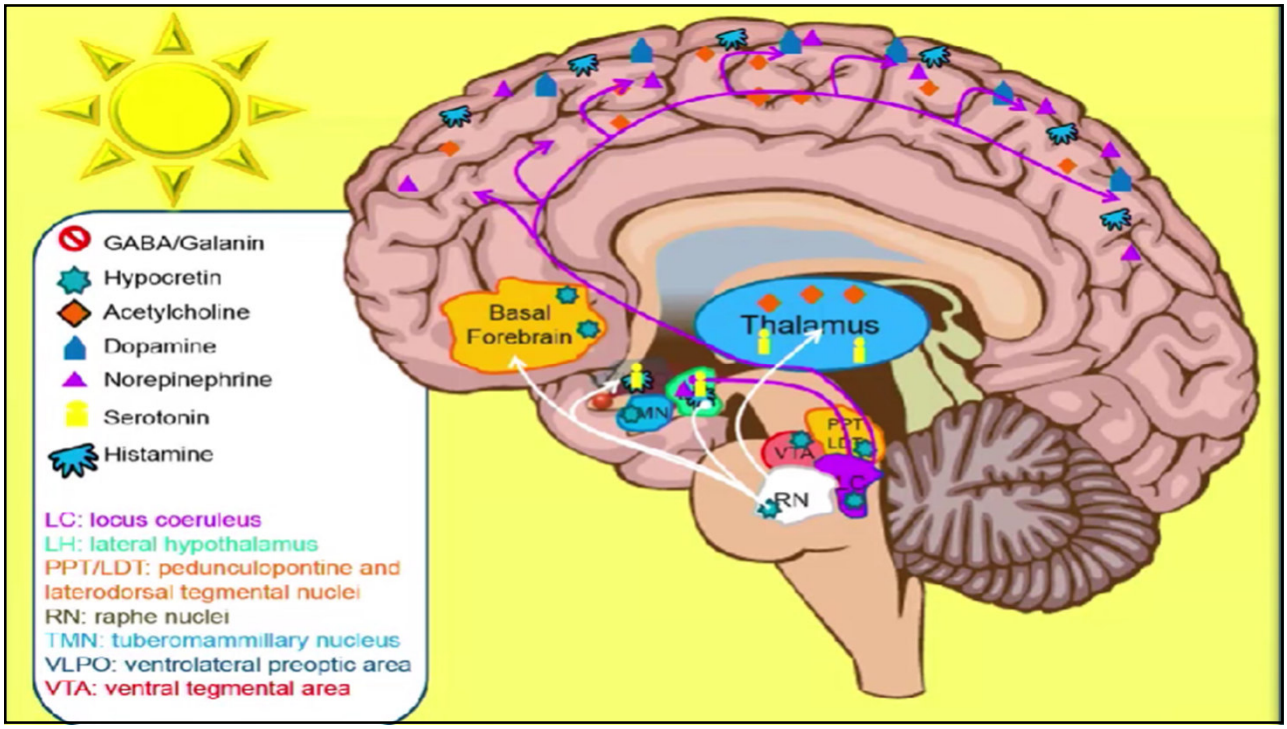
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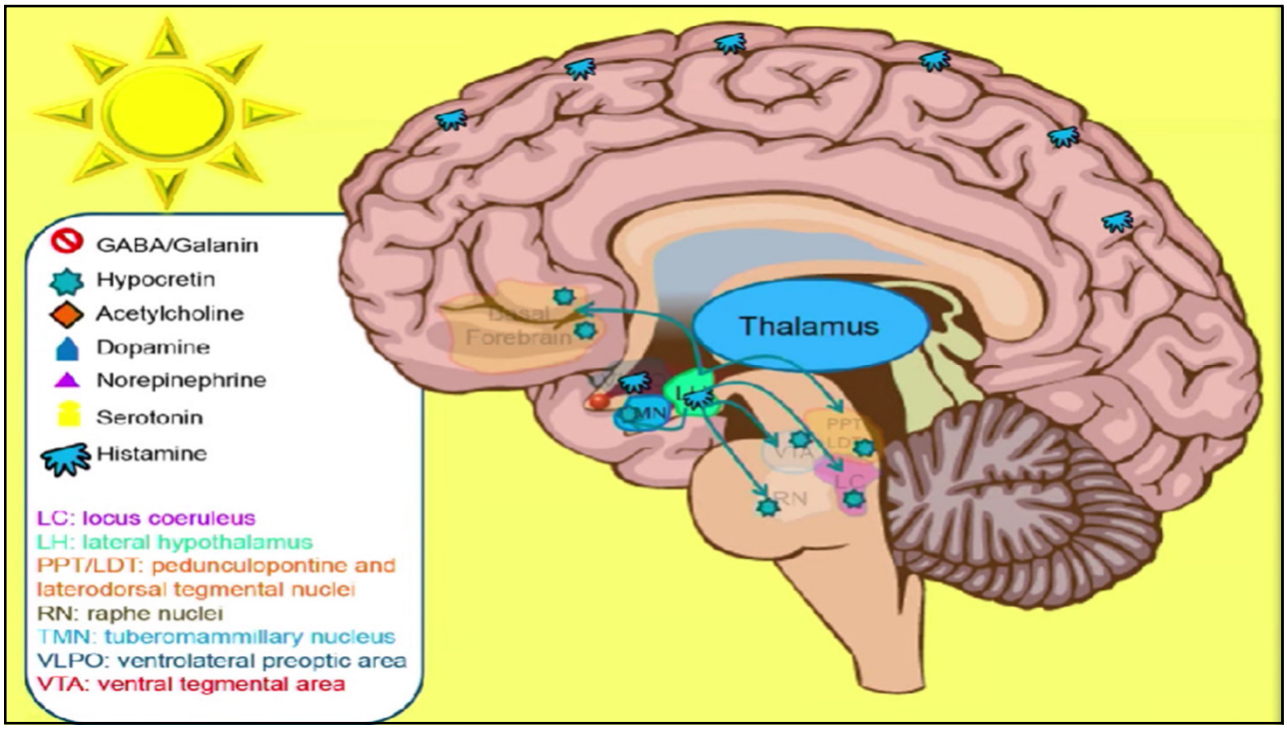

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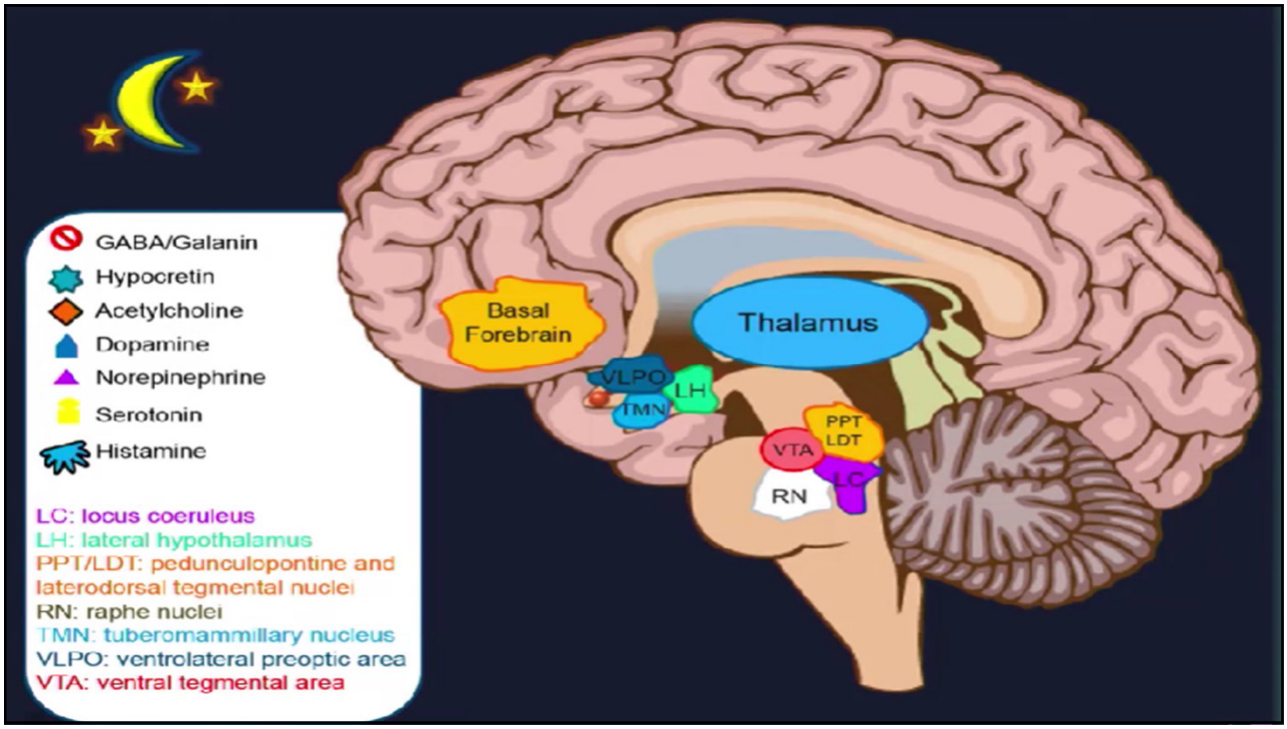

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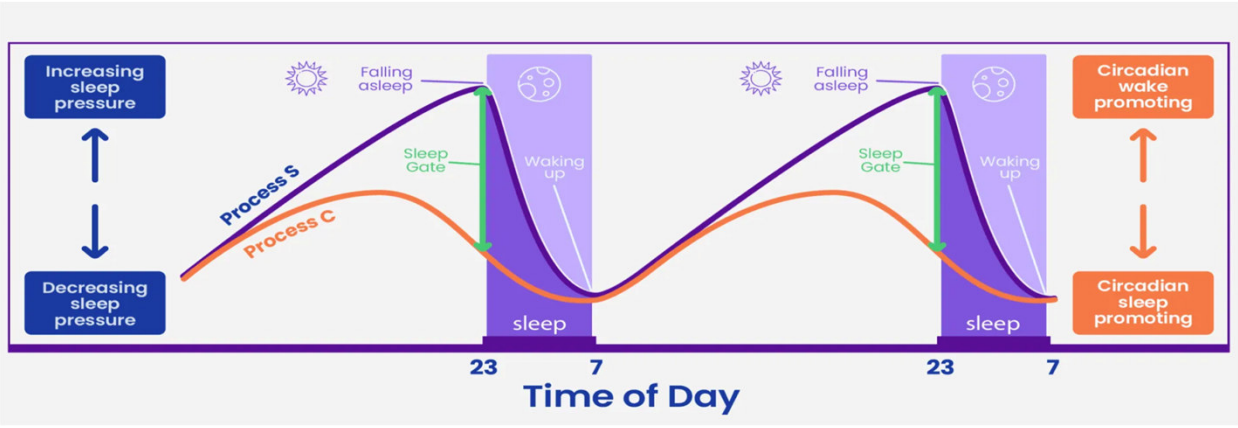
The Two-Process Theory of Sleep-Wake Control



Process C:
The body's internal clock that regulates sleep and controls hormone production, body temperature and alertness based on the light-dark cycle.

Process S:
The build-up of sleep or homeostatic pressure that builds up during wakefulness and dissipates during sleep, with greater pressure the longer you are awake.

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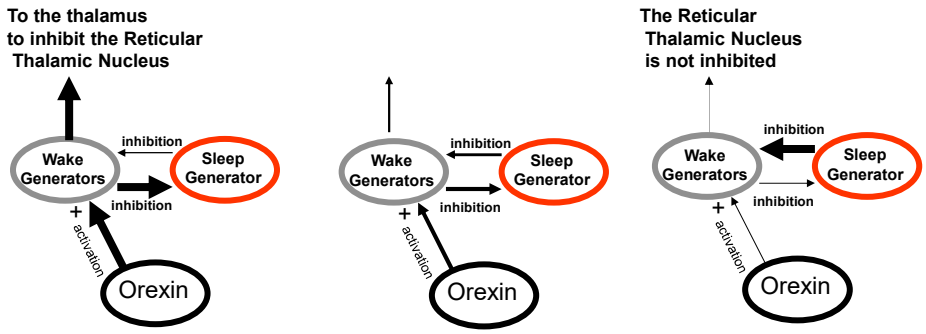
Flip Flop Switch



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Where are Wake and Sleep Promoting Neurotransmitters Produced ?

Area of the Brain	Neurotransmitter	Side of the Sleep Switch
Ventrolateral Preoptic Nucleus VLPO	GABA	Sleep
Locus Coeruleus	Norepinephrine	Wake
Substantia Nigra in the ventral tegmental area	Dopamine	Wake
Dorsal Medial Nucleus In the raphi nucleus	Serotonin	Wake
Tuberomammillary Nuclei	Histamine	Wake
Lateral Hypothalmus	Orexin/Hypocretin	Wake

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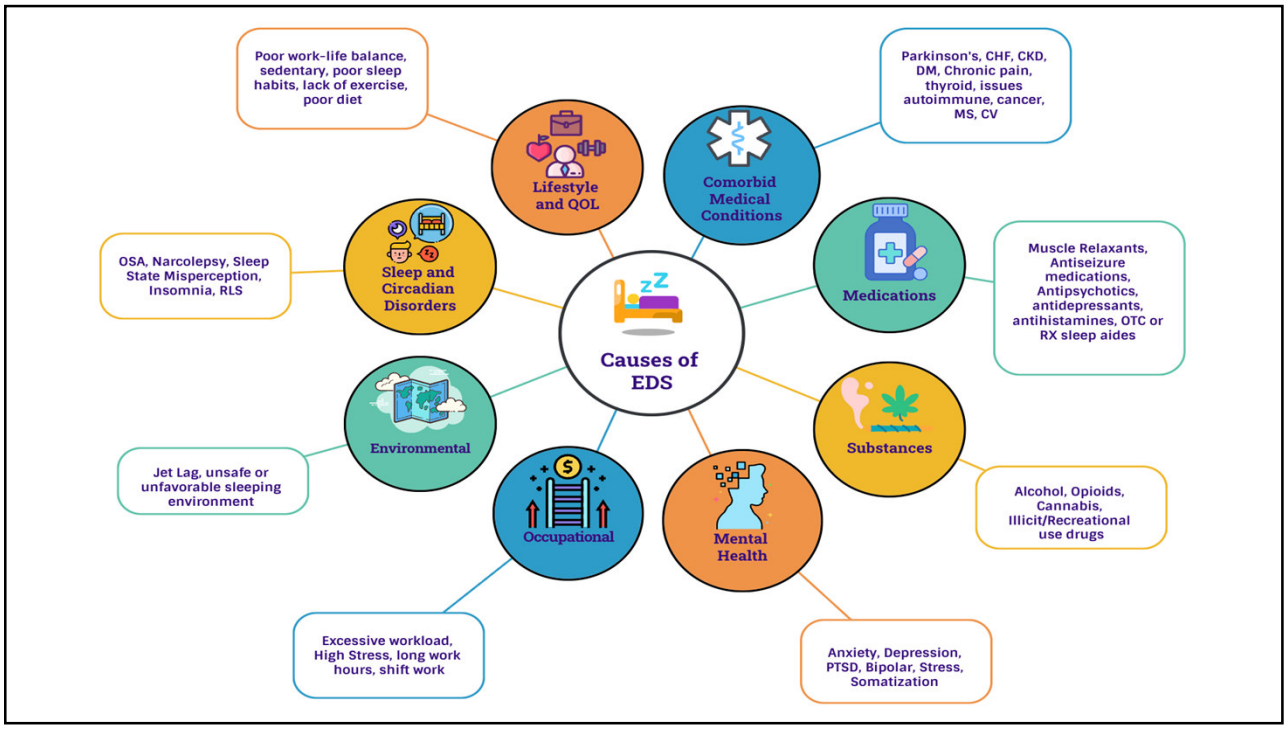

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Hypersomnia Sleep Disorders

- A group of long-lasting (chronic) sleep disorders of the brain.
  - They cause excessive daytime sleepiness (EDS).
    - A strong daytime sleepiness or need to sleep during the day, even with enough sleep the night before.
- People with hypersomnia sleep disorders may have other symptoms that affect their sleep and their ability to function during the day.
- They often live without a correct diagnosis for a long time. They may blame themselves and struggle to keep up with work, studies, and relationships.

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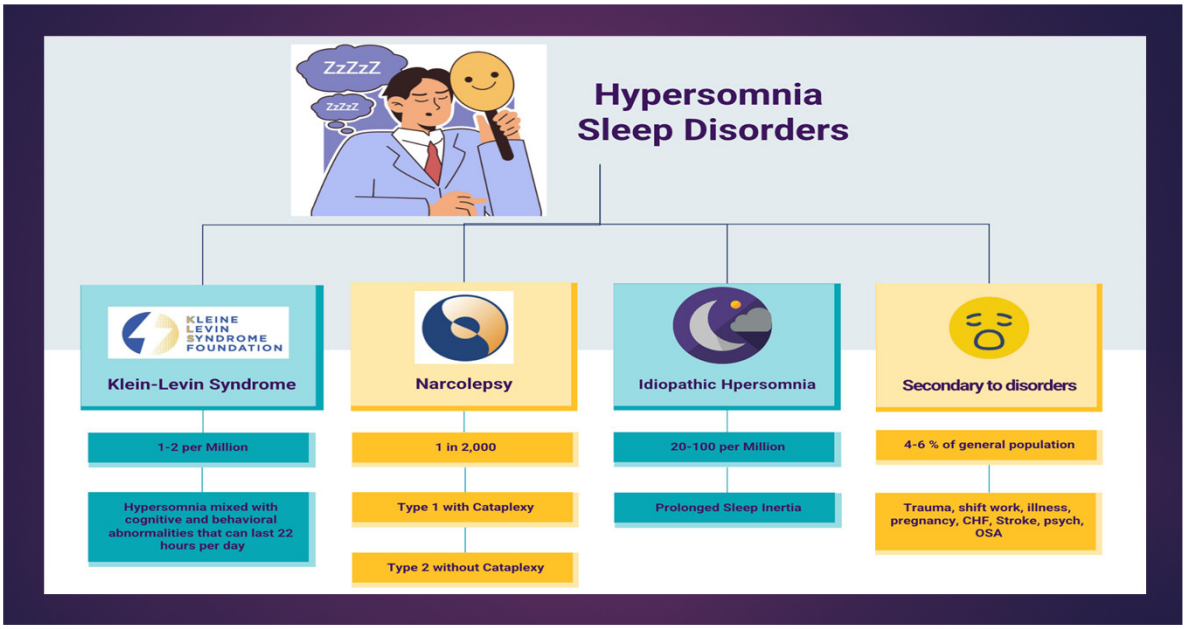

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Kleine-Levin Syndrome

- Kleine-Levin syndrome is a rare disorder characterized by:
  - the **need for excessive amounts of sleep** up to 20 hours a day
  - excessive food intake (**compulsive hyperphagia**)
  - **behavioral changes** such as an abnormally uninhibited sexual drive.
- Primarily affects *adolescent males*.
- When awake, affected individuals may exhibit *irritability, lack of energy (lethargy), and/or lack of emotions (apathy).*
- They may also *appear confused (disoriented) and experience hallucinations*
- The exact cause is not known.
  - In some cases, hereditary factors may cause some individuals to have a genetic predisposition to developing the disorder.
    - It is thought that symptoms may be related to *malfunction* of the portion of the brain that helps to regulate functions such as sleep, appetite, and body temperature (*hypothalamus*).
  - Some researchers speculate that Kleine-Levin syndrome may be an autoimmune disorder.

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Kleine-Levin Syndrome

- Symptoms are cyclical.
  - May persist for days to weeks, then the affected individual may go for weeks or months without experiencing symptoms.
  - In some cases, the symptoms eventually disappear with advancing age, but episodes may recur later during life.
- At least one of the following during the episode:
  - Cognitive dysfunction
  - Altered perception
  - Eating disorder
  - Disinhibited behavior (such as hypersexuality)
  - Sub-type: Menstrual-related Kleine-Levin Syndrome

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Narcolepsy

- Narcolepsy is a ***chronic condition*** that causes ***excessive daytime sleepiness*** and leads to an increased tendency to fall asleep during daytime activities.
  - affects 1 in 2000 people (280,000 in US)
- Some people who suffer from Narcolepsy also experience ***cataplexy***, which involves brief sudden episodes of muscle weakness or paralysis often brought on by strong emotions.
- Patients often experience other sleep-related problems, such as ***disrupted/ fragmented sleep***, ***sleep paralysis***, and ***hallucinations*** when falling asleep or waking up.
- Symptoms begin between ***age 10-20*** and ***start with sleepiness*** and then other symptoms follow
- Often classified as Narcolepsy ***Type 1*** and Narcolepsy ***Type 2***
  - Type 1- typically with cataplexy, low levels of neuropeptide orexin (hypocretin)
  - Type 2- without cataplexy, orexin levels are normal, less severe symptoms and little know about cause

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Narcolepsy

- Cause of narcolepsy is not completely understood.
  - Current research suggests that narcolepsy may be the result of a combination of factors working together to cause a lack of orexin.
- ***Autoimmune disorders:*** When cataplexy is present, the cause is most often the loss of brain cells that produce orexin.
  - The reason for this cell loss is unknown, it appears to be linked to abnormalities in the immune system.
  - Occur when the body's immune system turns against itself and mistakenly attacks healthy cells or tissue.
  - It is believed that the body's immune system selectively attacks the orexin-containing brain cells because of a combination of genetic and environmental factors.
- ***Family history***—Most cases of narcolepsy are sporadic, meaning the disorder occurs in individuals with no known family history. However, clusters in families sometimes occur.
  - up to 10% of individuals diagnosed with narcolepsy with cataplexy report having a close relative with similar symptoms.
- ***Brain injuries***—Rarely, narcolepsy results from traumatic injury to parts of the brain that regulate wakefulness and REM sleep or from tumors and other diseases in the same regions.

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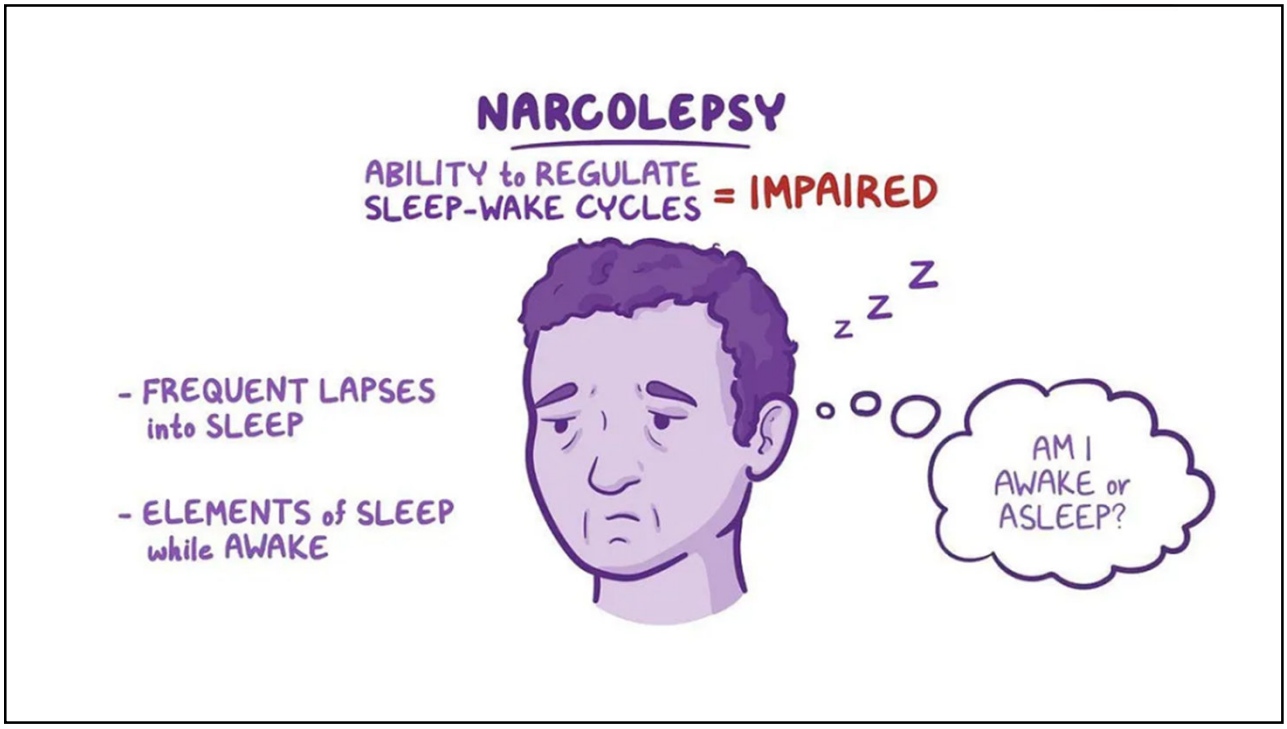

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Sleep Stages

Sleep consists of two distinct states that alternate in cycles and reflect differing levels of brain nerve cell activity.

Non-Rapid Eye Movement Sleep (Non-REM)

- Non-REM sleep is also termed quiet sleep. Non-REM is further subdivided into 3 stages of progression:
  - Stage 1 (light sleep)
  - Stage 2 (so-called true sleep)
  - Stage 3 (deep "slow-wave" or delta sleep)
- With each descending stage, awakening becomes more difficult. It is not known what governs Non-REM sleep in the brain. A balance between certain hormones particularly growth and stress hormones may be important for deep sleep.

Rapid Eye-Movement Sleep (REM)

- REM sleep is termed active sleep.
- Most vivid dreams occur in REM sleep.
- REM-sleep brain activity is comparable to that in waking, but the muscles are totally relaxed, possibly preventing people from acting out their dreams.
  - Except for vital organs like lungs and heart, the only muscles not relaxed during REM are the eye muscles.
- REM sleep may be critical for learning and for day-to-day mood regulation. When people are sleep-deprived, their brains must work harder than when they are well-rested.

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Sleep Stage	Physiologic Findings
Stage 1 Light Sleep	• Rhythm on EEG begins to slow, may see vertex waves • Slow rolling eye movements begin • Breathing and heartrate slow down • Muscles relax • Body temperature decreases
Stage 2 Deeper Sleep	• Deep relaxation occurs • Sleep spindles and K complexes appear on EEG • Slow rolling eye movements continue
Stage 3 Delta, Deep or Slow-Wave Sleep	• Heartbeat and breathing slow down more • Delta waves are present on EEG • Slow rolling eye movements continue
REM Dream State	• REMs present and alternate with tonic (non-moving) eyes • Muscles temporarily cannot move (REM atonia) • Often vivid dreams • EEG rhythm similar to wake, but no movement and REMs observed • Heart rate and breathing rate vary

Sleep Stages

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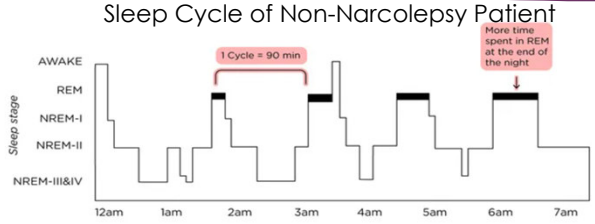
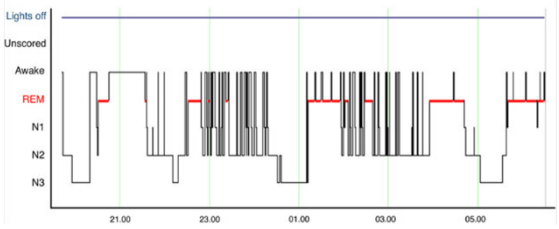
The REM/Non-REM Cycle

Sleep Cycle of Non-Narcolepsy Patient



- The cycle between quiet (non-REM) and active (REM) sleep generally follows this pattern:
  - After about 90 minutes of non-REM sleep, eyes move rapidly behind closed lids, signifying REM sleep.
  - As sleep progresses the non-REM/REM cycle repeats.
  - With each cycle, non-REM sleep becomes progressively lighter, and REM sleep becomes progressively longer, lasting from a few minutes early in sleep to perhaps an hour at the end of the sleep episode.

Sleep Cycle of Narcolepsy Patient



- REM cycle noted within first 15 minutes of sleep initiation
- Cycle between non-REM and REM does not follow typical 90 minutes and results in increased number of REM periods.
- The timing of non-REM and REM stages is very erratic, but REM continues to get longer as night progresses

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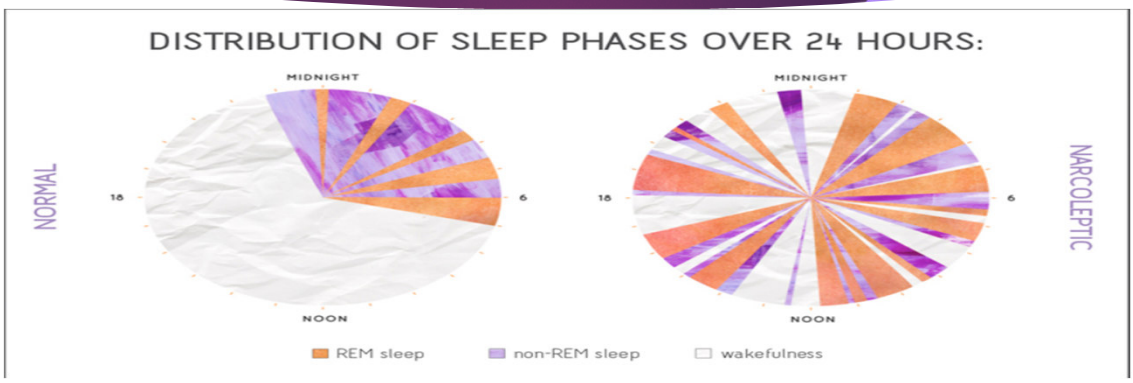
Distribution of Sleep Phases



Without orexin, sleep wake cycles become confused, and the number of REM periods are greatly increased.
REM is the phase of sleep when most dreaming occurs, and the body is paralyzed to stop us from acting them out. The brain is also just as active during this phase as it is while awake, so the sleep is not at all restful.

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Narcolepsy Type 1 Diagnostic Criteria per the International Classification of Sleep Disorders, Third Edition (ICSD-3)

- 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 at least 3 months.
  - B. The presence of ***one or both*** of the following:
    - 1- Cataplexy and a mean sleep latency of ≤ 8 minutes and two of more sleep onset rapid eye movement periods (SOREMPs) on a multiple sleep latency test (MSLT) performed according to standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace one or more of the SOREMPs on the MSLT.
    - 2- Hypocretin-1 concentration in the cerebrospinal fluid (CSF), measured by immunoreactivity, is either ≤ 110 p/g mL or less than 1/3 of mean values obtained in normal subjects with the same standardized assay.
  - In young children, narcolepsy may sometimes present as an excessively long night sleep or as a resumption of previously discontinued daytime napping.
  - If narcolepsy type 1 is strongly suspected clinically but the MSLT criteria of B1 are not met, a possible strategy is to repeat the MSLT.

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Narcolepsy Type 2 Diagnostic Criteria per the International Classification of Sleep Disorders, Third Edition (ICSD-3)

- Criteria A through E must be met.
  - A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months.
  - B. A mean sleep latency of ≤ 8 minutes and two or more 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 substance or their withdrawal.

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DSM- 5 Diagnostic Criteria for Narcolepsy

- Recurrent periods of an irrepressible need to sleep, lapsing into sleep, or napping occurring within the same day, which must have been occurring at least 3/week over the past 3 months.
- At least one of the following is present:
  - A. Episodes of cataplexy occurring at least a few times a month and defined as either:
    - 1- In individuals with long-standing disease, brief (seconds to minutes) episodes of sudden bilateral loss of muscle tone with maintained consciousness that are precipitated by laughter or joking.
    - 2- In children or individuals within 6 months of onset, spontaneous grimaces or jaw-opening episodes with tongue thrusting or a global hypotonia, without any obvious emotional triggers.
  - B. Hypocretin deficiency measured by CSF hypocretin-1 immunoreactivity values (≤ 1/3 of values obtained in healthy subjects tested using the same assay, or ≤ 110 pg/mL). Low CSF hypocretin-1 levels must not be observed in the context of acute brain injury, inflammation, or infection.
  - C. Nocturnal sleep polysomnogram showing rapid eye movement (REM) sleep latency ≤ 15 minutes, or an MSLT showing a mean sleep latency ≤8 minutes and 2 or more SOREMPs.

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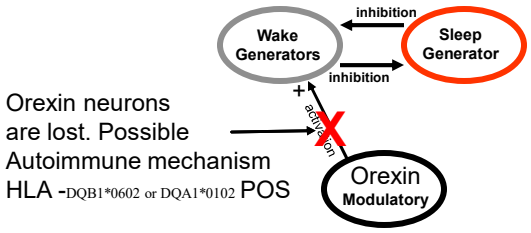
Narcolepsy Type I is tightly associated with a deficiency of Orexin levels.

Flip Flop Switch



Orexin = Hypocretin

Orexin neurons are lost. Possible Autoimmune mechanism HLA -DQB1*0602 or DQA1*0102 POS

Narcolepsy is a disorder is sleep state disassociation, mainly between wake and sleep

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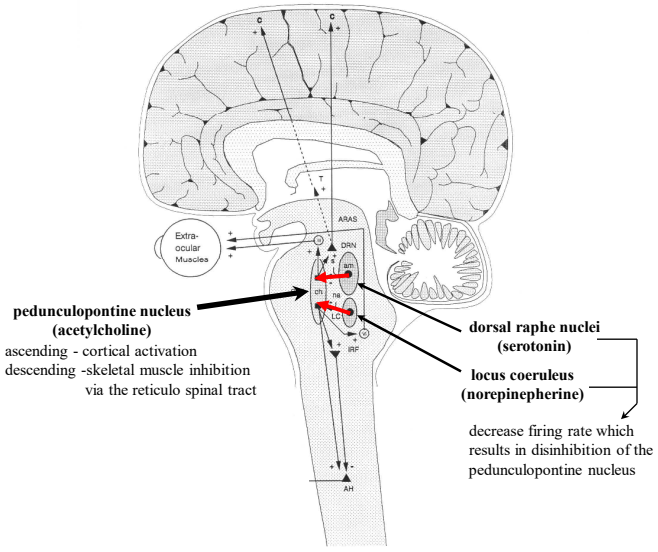
Brainstem regulation and control of NREM



pedunculopontine nucleus (acetylcholine)
ascending - cortical activation
descending -skeletal muscle inhibition via the reticulo spinal tract

dorsal raphe nuclei (serotonin)

locus coeruleus (norepinepherine)

decrease firing rate which results in disinhibition of the pedunculopontine nucleus

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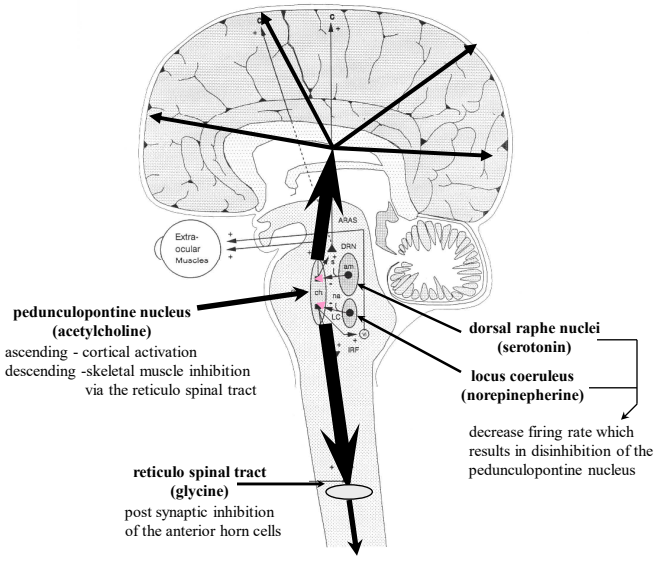
Brainstem regulation and control of REM



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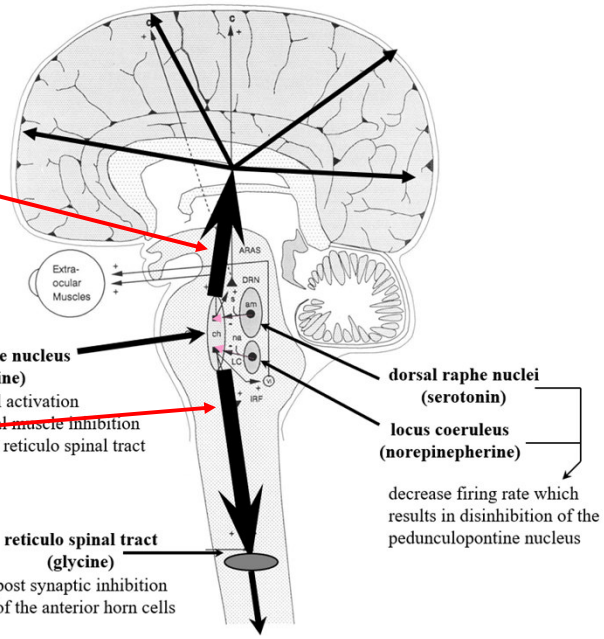
Features of narcolepsy are associated with components of REM sleep

Hypnagogic (on falling asleep) or Hypnopompic (on waking up) hallucinations

Sleep paralysis
Cataplexy



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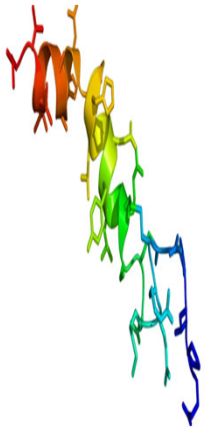
Narcolepsy Type 1

- Linked to a loss of orexin-producing neurons in the hypothalamus, leading to low orexin levels.
  - Orexin neurons have an excitatory effect on several regions of the brain that are involved in promoting wakefulness and suppressing REM sleep
    - The loss of these neurons leads to deficiencies in maintaining wakefulness and is linked to dysregulation of REM sleep
      - This REM sleep dysregulation is thought to cause episodes of muscle paralysis and other aspects of REM sleep to occur during wakefulness, which is the basis for cataplexy
- The cause of the loss of orexin neurons in narcolepsy is not completely understood, but evidence leads to autoimmune mechanism
  - Combination of genetic and environmental factors leads to an inflammatory process in brain that causes the immune-mediated destruction of orexin neurons, bringing about the symptoms of narcolepsy



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Narcolepsy Type 1

- An autoimmune process kills off all the orexin producing neurons during adolescents resulting in 5 key symptoms
  - 1- Excessive daytime sleepiness despite adequate sleep at night
  - 2- Muscle weakness (cataplexy)
  - 3- Inability to move at the start or end of sleep
  - 4- Vivid hallucinations at the start or end of sleep
  - 5- Fragmented sleep

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Narcolepsy Type 2

- Known as narcolepsy without cataplexy
- A rare neurologic disease characterized by excessive daytime sleepiness associated with uncontrollable sleep urges and sometimes sleep paralysis, and hypnagogic/hypnopompic hallucinations.
- Usually do not have muscle weakness triggered by emotions.
- Usually also have less severe symptoms than Narcolepsy Type 1 and have normal levels of the brain hormone orexin (hypocretin)
- The majority of narcolepsy cases — about 80%

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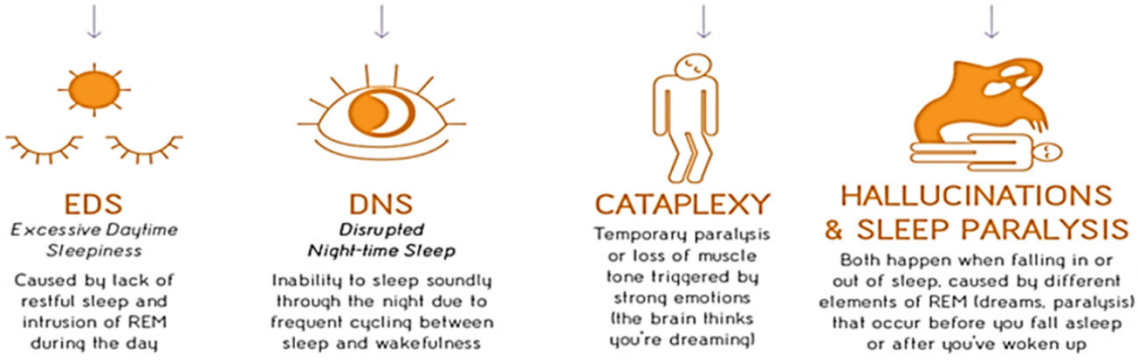
Classic Pentad of Narcolepsy



Only a minority of patients with narcolepsy experience all 5 symptoms

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Excessive daytime sleepiness

- The inability to stay awake and alert during the major waking episodes of the day, resulting in periods of irrepressible need for sleep or unintended lapses into drowsiness or sleep. (ICSD-3 AASM, 2023)
- Sleepiness is usually the most challenging symptom
  - May doze of with little to no warning in any situation
    - Usually sitting down or working at computer but don't sleep more than healthy people in given 24 hour period
    - May continue doing tasks while asleep (automatic behavior)- "highway hypnosis"
      - In Narcolepsy patients this happens daily
  - Short 15 minute nap can substantially improve alertness for a few hours
    - Suggest the sleepiness of narcolepsy is caused by problem of brain circuits that normally promote full alertness rather than the poor quality or insufficient sleep
- When a healthy person goes to bed they go through the sleep cycle lasting an hour or more before they reach rapid eye movement (REM)- stage of sleep categorized by dreaming
- Narcolepsy- people fall asleep very quick in as little a few minutes and quickly enter REM
  - Results in very vivid dreams even in naps

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Cataplexy

- Refers to episodes of muscle weakness triggered by strong emotions
  - Positive emotions (laughing at joke or winning a game) are most common triggers
    - May occur with intense anger, fear or surprise
  - ***Mild***- usually only effects head, face and neck (jaw dropping involuntarily, eye lid droop)
  - ***Severe***- can cause total body weakness or paralysis causing person to slump to ground and unable to move for a minute or two even though they are awake
- Severe impact on life both from physical perspective (can get hurt when collapse), as well as psychological perspective (anxious about having cataplexy in public and avoid situations that might elicit episodes)
  - - Social Avoidance
- In children and in people whose symptoms started within the past six months it can look sudden, uncontrollable grimacing or face-scrunching, sticking tongue out or loss of muscle tone.

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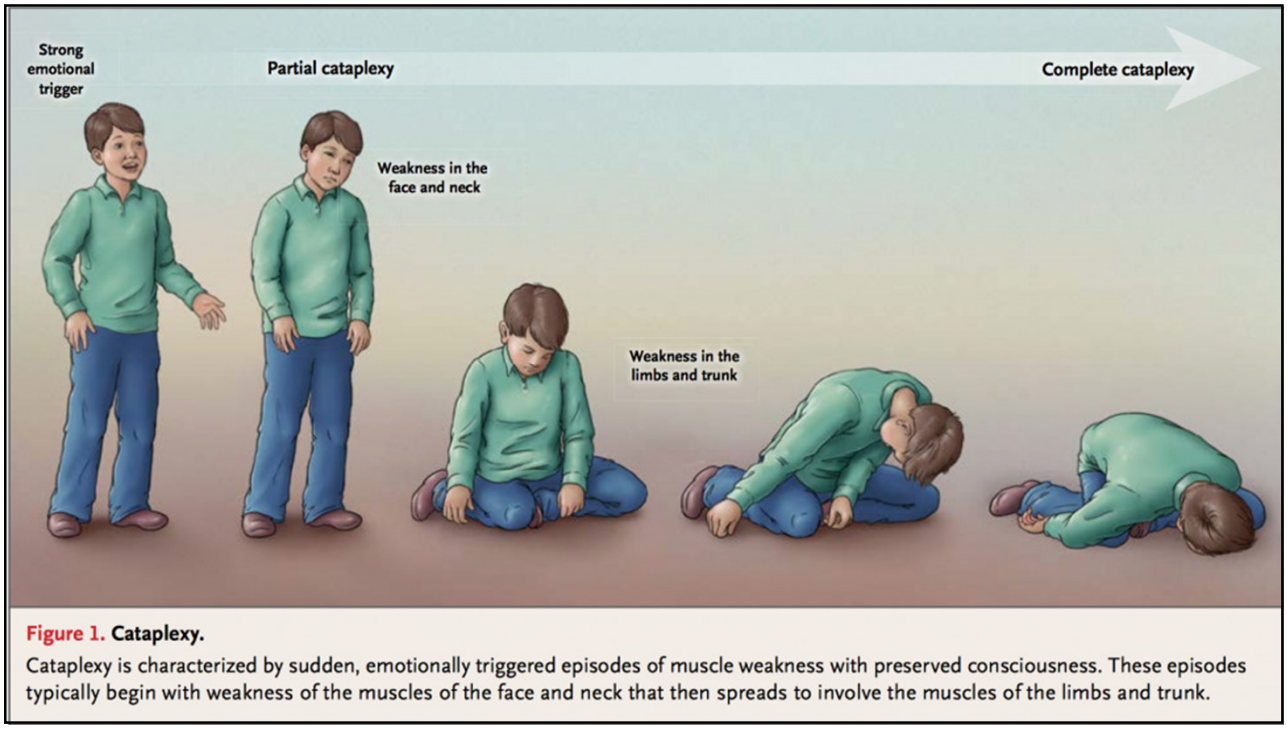

Figure 1. Cataplexy.
Cataplexy is characterized by sudden, emotionally triggered episodes of muscle weakness with preserved consciousness. These episodes typically begin with weakness of the muscles of the face and neck that then spreads to involve the muscles of the limbs and trunk.

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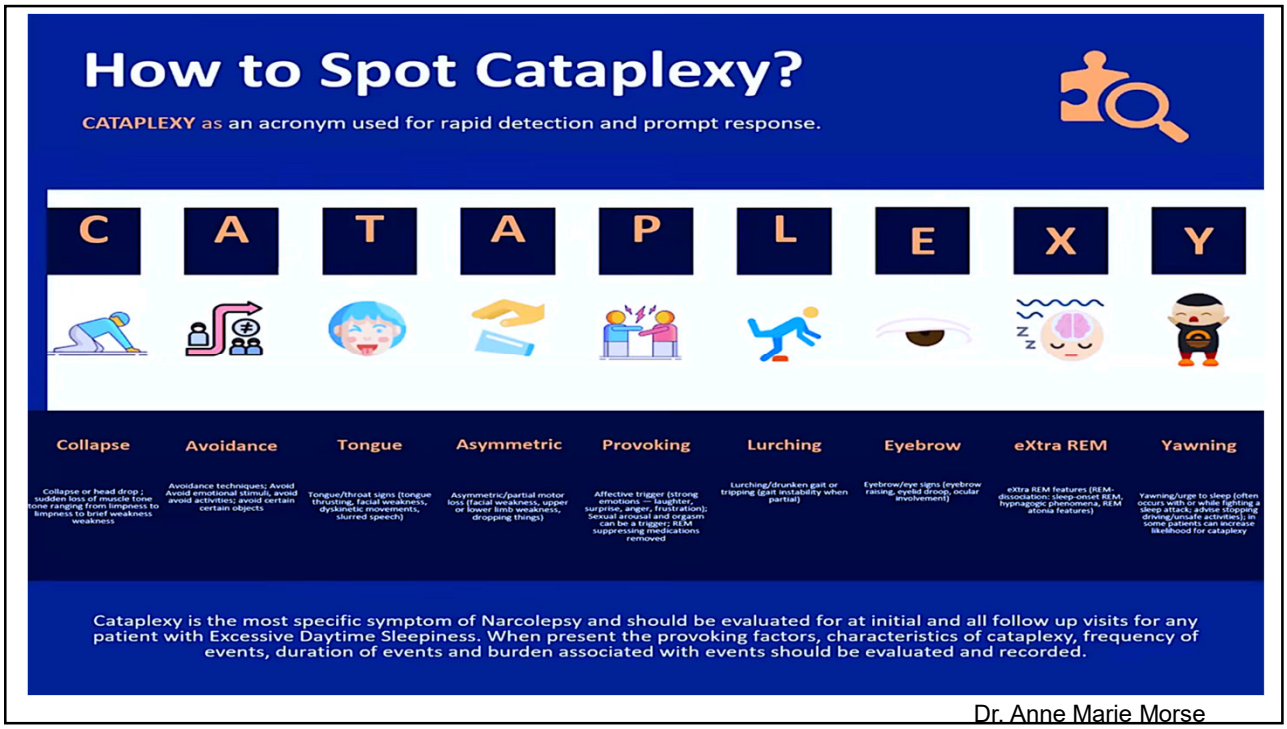

Dr. Anne Marie Morse

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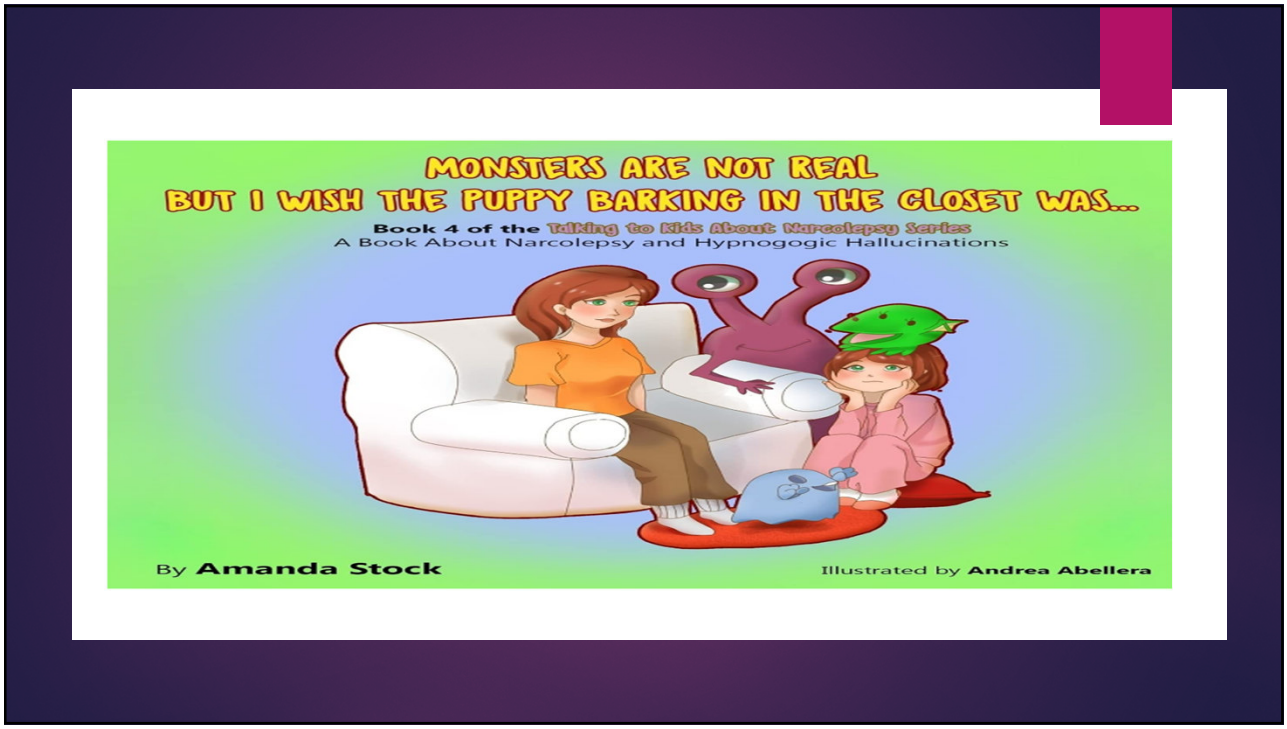

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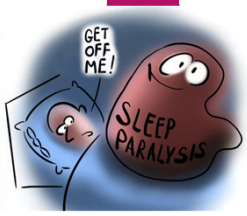
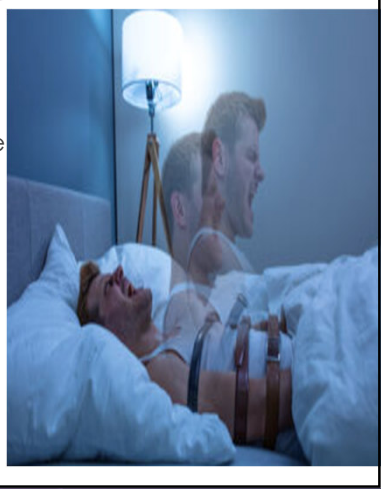
Sleep Paralysis



- Complete inability to move for a few moments immediately after awakening or just when falling asleep
- During REM sleep the brain is very active but the voluntary muscles of the body are paralyzed to prevent acting out dreams
  - This paralysis generally subsides upon awakening, but occasionally regain consciousness before paralysis has worn off
  - May be more frightening because the immobility may be accompanied by hypnopompic hallucinations or a sense of suffocation (75%)
    - Both paralysis and hypnopompic hallucinations can occur in healthy people if they have not been getting enough sleep



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Disrupted Nocturnal Sleep

- Although patients are sleeping through most of the day, there is fragmented sleep at night
  - Same as maintaining wakefulness during the day, they have difficulty maintaining sleep through the night
    - **"Very rarely am I fully awake and very rarely am I fully asleep- I live in between"**
- Spontaneously wake several times at night and can take 10-15 or more minutes to fall back asleep

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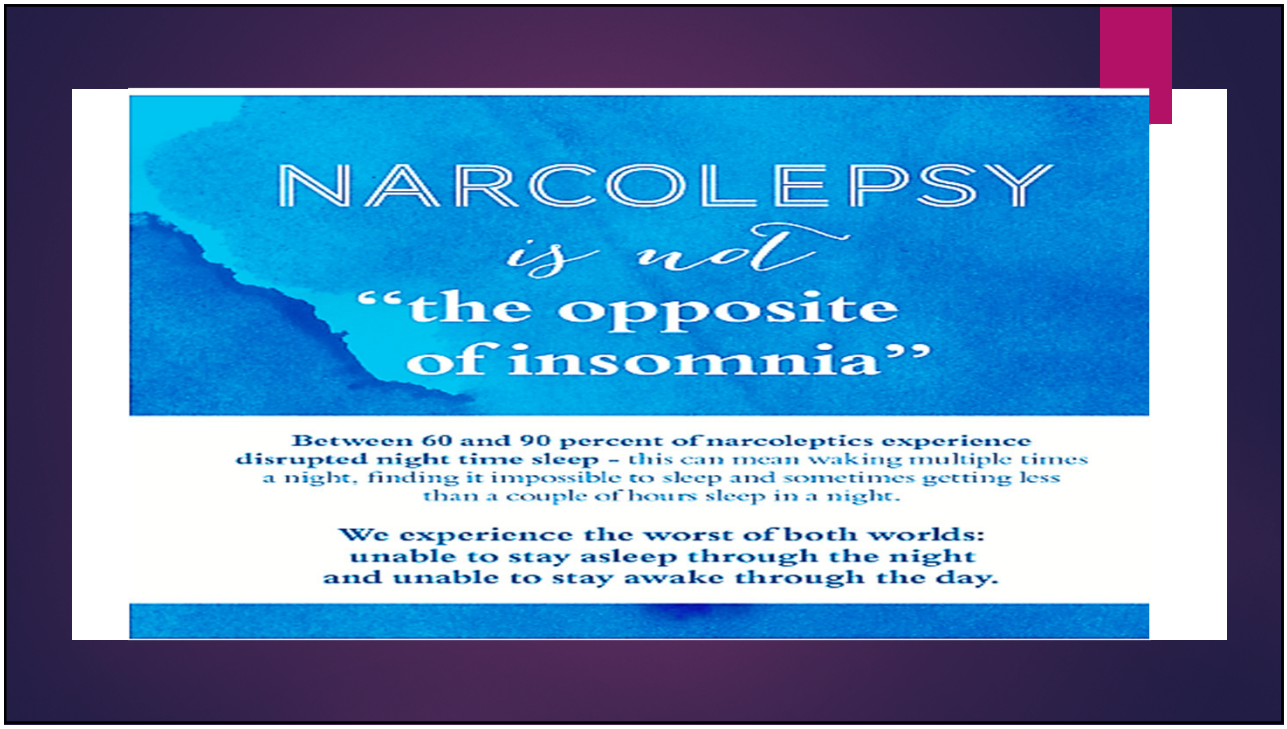

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Presentation in Children

- Sleepiness may present with reappearance of regular napping
- MSLT: no normative data in children < 6-year.
  - Adolescents: the most common etiologies of short sleep onset in MSLT, often with multiple SOREMPs, are chronic sleep deprivation and delayed sleep phase disorder
- Behavioral problems may occur at the onset of the disorder. Symptoms may be hidden by the patients.
- Inattentiveness, insomnia, lack of energy, bizarre hallucinations, or combination thereof can lead to psychiatric misdiagnosis (ADD/ADHD)
  - Medications for wrong diagnosis can mask the symptoms of Narcolepsy

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Missed vs Misdiagnosis

- Narcolepsy is often misdiagnosed as psychological or emotional disorders such as depression, ADD, ADHD, bipolar, and even physiological disorders as in sleep apnea, insomnia, malingering, seizures.
  - Small airway patient with mild OSA or UARS may actually have narcolepsy- if optimally treating the airway and patient still suffers with EDS then need to consider narcolepsy as a differential diagnosis.
- A diagnosis of narcolepsy may be missed for many 10-25 years

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Idiopathic Hypersomnia (IH)

Idiopathic Hypersomnia (IH) is a chronic sleep disorder of the brain, and the cause is unknown.

- NOT a disorder of REM sleep as there is no REM sleep present on MSLT
- Affects the brain's ability to control sleep and wakefulness
  - The sleep drive is too active therefore the sleep mechanisms are dominating
- Causes excessive daytime sleepiness (EDS) in which there is a strong need to sleep during the day, even though there was enough sleep the night before
  - Take long naps but do not feel any better upon awakening.

People who have IH may spend most of their day either sleeping or thinking about, craving, or even fighting the urge to sleep, which can severely impact their quality of life.

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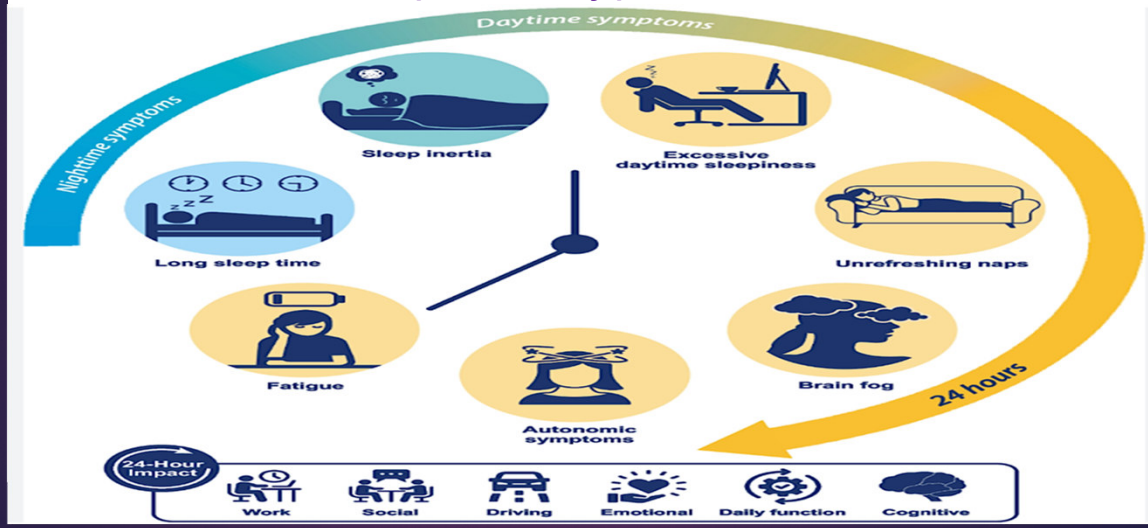
Idiopathic Hypersomnia



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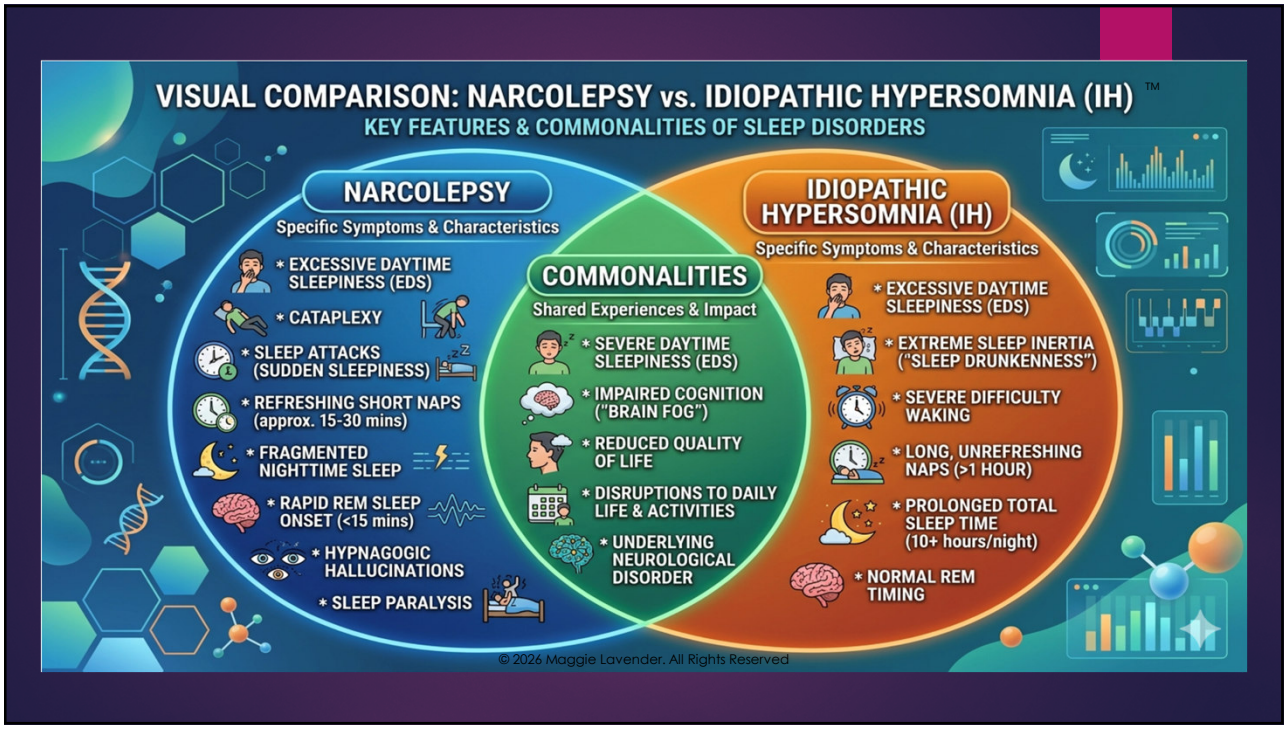

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Diagnostic techniques to differentiate between IH and Narcolepsy

- A clinical examination and detailed medical history are essential for diagnosis and treatment of narcolepsy.
  - Sleep journal noting the times of sleep and symptoms over a one- to two-week period.
  - A physical exam can rule out or identify other neurological/physical conditions that may be causing the symptoms.
  - **The Epworth Sleepiness Scale (ESS)-** A simple questionnaire to measure excessive sleepiness and differentiate it from normal daytime sleepiness.
  - **The Idiopathic Hypersomnia Severity Scale (IHSS)-** 14 item questionnaire used to assess the severity, frequency, and functional impact of hypersomnia symptoms, particularly sleep inertia and excessive daytime sleepiness
- Two specialized tests (performed in a sleep disorders clinic) are required to establish a diagnosis of narcolepsy:
  1. **Polysomnogram (PSG or sleep study)**
  2. **Multiple sleep latency test (MSLT)**
- Occasionally, it may be helpful to measure the level of hypocretin in the fluid that surrounds the brain and spinal cord. A sample of the cerebrospinal fluid is drawn using a lumbar puncture (also called a spinal tap) and measure the level of hypocretin-1.

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Epworth Sleepiness Scale

Epworth Sleepiness Scale

Scale
0= No chance of dozing 1= Slight chance of dozing 2= Moderate chance of dozing 3= High chance of dozing

How often do you doze?

Sitting and reading	0	1	2	3
Watching television	0	1	2	3
Sitting in a public inactive place (theater or meeting)	0	1	2	3
Riding in a car for one hour without a break (as a passenger)	0	1	2	3
Lying down in the afternoon when circumstances permit	0	1	2	3
Sitting and talking to someone	0	1	2	3
Sitting quietly after lunch, without alcohol	0	1	2	3
Stopped in traffic for a few minutes	0	1	2	3

Total _____

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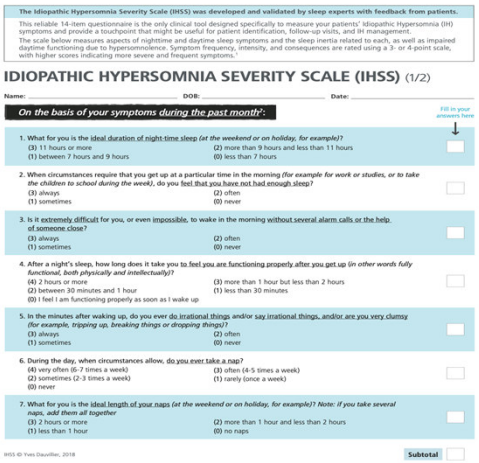
Idiopathic Hypersomnia Severity Scale



The Idiopathic Hypersomnia Severity Scale (IHSS) was developed and validated by sleep experts with feedback from patients.

This reliable 14-item questionnaire is the only clinical tool designed specifically to measure your patients' Idiopathic Hypersomnia (IH) symptoms and provide a touchpoint that might be useful for patient identification, follow-up visits, and IH management.

The scale below measures aspects of nighttime and daytime sleep symptoms and the sleep inertia related to each, as well as impaired daytime functioning due to hypersomnolence. Symptom frequency, intensity, and consequences are rated using a 3- or 4-point scale, with higher scores indicating more severe and frequent symptoms.[1]

IDIOPATHIC HYPERSOMNIA SEVERITY SCALE (IHSS) (1/2)

Name: _____ DOB: _____ Date: _____

***On the basis of your symptoms during the past month*[1]:**

Fill in your answers here

1. What for you is the ideal duration of night-time sleep *(at the weekend or on holiday, for example)*?
(3) 11 hours or more (2) more than 9 hours and less than 11 hours
(1) between 7 hours and 9 hours (0) less than 7 hours

2. When circumstances require that you get up at a particular time in the morning *(for example for work or studies, or to take the children to school during the week)*, do you feel that you have not had enough sleep?
(3) always (2) often
(1) sometimes (0) never

3. Is it extremely difficult for you, or even impossible, to wake in the morning without several alarm calls or the help of someone close?
(3) always (2) often
(1) sometimes (0) never

4. After a night's sleep, how long does it take you to feel you are functioning properly after you get up *(in other words fully functional, both physically and intellectually)*?
(4) 2 hours or more (3) more than 1 hour but less than 2 hours
(2) between 30 minutes and 1 hour (1) less than 30 minutes
(0) I feel I am functioning properly as soon as I wake up

5. In the minutes after waking up, do you ever do irrational things and/or say irrational things, and/or are you very clumsy *(for example, tripping up, breaking things or dropping things)*?
(3) always (2) often
(1) sometimes (0) never

6. During the day, when circumstances allow, do you ever take a nap?
(4) very often (6-7 times a week) (3) often (4-5 times a week)
(2) sometimes (2-3 times a week) (1) rarely (once a week)
(0) never

7. What for you is the ideal length of your naps *(at the weekend or on holiday, for example)? Note: if you take several naps, add them all together*
(3) 2 hours or more (2) more than 1 hour and less than 2 hours
(1) less than 1 hour (0) no naps

IHSS © Yves Dauvilliers, 2018 Subtotal

IDIOPATHIC HYPERSOMNIA SEVERITY SCALE (IHSS) (2/2)

8. In general, how do you feel after a nap?
(3) very sleepy (2) sleepy
(1) awake (0) wide awake

9. During the day, while carrying out activities that are not very stimulating, do you ever struggle to stay awake?
(4) very often (at least twice a day) (3) often (4-7 times a week)
(2) sometimes (2-3 times a week) (1) rarely (once a week or less)
(0) never

10. Do you consider that your hypersomnolence has an impact on your general health *(i.e. lack of energy, no motivation to do things, physical fatigue on exertion, decrease in physical fitness)*?
(4) very significant (3) significant
(2) moderate (1) minor
(0) no impact

11. Do you consider that your hypersomnolence is a problem in terms of your proper intellectual functioning *(i.e. problems with concentration, memory problems, decrease in your intellectual performance)*?
(4) very significant (3) significant
(2) moderate (1) minor
(0) no problem

12. Do you consider that your hypersomnolence affects your mood *(for example sadness, anxiety, hypersensitivity, irritability)*?
(4) very severely (3) severely
(2) moderately (1) slightly
(0) not at all

13. Do you consider that your hypersomnolence prevents you from carrying out daily tasks properly *(family-related or household tasks, school, leisure or job-related tasks)*?
(4) very significantly (3) significantly
(2) moderately (1) slightly
(0) not at all

14. Do you consider that your hypersomnolence is a problem in terms of your driving a car?
(4) very significant (3) significant
(2) moderate (1) minor
(0) no problem/I do not drive

Interpreting IHSS Scores TOTAL SCORE

Patients' IHSS scores will range from 0 to 50, with higher scores indicating more severe IH symptoms. A score of 22 or below is typical for people without any sleep disorder. Additionally, a cutoff score of 26 can reliably discriminate between treated and untreated patients with IH. A 4-point change in the IHSS represents a minimum clinically important difference.[1,2]

For any information on the use of the IHSS, please contact Mapi Research Trust, Lyon, France. Internet: https://eprovide.mapi-trust.org

Sources: 1. Dauvilliers Y, Evangelista E, Barateau L, et al. Measurement of symptoms in idiopathic hypersomnia: the Idiopathic Hypersomnia Severity Scale. Neurology. 2019;92(5):e517-e527. 2. Dauvilliers Y. Idiopathic hypersomnia severity scale. 2018. Accessed October 3, 2022. http://links.lww.com/WNL/A854. 3. Dauvilliers Y, Evangelista E, Barateau L, et al. Idiopathic Hypersomnia Severity Scale to better quantify symptoms severity and their consequences in Idiopathic hypersomnia. J Clin Sleep Med. 2022;18(3):817-829.

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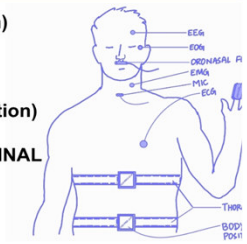
PSG or Sleep Study Polysomnogram

- Continuously records brain waves, breathing, and eye movments during sleep, as well as a number of nerve and muscle functions during nighttime sleep. The study is used to evaluate sleep disorders, such as sleep apnea, periodic limb movement disorder (PLMD), Narcolepsy, and hypersomnia.
- Can help reveal whether REM sleep occurs early in the sleep cycle and if an individual's symptoms result from another condition such as sleep apnea.

***Mnemonic:* SLEEP TOM**

SATURATION (oxygen)
LIMB ACTIVITY
EEG & EOG
ECG & EMG
POSITION (Body position)

THORACIC & ABDOMINAL MOVEMENT
ORONASAL FLOW
Mic (snoring mic)



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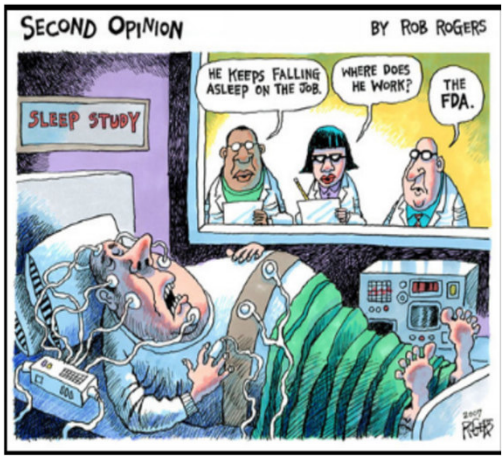

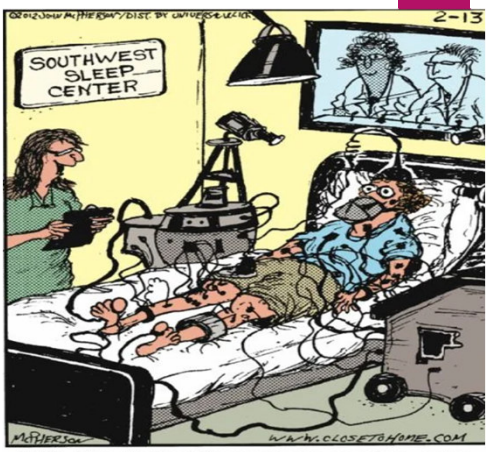

"OK, Mrs. Tully. We want you to relax, get a good night's sleep, and we'll evaluate any sleep issues that you have."

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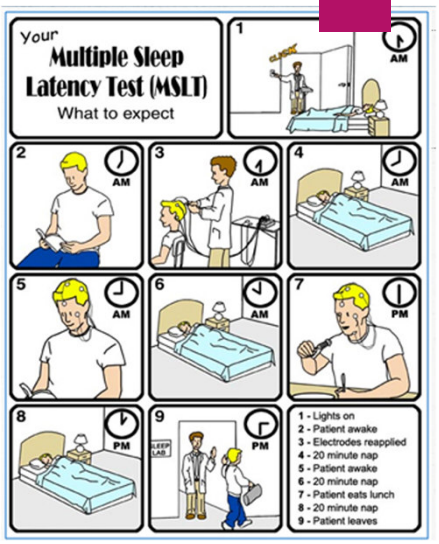
MSLT
Multiple Sleep Latency Test

- Most widely used and accepted, validated, objective measure of the ability or tendency to fall asleep.
- Assesses daytime sleepiness by measuring how quickly a person falls asleep and whether they enter REM sleep.
- Takes place the day after an overnight sleep study (polysomnogram).
  - In order to ensure the patient has a good night's sleep and to exclude other sleep disorders.
- What is being measured?
  - Mean sleep latency (MSL)
  - The number of sleep-onset rapid eye movement (REM) periods (SOREMPs)- within 15 minutes of sleep onset



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MSLT

- Full-day test that consists of four to five scheduled 20-40 minute naps in order to measure the time it takes to fall asleep. After the first nap trial, each nap trial is 2 hours after the start of the prior nap trial.
  - People with healthy sleep habits fall asleep in about 15 to 20 minutes.
    - ***Mild hypersomnia-*** 10-15 minutes
    - ***Moderate hypersomnia-*** 5-10 minutes
    - ***Severe hypersomnia-*** under 5 minutes
  - Literature states that in patients with narcolepsy, PSG and MSLT will show a much shorter duration of time (fewer than 8 minutes) from wakefulness into sleep.
- At least 2 of the naps are REM-onset (the active sleep phase associated dreaming).
  - Most narcolepsy patients don't meet this criteria but have all of the classic symptoms and meet all other criteria then the 2 SOREMPs weigh more for diagnosis.

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Treatment

- There is no cure for hypersomnia sleep disorders (idiopathic hypersomnia and narcolepsy).
  - Some of the symptoms can be treated with medicines and lifestyle changes.

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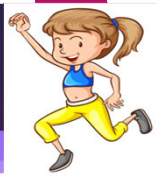
Lifestyle changes



- Drug therapy should accompany various lifestyle changes. Remembering the following seven tips may be helpful:
  1. Take short naps. Many individuals take short, regularly scheduled naps at times when they tend to feel sleepiest.
  2. Maintain a regular sleep schedule. Going to bed and waking up at the same time every day, even on the weekends, can help people sleep better.
  3. Avoid caffeine or alcohol before bed. Individuals should avoid alcohol and caffeine for several hours before bedtime.
  4. Avoid smoking, especially at night.
  5. Exercise daily. Exercising for at least 20 minutes per day at least four or five hours before bedtime also improves sleep quality and can help people with narcolepsy avoid gaining excess weight.
  6. Avoid large, heavy meals right before bedtime. Eating very close to bedtime can make it harder to sleep.
  7. Relax before bed. Relaxing activities such as a warm bath before bedtime can help promote sleepiness. Also make sure the sleep space is cool and comfortable.
- Safety precautions, particularly when driving, are important for everyone with narcolepsy. Suddenly falling asleep or losing muscle control can transform actions that are ordinarily safe, such as walking down a long flight of stairs, into hazards.

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Medications

Antidepressants—Two classes of antidepressant drugs have proven effective in controlling cataplexy in many individuals: tricyclics (including imipramine, desipramine, clomipramine, and protriptyline) and selective serotonin and noradrenergic reuptake inhibitors (including venlafaxine, fluoxetine, and atomoxetine).

Amphetamine-like stimulants—In cases where modafinil, armodafinil or Sunosi is not effective, doctors may prescribe amphetamine-like stimulants such as methylphenidate or adderall to alleviate EDS. However, these medications must be carefully monitored because they can have side effects.

CNS stimulants and wake promoting agents—Modafinil is usually prescribed first because it is less addictive and has fewer side effects than older stimulants. Next in line is armodafinil and Sunosi. For most people these drugs are generally effective at reducing daytime drowsiness and improving alertness.

Histamine 3 receptor antagonist/inverse agonist—Pitolisant was recently approved by FDA as the only non-scheduled product for treating excessive daytime sleepiness or cataplexy in adults with narcolepsy. Pitolisant, which has been commercially available in the U.S. since 2019, is thought to increase histamine levels in the brain. The most common adverse reactions to Pitolisant are insomnia, nausea, and anxiety.

Sodium oxybate and Mixed salt oxybate—Sodium oxybate (also known as gamma hydroxybutyrate or GHB) has been approved by the U.S. Food and Drug Administration (FDA) to treat cataplexy and excessive daytime sleepiness in individuals with narcolepsy. Due to safety concerns associated with the use of this drug, the distribution of sodium oxybate is tightly restricted. (Xyrem, Xywav, Lumryz)

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Treatment Options

Table: FDA Approved Medications for Treatment of Symptoms of Narcolepsy[1,3,6]

Agent	Used to Treat	Mechanism of Action	Adverse Effects
Modafinil	EDS	Probable selective inhibition of dopamine reuptake.	Headache, anxiety, nausea, dry mouth, diarrhea, reduced efficacy of oral contraceptives, and rarely, Stevens-Johnson syndrome.
Armodafinil	EDS		
Methylphenidate	EDS	Inhibition of reuptake of DA, ST, and NE.	Hypertension, arrhythmias, anorexia, and psychosis.
Dextroamphetamine	EDS		
Amphetamine/ Dextroamphetamine	EDS		
Sodium oxybate	Cataplexy, EDS	Metabolite of gamma aminobutyric acid, used to treat multiple symptoms of narcolepsy.	Nausea, mood swings, enuresis, sleep apnea, psychosis is rare. High sodium content contributes to hypertension, heart failure, renal failure.
Venlafaxine	Cataplexy	Inhibition of reuptake of DA, ST, and NE.	Nausea, dizziness, dry mouth, headache, insomnia, sexual dysfunction.
Fluoxetine	Cataplexy	Inhibits the presynaptic reuptake of the SE.	Nausea, dry mouth, headache, diarrhea, sexual dysfunction.
Clomipramine	Cataplexy	Block reuptake of SE and NE in presynaptic terminals.	Dry mouth, light-headedness, constipation, urinary retention.
Protriptyline	Cataplexy		
Pitolisant	Cataplexy, EDS	Blocks histamine inhibition, enhances histamine release, and modulates neurotransmitter responses to increase acetylcholine and DA levels in the cerebral cortex but not in the striatal cortex.	Insomnia, headache, nausea, anxiety, QTc prolongation. Pitolisant is contraindicated in patients with severe hepatic impairment.
Solriamfetol	EDS	DA/NE reuptake inhibitor that increases extracellular concentrations of DA and NE in the striatum and prefrontal cortex to promote wakefulness; effects are attributed to DA and NE transporters, and not to histamine or orexin	Headache, nausea, decreased appetite, nasopharyngitis, dry mouth, and anxiety. Dose-dependent effects on blood pressure and heart rate have been reported.

DA = dopamine; EDS = excessive daytime sleepiness; NE = norepinephrine; REM = rapid eye movement; ST = serotonin.

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Antidepressants

SNRIs

SSRIs

- Works by **increasing serotonin levels, norepinephrine, and dopamine in the brain** by blocking transport proteins and stopping their reuptake at the presynaptic terminal.
  - This action leads to more transmitters available at the synapse and ultimately increases the stimulation of postsynaptic receptors.
- **SNRIs act primarily upon serotonergic and noradrenergic neurons but have little or no effect upon cholinergic or histaminergic receptors.**
- More potent inhibitor of serotonin reuptake than norepinephrine reuptake.
  - Essentially a selective serotonin reuptake inhibitor at 75 mg, and
  - With higher doses up to 225 mg/day, it has significant effects on the norepinephrine transporter in addition to serotonin

- Works by blocking the reuptake of serotonin into presynaptic serotonin neurons by blocking the reuptake transporter protein located in the presynaptic terminal, therefore **increasing serotonin levels in the brain.**
  - Has mild activity at the 5HT2A and 5HT2C receptors.
  - Has minimal activity on noradrenergic reuptake.
- Active metabolite is norfluoxetine, which gets produced when the cytochrome P450 enzyme (CYP2D6) acts on it.
  - Important to remember that fluoxetine has several drug-drug interactions due to its metabolism at the CYP2D6 isoenzyme. Additionally, norfluoxetine can have an inhibitory effect on CYP3A4.

Helps reduce the number of cataplexy events in patients with narcolepsy.

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Stimulants and other Wake Promoting Agents

Schedule II

- ***Methylphenidate*** (MPH) non-competitively blocks the reuptake of dopamine and noradrenaline into the terminal by blocking the dopamine transporter (DAT) and noradrenaline transporter (NAT)**, increasing levels of dopamine and noradrenaline** in the synaptic cleft.
- ***Amphetamine*** (Adderall and Vyvanse) is a central nervous (CNS) system stimulant that functions **by increasing the amounts of dopamine, norepinephrine, and serotonin** (to a lesser extent) in the synaptic cleft through a variety of mechanisms.
- ***Only helps EDS- NO effect on cataplexy***
- ***Systemic action and can increase HR and BP***

Schedule III

- ***Modafinil and Armodafinil*** are thought to act as an inhibitor of dopamine transporter (DAT) through weak competitive binding and enhance neuronal activity in hypothalamus therefore **increasing dopamine levels**.
  - *Modafinil*- racemic mixture of S- and R-enantiomers
  - *Armodafinil*- longer-lasting R enantiomer of racemic modafinil
    - Broken down slower and is the more active compound that blocks the dopamine transporter better

Schedule IV

- ***Sunosi*** is thought to work by selectively inhibiting the reuptake of dopamine and norepinephrine, therefore increases both dopamine and norepinephrine
  - It is not considered a stimulant

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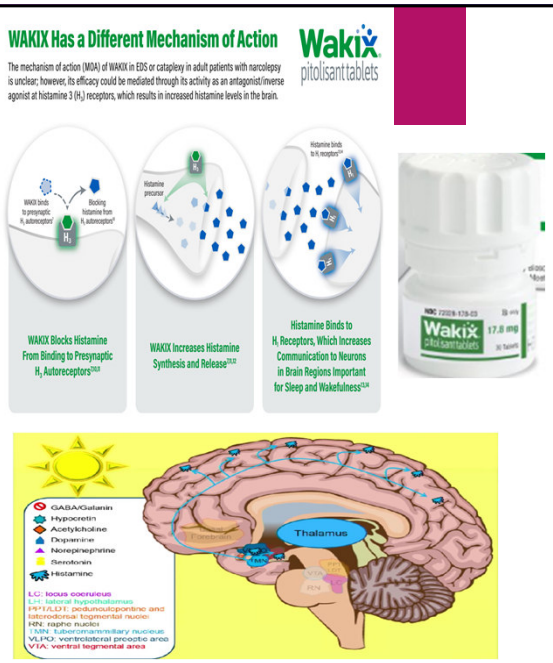
Non-stimulant Wake Promoting Agent

- WAKIX was FDA approved Aug. 15, 2019 for the treatment of excessive daytime sleepiness (EDS) or cataplexy in adult patients with narcolepsy with once daily morning dosing.
- Pediatric indication on June 24, 2024 for excessive daytime sleepiness (EDS), February 2026 for cataplexy in children 6 years of age and older with narcolepsy.
- Wakix, a first-in-class medication, is a selective histamine 3 (H_3) receptor antagonist/inverse agonist that works through a novel mechanism of action to increase the synthesis and release of histamine, a wake-promoting neurotransmitter in the brain.



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Sodium Oxybate

- Sodium oxybate was approved in 2002 by the U.S Food and Drug Administration (FDA) for *cataplexy or excessive daytime sleepiness (EDS)* treatment in *patients with narcolepsy* who are *seven years of age and older.*
  - Changed the management of Narcolepsy
- Sodium oxybate is the sodium salt of gamma-hydroxybutyrate (GHB), an endogenous compound and metabolite of the neurotransmitter GABA. It is postulated that the therapeutic effects of sodium oxybate on cataplexy and excessive daytime sleepiness are attributed to **GABA-B receptor agonist** activity.
- The precise mechanism by which sodium oxybate improves symptoms in patients with narcolepsy is not well understood. There is a hypothesis that **improved sleep might be due to the increased time spent in Stages N2 and N3, and the decrease shift to stages N1/Wake/REM, resulting in a deeper sleep**

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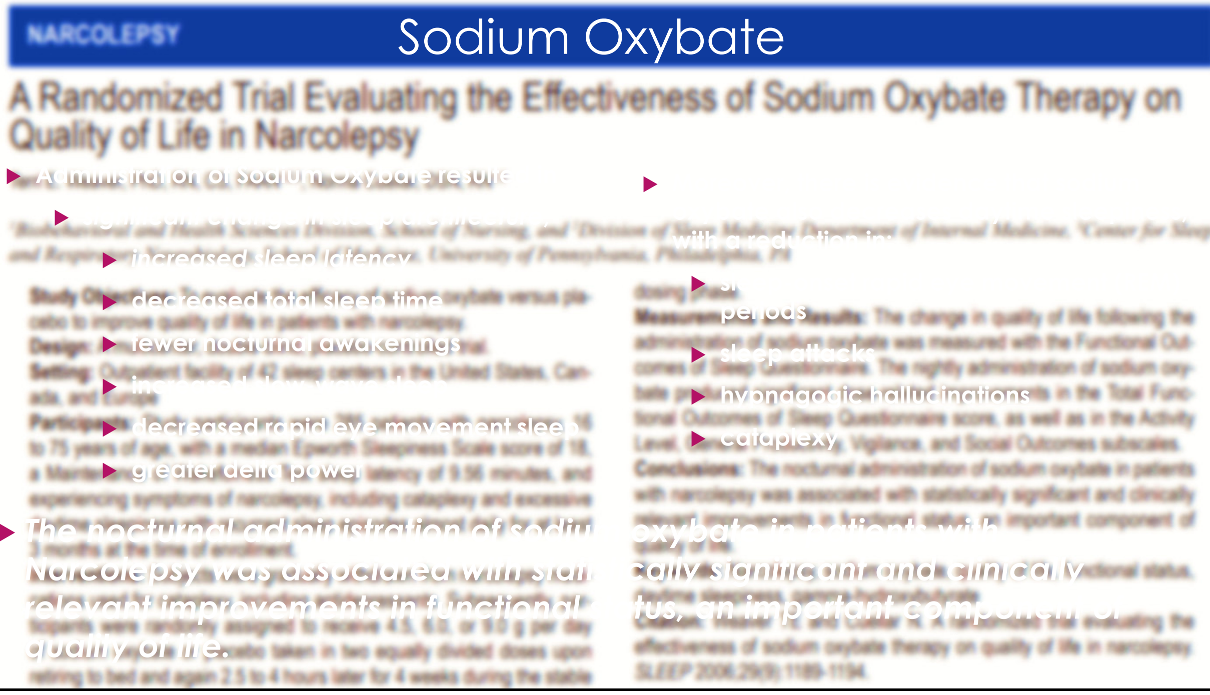
Sodium Oxybate



- Administration of Sodium Oxybate resulte
  - increased sleep latency
  - decreased total sleep time
  - fewer nocturnal awakenings
  - decreased rapid eye movement sleep
  - greater delta power
- with a reduction in:
  - periods
  - sleep attacks
  - hypnagogic hallucinations
  - cataplexy
- *The nocturnal administration of sodiu oxybate in patients with Narcolepsy was associated with stati cally significant and clinically relevant improvements in functional tus, an important component of quality of life.*

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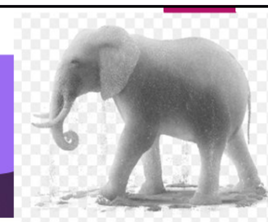
Sodium Oxybate Formulations



XYREM (sodium oxybate) oral solution CIII

XYREM® (sodium oxybate) oral solution, 0.5 g/mL is a prescription medicine used to treat the following symptoms in people 7 years of age or older with narcolepsy: sudden onset of weak or paralyzed muscles (cataplexy) and excessive daytime sleepiness (EDS)

1640 mg sodium per 9 gram dose

xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution CIII

XYWAV® (calcium, magnesium, potassium, and sodium oxybates) oral solution, 0.5 g/mL total salts (equivalent to 0.413 g/mL of oxybate) is a prescription medicine used to treat the following symptoms in people 7 years of age or older with narcolepsy: sudden onset of weak or paralyzed muscles (cataplexy) and excessive daytime sleepiness (EDS).

131 mg sodium per 9 gram dose

Lumryz (sodium oxybate) for extended-release oral suspension CIII

LUMRYZ is an extended-release sodium oxybate approved by the U.S. Food and Drug Administration (FDA) as the one and only once-at-bedtime treatment for cataplexy or excessive daytime sleepiness (EDS) in adults and children 7 years of age or older with narcolepsy.

1640 mg sodium per 9 gram dose

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Nature and Science of Sleep

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REVIEW

Comparative Efficacy and Safety of Multiple Wake-Promoting Agents for the Treatment of Excessive Daytime Sleepiness in Narcolepsy: A Network Meta-Analysis

Shuqin Zhan[1], Hui Ye[2], Ning Li[1], Yimeng Zhang[1], Yueyang Cheng[1], Yuanqing Wang[1,3], Shimin Hu[1], Yue Hou[1]

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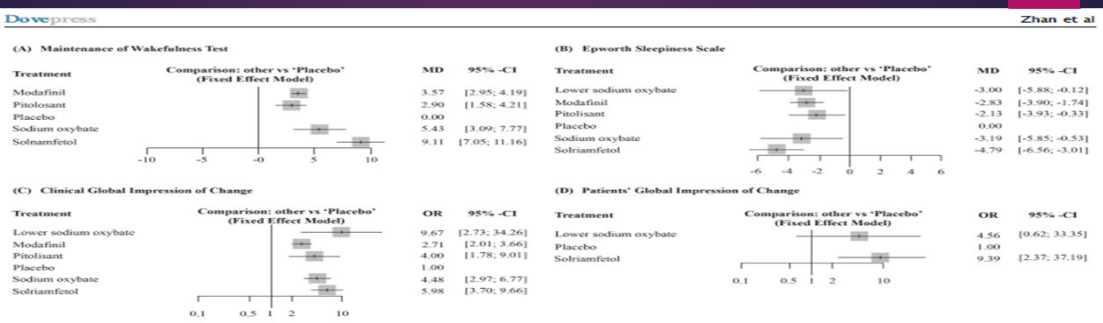

*Modafinil, SXB, pitolisant, solriamfetol, and LXB showed a significant efficacy compared with placebo for MWT and ESS outcomes at **varying degrees**, indicating these wake-promoting agents could effectively alleviate sleepiness and sustain wakefulness.*

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Treatment of Idiopathic Hypersomnia

- Only FDA approved treatment for adults with IH is Xywav
- Other treatment choices will work but it is considered off label use-
  - Stimulants
  - Modafinil
  - Armodafinil
  - Sunosi
- Lumryz currently being investigated to treat idiopathic hypersomnia (IH).
  - The Phase 3 REVITALYZ trial (NCT06525077) is assessing its efficacy/safety, with results expected in Q2 2026.
  - It is already FDA-approved for narcolepsy and has received orphan drug designation for IH

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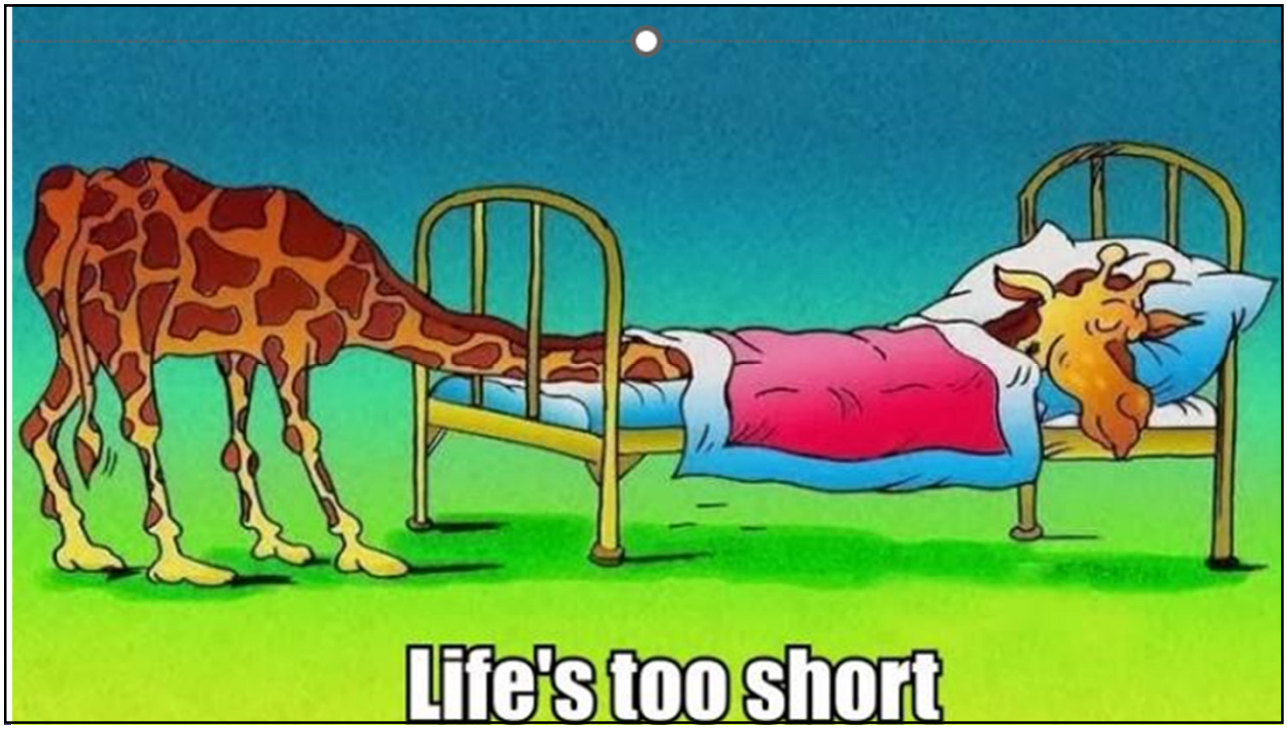

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Looking into the Future

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Orexin Receptor 2 Agonist in Narcolepsy Type 1

Y. Dauvilliers, E. Mignot, R. del Río Villegas, Y. Du, E. Hanson, Y. Inoue, H. Kadali, E. Koundourakis, S. Meyer, R. Rogers, T.E. Scammell, S.I. Sheikh, T. Swick, Z. Szakács, P. von Rosenstiel, J. Wu, H. Zeitz, N.V. Murthy, G. Plazzi, and C. von Hehn

ABSTRACT

Orexin Receptor Agonists as Possible Treatment for Narcolepsy and Idiopathic Hypersomnia

Ahmed F. Abdel-Magid*

Cite This: ACS Med. Chem. Lett. 2022, 13, 1411−1412

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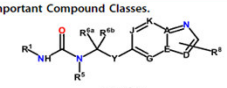
Important Compound Classes.



Formula 1

Title. Urea Orexin Receptor Agonists
Patent Publication Number. WO 2022/132696 A1
URL: https://patents.google.com/patent/WO2022132696A1/en?oq=WO+2022%2f132696+A1
Publication Date. June 23, 2022
Priority Application. US63/126,262
Priority Date. December 16, 2020
Inventors. Armacost, K. A. Chiriac, M. I.; Hurzy, D. M.; Kern, J. C. Liu, J.; Manley, P. J.; Nantermet, P.; Rada, V. L.; Rudd, M. T.; Stump, C. A.
Assignee Company. Merck Sharp & Dohme Corp., 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).
Disease Area. Excessive daytime sleepiness disorders such as narcolepsy, and idiopathic hypersomnia
Biological Target. Orexin receptors OX1R and OX2R
Summary. The invention in this patent application relates to urea derivatives represented generally by formula 1. These compounds are agonists of the orexin receptors and may potentially be used for the treatment or prevention of

intramolecular disulfide bridges. The second form, orexin B (OX-B), also known as hypocretin-2, is a linear 28 amino acid polypeptide. There are also two known (cloned and characterized) orexin receptors belonging to the super family of G-protein-coupled receptors (GPCRs) in mammals:

- orexin-1 receptor (OX or OX1R), which has binding selectivity for OX-A
- orexin-2 receptor (OX2 or OX2R), which has similar binding affinity for both OX-A and OX-B

Narcolepsy is a chronic neurological sleep disorder that causes excessive daytime sleepiness and sudden attacks of sleep. While patients may sleep well at night, they still suffer from daytime sleepiness and may fall asleep uncontrollably under normal or even hazardous circumstances. However, they may only need short naps to feel refreshed. Idiopathic hypersomnia is another sleep disorder with excessive daytime sleepiness. It is described as a pathological condition in which patients sleep long hours at night but may still need long naps of deeper sleep during the day.

The two orexin neuropeptides, OX-A and OX-B, play important roles in regulating the states of sleep and wakefulness. Researchers have determined that the loss of orexin-producing neurons causes narcolepsy in humans and rodents. This finding may provide an opportunity for potentially novel therapeutic approaches to treat excessive daytime sleepiness disorders, such as narcolepsy and idiopathic

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Orexin Receptor Agonists

- ***What are the implications for patients with narcolepsy in terms of treatment with Orexin Receptor Agonists?***
  - There is significant unmet need for patients with narcolepsy. **Current therapies only manage excessive daytime sleepiness and cataplexy and require patients to take several different therapies to address the multitude of symptoms they experience.**
  - OX2R agonists **target the underlying cause of the disease** (severe loss or absence of the neuropeptide orexin), which led to statistically **significant improvement in daytime wakefulness and weekly cataplexy rates were reduced** or abolished.

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Orexin Receptor Agonists

- **Current Studies and Upcoming Studies for Selective Orexin 2 Agonists:**
  - **Takada (Oveporexton) for Selected Central Hypersomnia Conditions**
    - FDA priority review for potential 2026 launch
    - Phase 3 trials ("FirstLight" and "RadiantLight")
  - **Alkermes (Alixorexton) for Narcolepsy Type 1 and Narcolepsy Type 2**
    - FDA granted Breakthrough Therapy Designation
    - A Phase 2, Parallel-Group, Dose-Range-Finding Study with Randomized Double-Blind Treatment and Open-Label Periods to Evaluate the Safety and Efficacy of ALKS 2680 in Subjects with Narcolepsy Type 1 and Narcolepsy Type 2
    - An Open-Label, Long-Term Extension Study to Investigate the Safety, Tolerability, and Durability of Treatment Effect of ALKS 2680 in Subjects With Narcolepsy Type 1 and Type 2
    - Phase 3 "Brillance" study initiated to evaluate once daily and split-dose regimens
  - **Alkermes (Alixorexton) for Idiopathic Hypersomnia**
    - A Phase 2, Randomized, Parallel-Group, Double-Blind, Dose-Range-Finding Study to Evaluate the Safety and Efficacy of ALKS 2680 in Subjects with Idiopathic Hypersomnia (Vibrance-3)
  - **Contessa Pharmaceuticals (Cleminorexton) for Narcolepsy and Idiopathic Hypersomnia**
    - A phase 2a, Randomized, Double-blind, Placebo-controlled Study of the Safety, Tolerabilty, Pharmacokinetics, and Pharmacodynamics of ORX750 in Subjects with Narcolepsy and Idiopathic Hypersomnia (CRYSTAL-1)
  - **Eisai Inc. (E2086) for Narcolepsy Type 1**
    - A Randomized, Double-Blind, Single-Dose, 5-Period Crossover Study to Evaluate the Efficacy, Safety and Tolerability of E2086 Compared to Placebo and Active Comparator in Adults Subjects with Narcolepsy Type 1 – phase Ib/II data presented late 2025

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Other Studies

- **Avadel (FT218) for Idiopathic Hypersomnia (REVITALYZ)**
  - Double-blind, Placebo-controlled, Randomized Withdrawal, Multicenter Study of the Efficacy and Safety of FT218 in the Treatment of Idiopathic Hypersomnia (IH)
- **Axsome (AXS-12 Reboxetine) for Narcolepsy (SYMPHONY)**
  - Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Assess the Efficacy and Safety of AXS-12 in the treatment of Cataplexy and Excessive Daytime Sleepiness in Subjects with Narcolepsy
    - Encore trial (phase 3) and Symphony trial (phase 3)
- **NLS Pharmaceutics (NLS-2 Mazindol Extended Release or Quilience) for Narcolepsy**
  - A Four-week, Double-blind, Placebo-controlled, Randomized, Multicenter, Parallel-group Study of the Safety and Efficacy on NLS-2 (Mazindol Extended Release) in Adults for the Treatment of Narcolepsy Type 1 and 2
- **Zevra therapeutics (KP1077 Serdexmethylphenidate SDX)**
  - Placebo-controlled, Double-Blind, Study to Determine the Safety and Efficacy of SDX in Patients with IH
    - Narcolepsy indication eligible for possible phase 3 study

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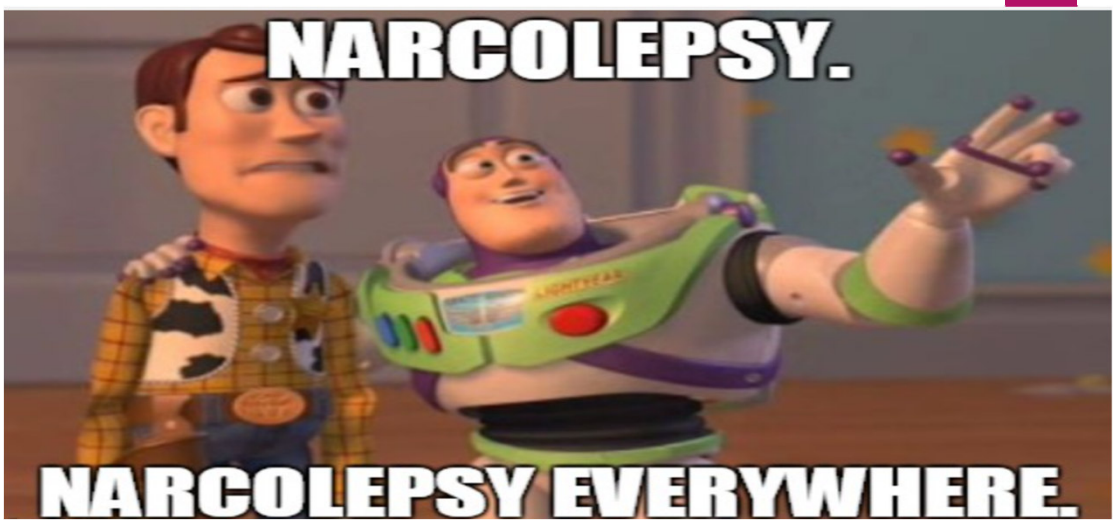

Don't forget about Idiopathic Hypersomnia!!

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Case Study

- 36 y/o female with complaints of **fatigue** and **sleep fragmentation** that has been present over the last 5 years but **worsening** in last 2 years after birth of child and increased life and work stressors. States **lack of motivation** some days to complete tasks and feels **overwhelmed** at times. **ESS 19**
- Basic blood work WNL, discussed sleep health improvements, discussed possible anxiety/depression, **denies SDB** but notes **history of bruxism** and wears OTC guard.
- **HST negative** for OSA.
- What is your next action?

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Case Study

- OTC sleep aides recommended, tried and failed as well as Ambien- no improvement noted.
- Pt complaining of difficulty waking in morning, needing caffeine and naps to get her through her day after occasional feelings of overwhelming exhaustion and weakness.
- NPSG ordered and revealed **mild Obstructive Sleep Apnea** (AHI 10 , RDI 23.9 , ODI 0.7 , minimum oxygen saturation 95 %, maximum Pes pull -16 cm H2O).
  - PAP 7 cm H2O EPR 3 initiated after titration study. Pt struggled with compliance and ability to keep on during night due to feeling of claustrophobia. **ESS 14**
  - Referred to DDS for OAT and pt able to tolerate through the night and states she is waking less often but sleep is still fragmented and fatigue and sleepiness has not improved.
- What is your next action?

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Case Study

- Further questioning reveals **sleepiness since childhood**, rare **sleep paralysis** and **hypnogogic hallucinations.**
- Discussion of "**overwhelming exhaustion and weakness**"
  - - pt notes that there are times she feels that her legs get so tired they struggle to keep her up and it is harder for her to think clearly and get her words out.
  - - often happens in stressed environment or at time she gets upset
  - - she will take a nap and symptoms improve ("I must have been tired")
- Diagnostic polysomnogram with OAT that demonstrated **very mild Obstructive Sleep Apnea** (AHI 5.3 , RDI 12.2 , ODI 0.4 , minimum oxygen saturation 95 %, maximum Pes pull -9 cm H2O).
- Multiple Sleep Latency Test (MSLT) performed that was consistent with the **diagnosis of narcolepsy** (4 episodes of sleep out of 4 scheduled naps, average sleep-onset latency of 1.5 minutes, 2 SOREMP).

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Case Study

- Initiated armodafinil 250 based on insurance requirement without improvement. (ESS 12-14)
- Initiated Xyrem and titrated to 4.5 g twice nightly and then crossed over to Xywav once available (ESS 4-5)
  - Occasionally takes Adderall 5 mg only on days she had limited sleep or longer work days
- Changed patient to **Lumryz** due to continued fragmentation of sleep and often missing 2nd dose and now patient sleeping "naturally".
  - **"I feel the best I have felt in my entire life"**

Current treatment consist of combination of oral appliance therapy, oxybate and stimulants.

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To the world you may be one person, but to *one person* you may be the world.

-- DR. SEUSS

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Thank You

Maggie Lavender MSN, APRN, FNP-C

mlavendernp@csma.pro

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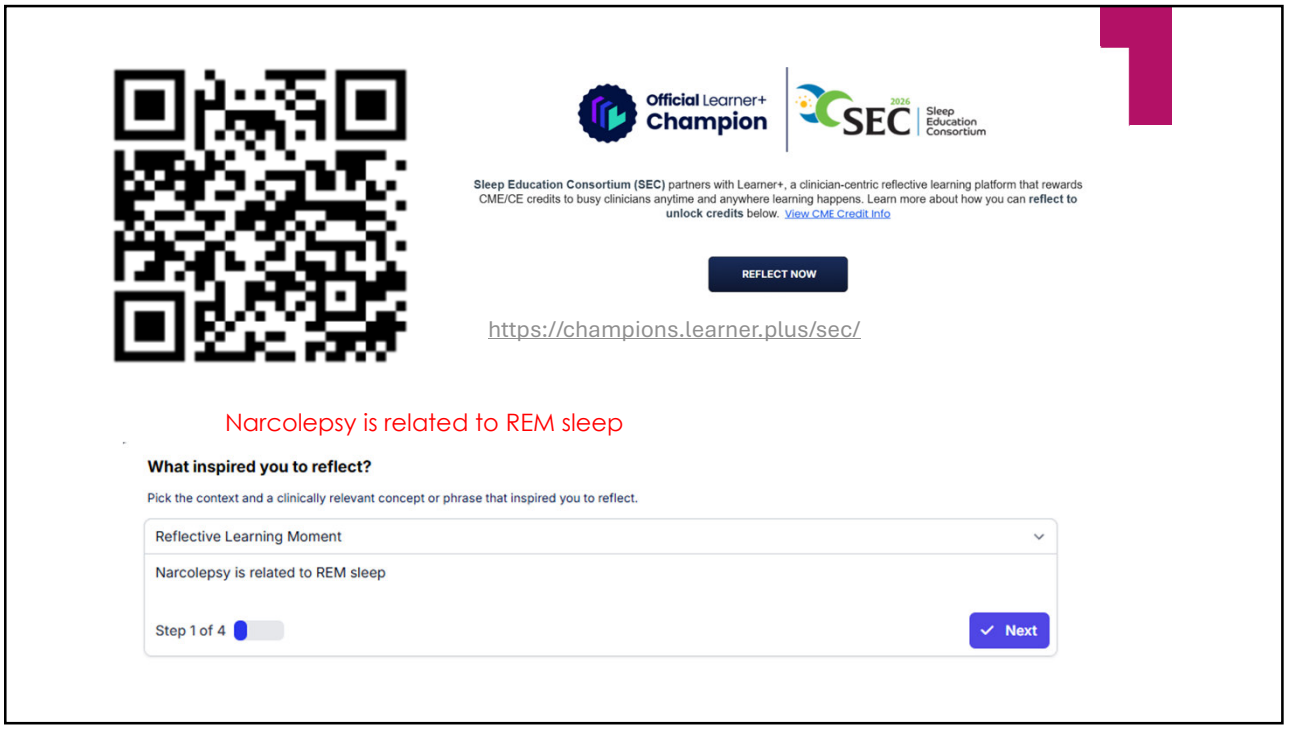
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SEC 2026 Sleep Education Consortium
Sleep Education Consortium (SEC) partners with Learner+, a clinician-centric reflective learning platform that rewards CME/CE credits to busy clinicians anytime and anywhere learning happens. Learn more about how you can reflect to unlock credits below. View CME Credit Info
REFLECT NOW
https://champions.learner.plus/sec/
Narcolepsy is related to REM sleep
What inspired you to reflect?
Pick the context and a clinically relevant concept or phrase that inspired you to reflect.
Reflective Learning Moment
Narcolepsy is related to REM sleep
Step 1 of 4
Next

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