

Everything that is sleepy may not Snore : Part 1

A closer look at Narcolepsy

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Conflicts of Interest

Content of this lecture does not involve conflicts listed below.
All possible conflicts have been duly resolved.

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Nyxoah
(Dual HGNS)

Plan of Action



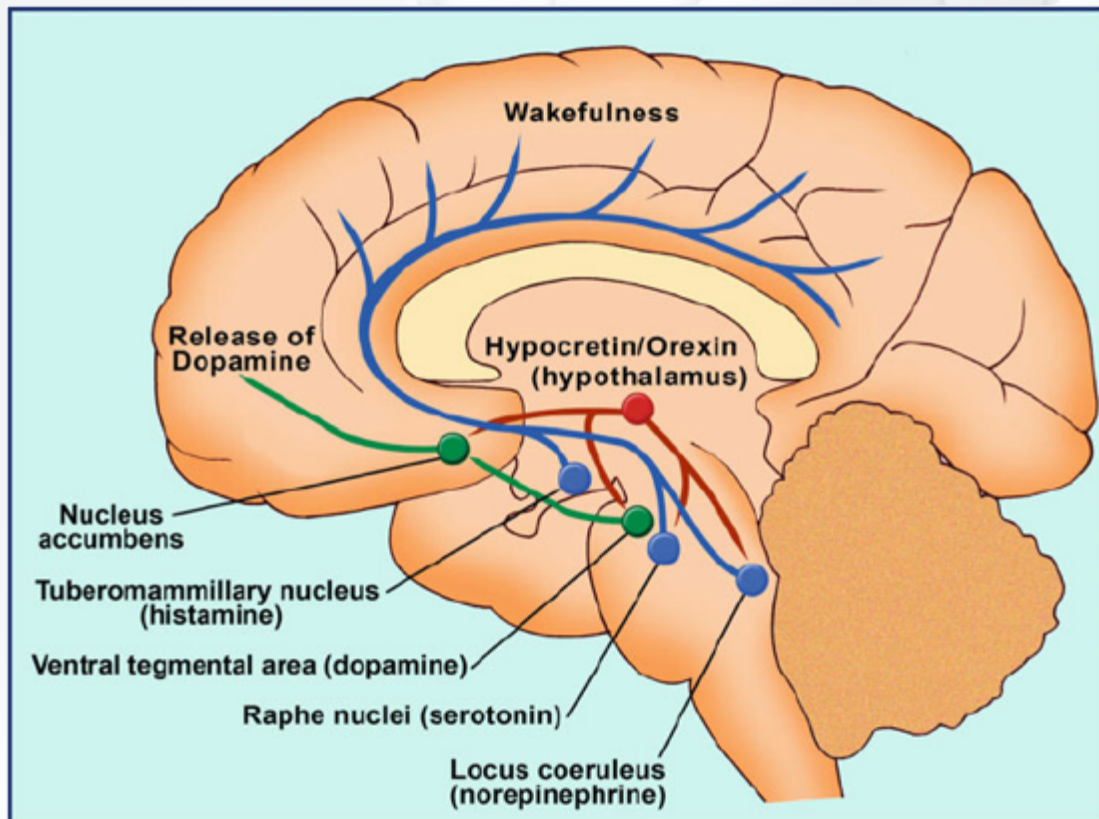


01

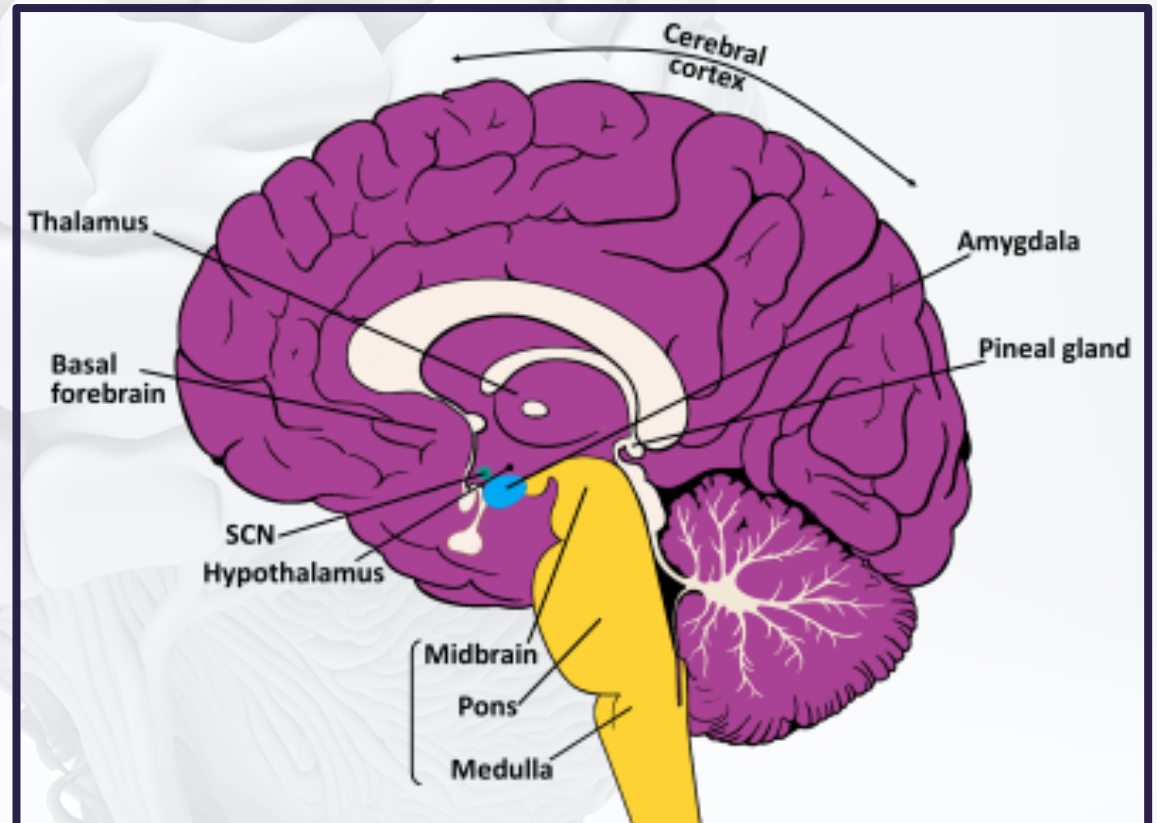
Introduction & Physiology

Introduction & Physiology

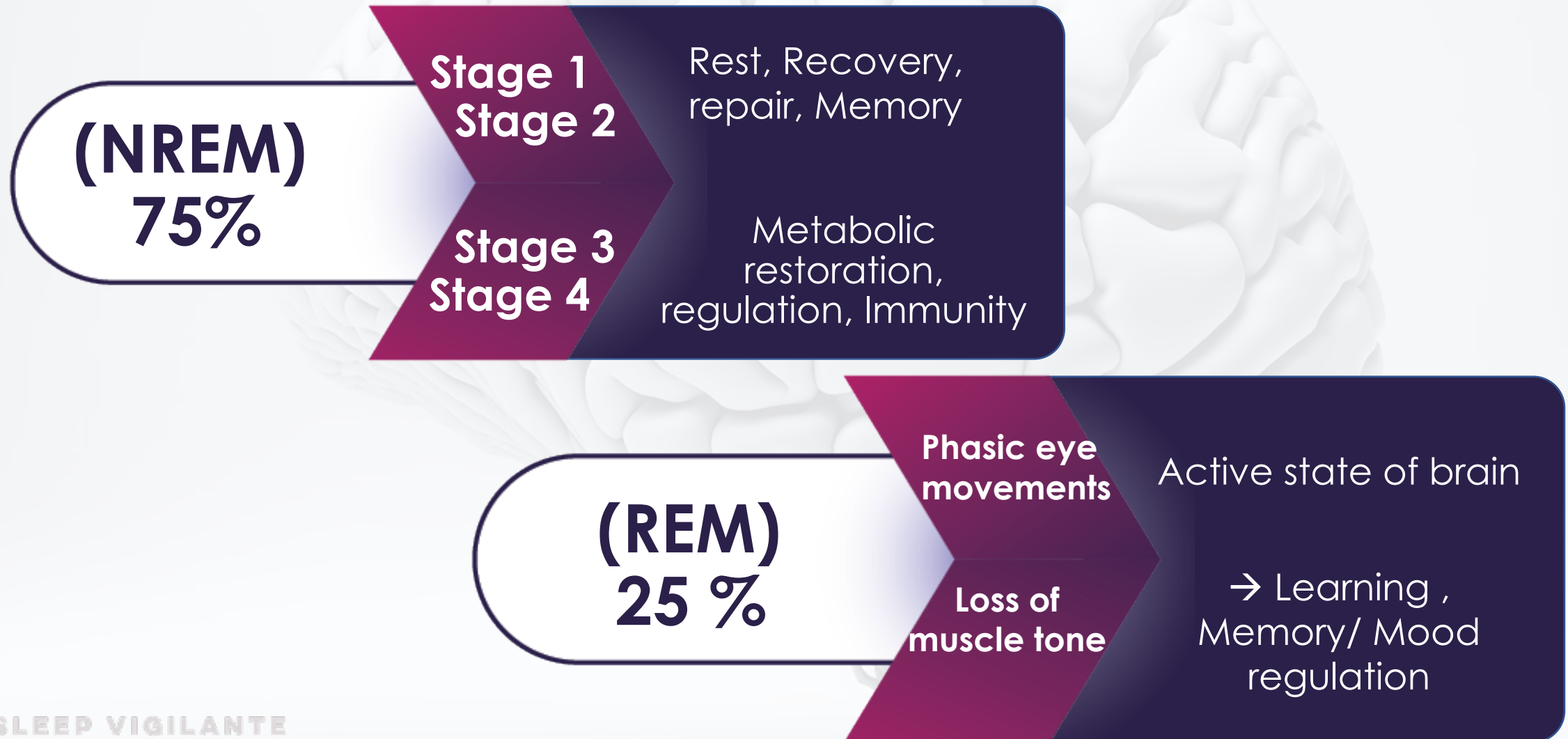
WAKEFULNESS



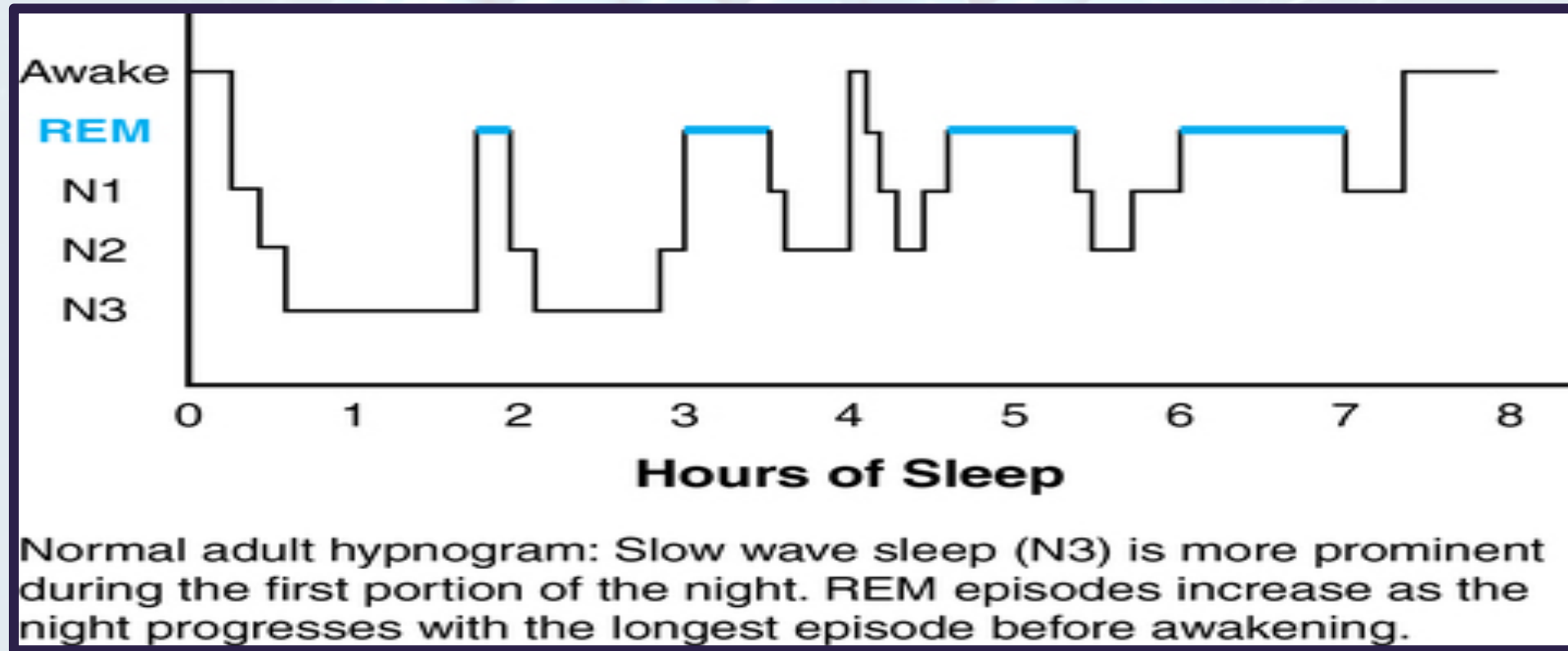
SLEEP



Why Sleep ?



Sleep - 1/3 of your life !

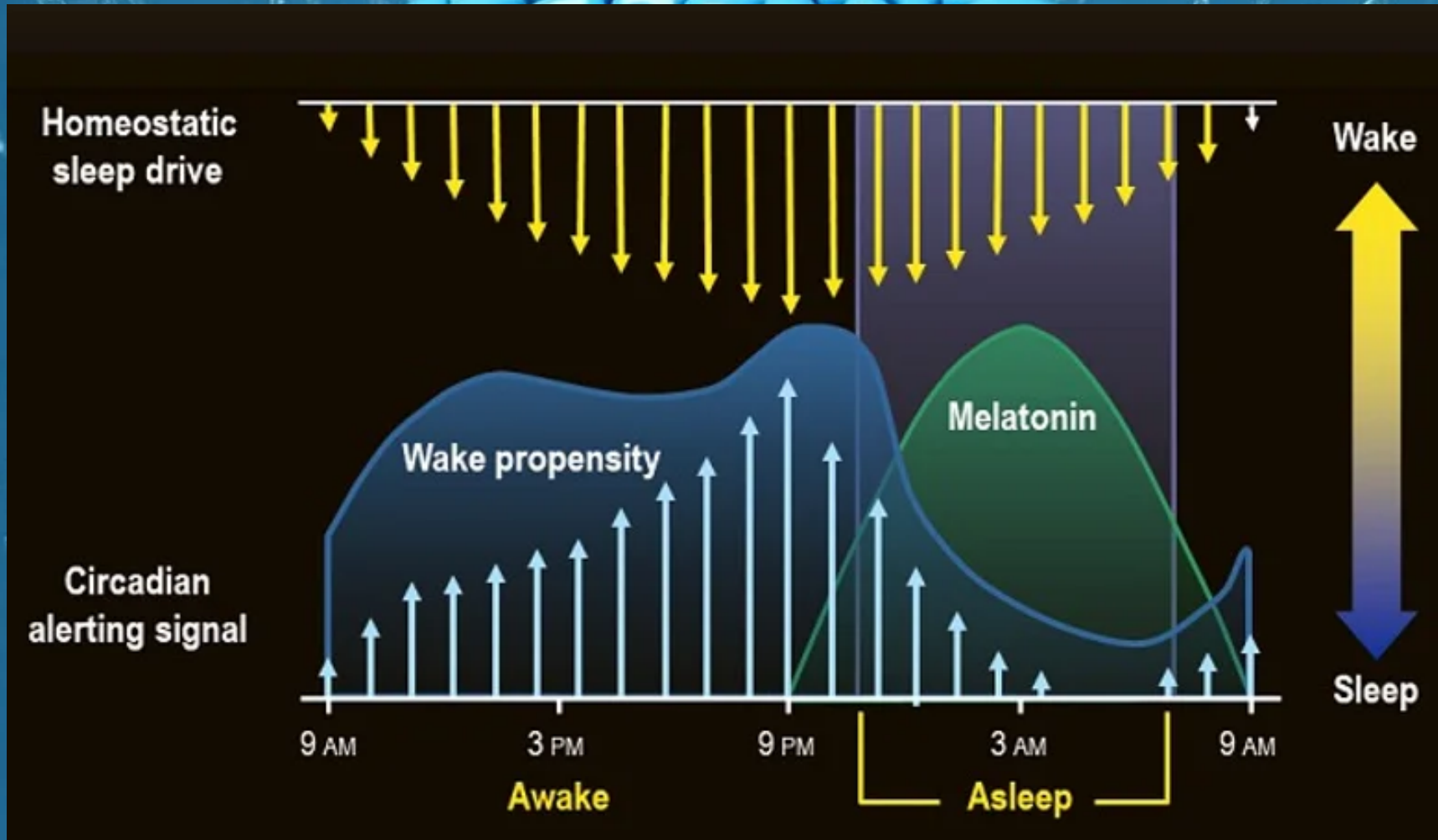




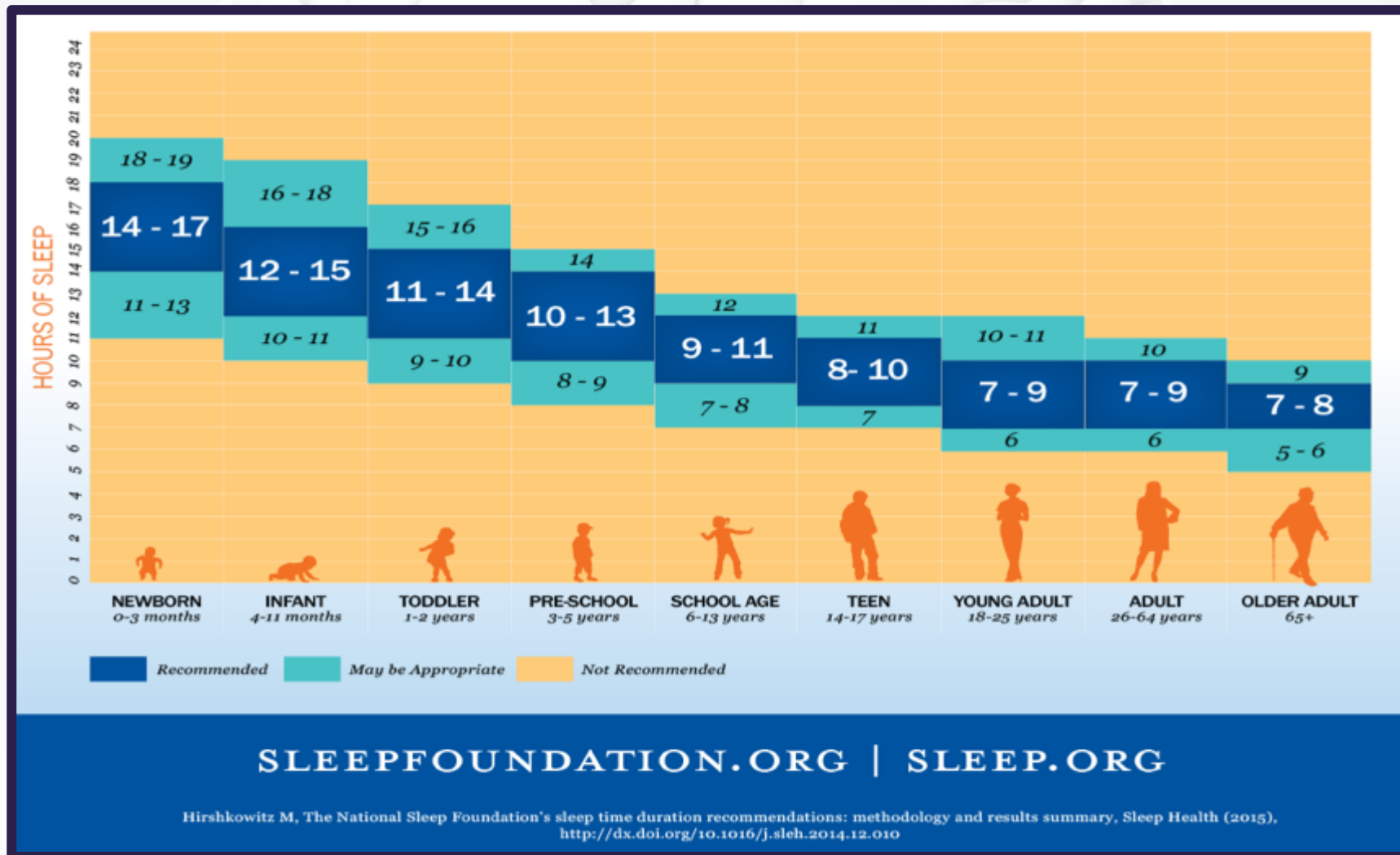
02

Sleep : How much & how ?

HOW DO WE SLEEP ? – 2 PROCESS MODEL



HOW MUCH ?





03

Approaching a Pt. with Excessive Daytime Sleepiness

Causes: Excessive daytime sleepiness

Excessive Daytime Sleepiness



```
graph TD; A[Excessive Daytime Sleepiness] --- B[REDUCED SLEEP]; A --- C[MEDICAL & PSYCHIATRIC DISORDERS]; A --- D[MEDICATIONS]; A --- E[SLEEP DISORDERS]
```

REDUCED SLEEP

Shift work,
Poor Sleep Habits

MEDICAL & PSYCHIATRIC DISORDERS

Anxiety, Depression,
Hypothyroidism,
Anemia, Parkinson's

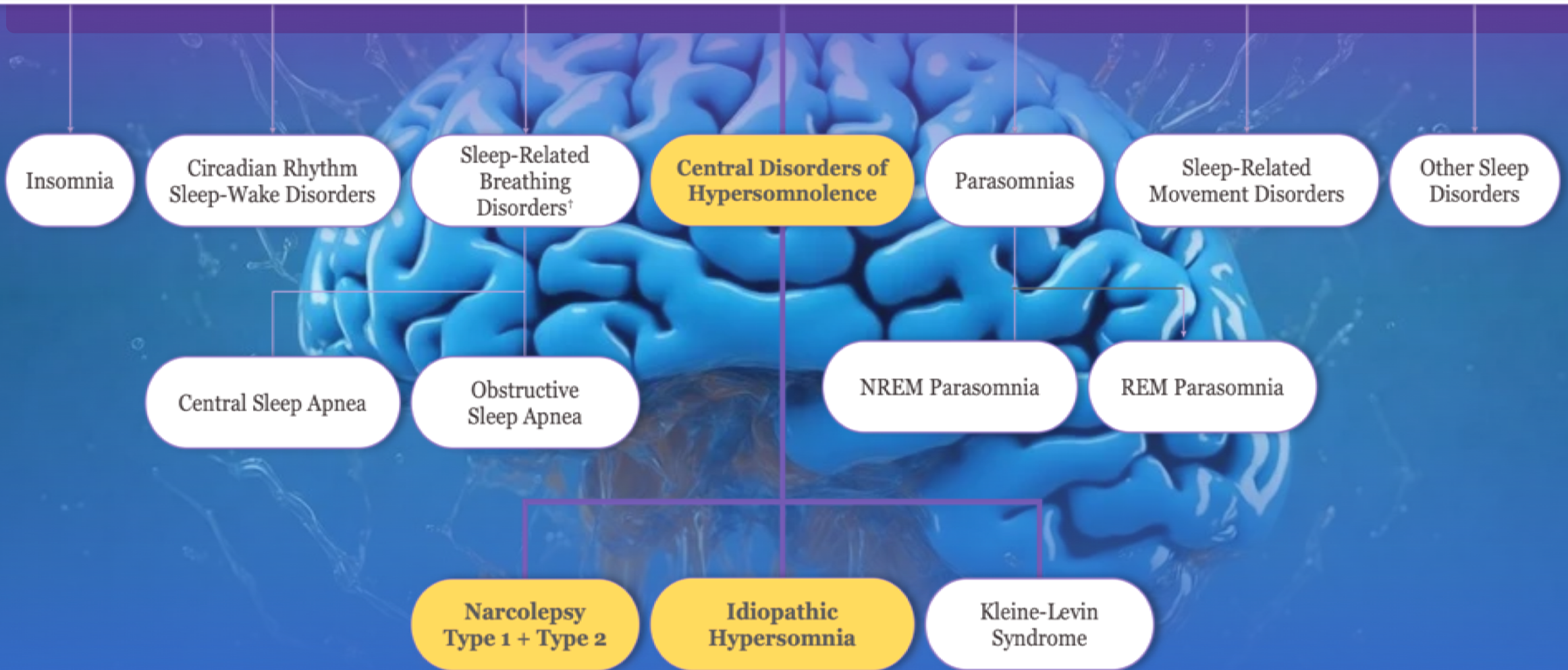
MEDICATIONS

Sedatives,
Analgesics,
Antidepressants,
Alcohol

SLEEP DISORDERS

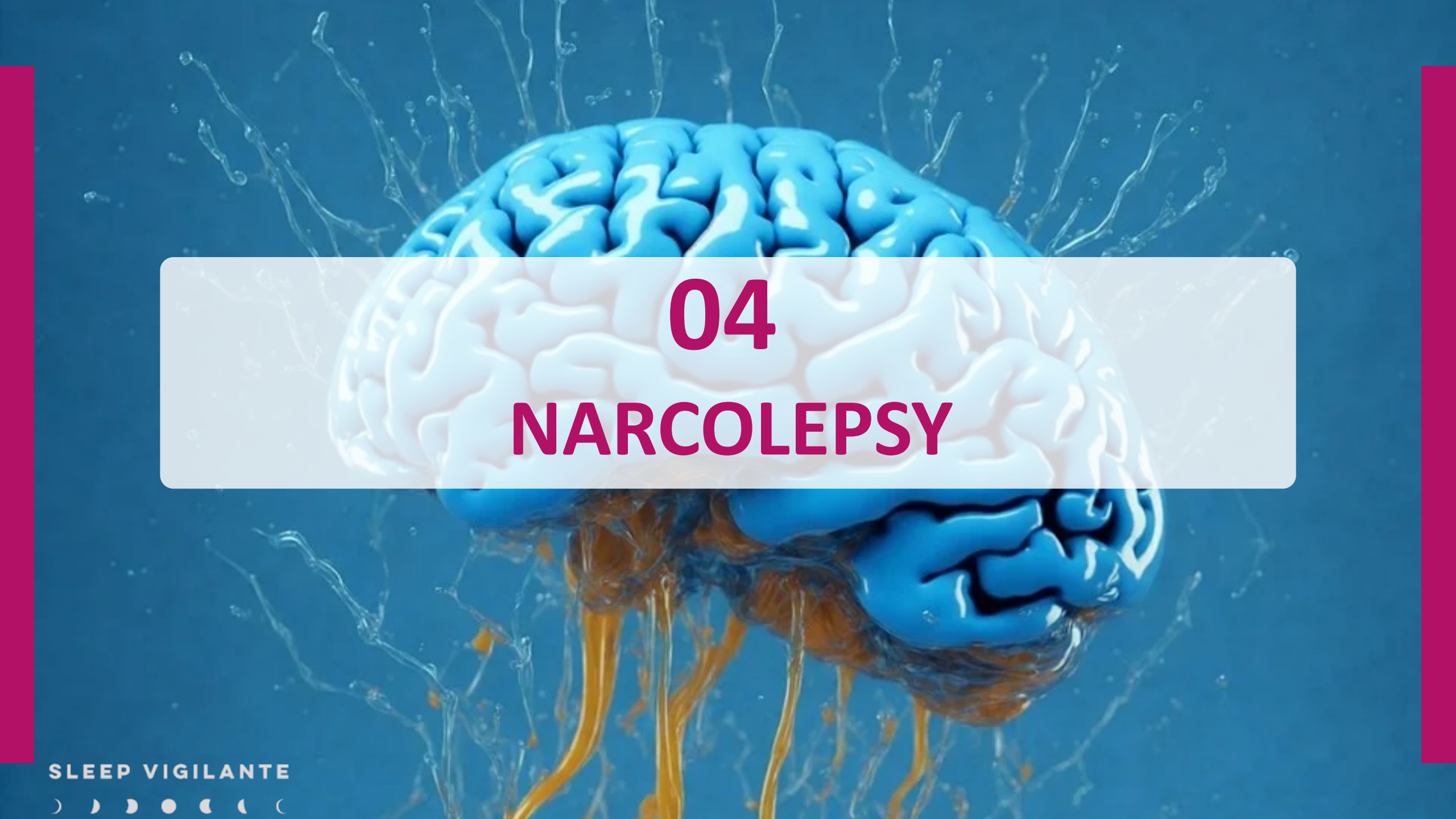
OSA, Narcolepsy,
Insomnia, Circadian,
Parasomnias

SLEEP DISORDERS



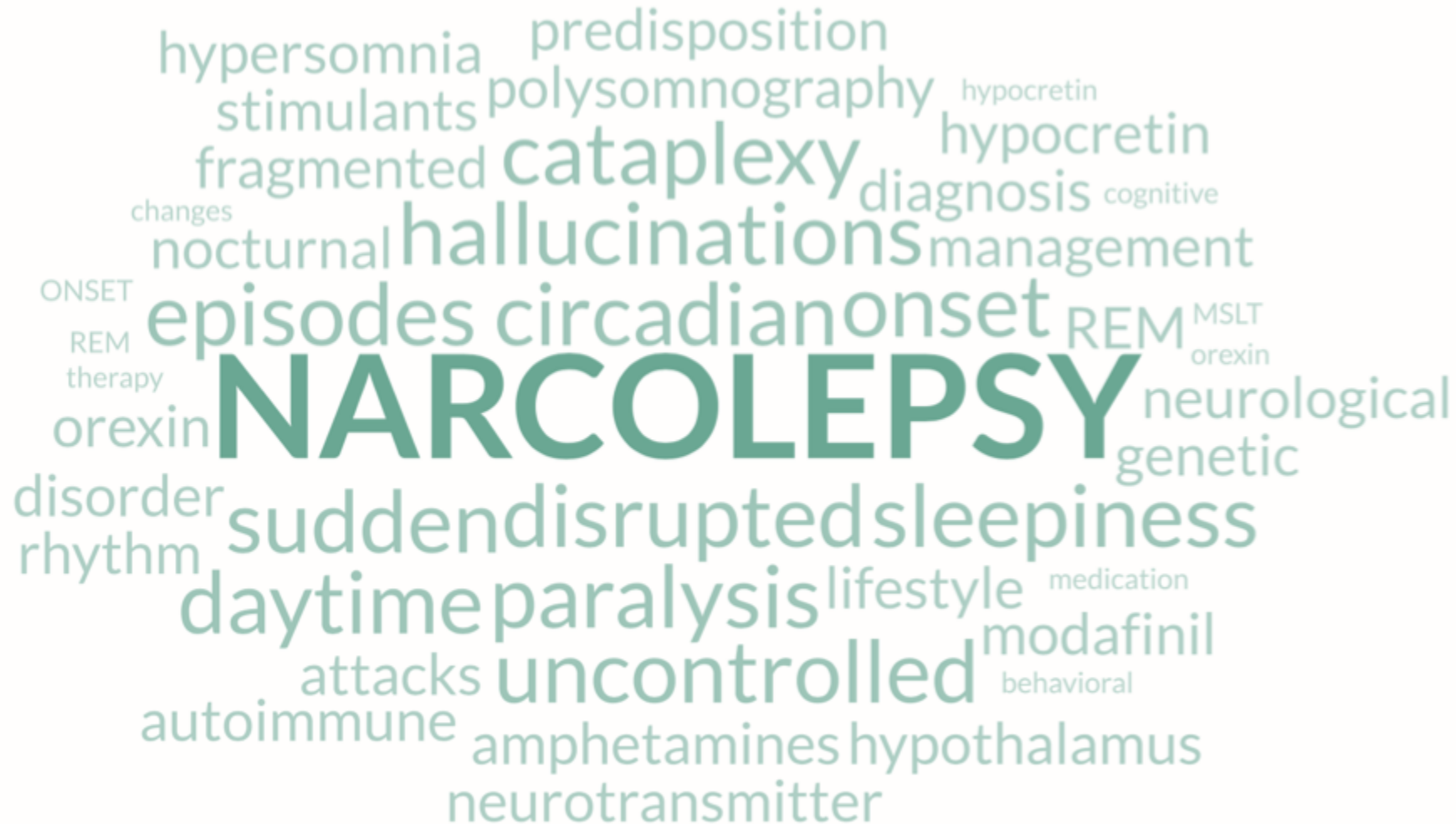
TOOLS- On your fingertips !





04 NARCOLEPSY

TOGETHER We Will Learn !



A word cloud centered around the word "NARCOLEPSY". The word "NARCOLEPSY" is the largest and most prominent, rendered in a bold, dark green font. Surrounding it are numerous other words in various sizes and shades of green, all related to the medical condition. The words are arranged in a circular pattern, with some appearing more frequently than others. The background of the word cloud is a light, textured blue.

hypersomnia predisposition
stimulants polysomnography hypocretin
fragmented cataplexy diagnosis cognitive
changes nocturnal hallucinations management
ONSET episodes circadian onset REM MSLT
REM therapy orexin orexin neurological
disorder NARCOLEPSY genetic
rhythm suddendisruptedsleepiness
daytimeparalysislifestyle medication
attacks uncontrolled modafinil
autoimmune amphetamines hypothalamus
neurotransmitter

Clinical Features-



ataplexy

Sudden partial or complete loss of Muscle tone (< 2-3 min). Consciousness intact. Often Face. limbs. Triggered by strong emotions ; laughter. All Type 1



allucinations

(Hypnagogic and/or Hypnopompic)

Dreamlike experiences (Visual) occurring at the transitions of sleep-wake (33-80%)



xcessive Daytime Sleepiness

100 % of all Narcolepsy patients. ESS > 10; often 15 or greater



leep Paralysis

disturbing, temporary inability to move voluntary muscles or speak during sleep-wake transitions (25-50%)



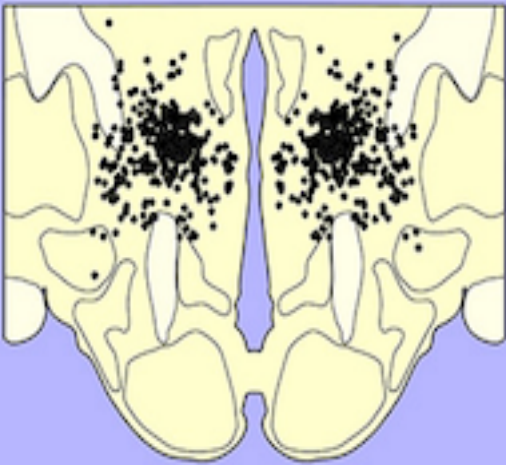
leep Disruption

Sleep Fragmentation / Arousal index 3 x higher. (30-95 %)

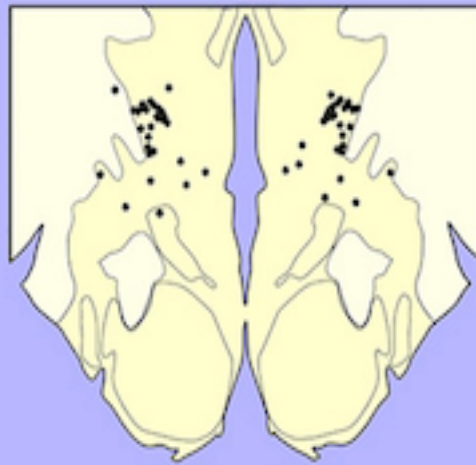
ROLE OF OREXIN / HYPOCRETIN

OREXIN / HYPOCRETIN – LATERAL HYPOTHALAMUS

Normal



Narcolepsy



Courtesy: Stanford

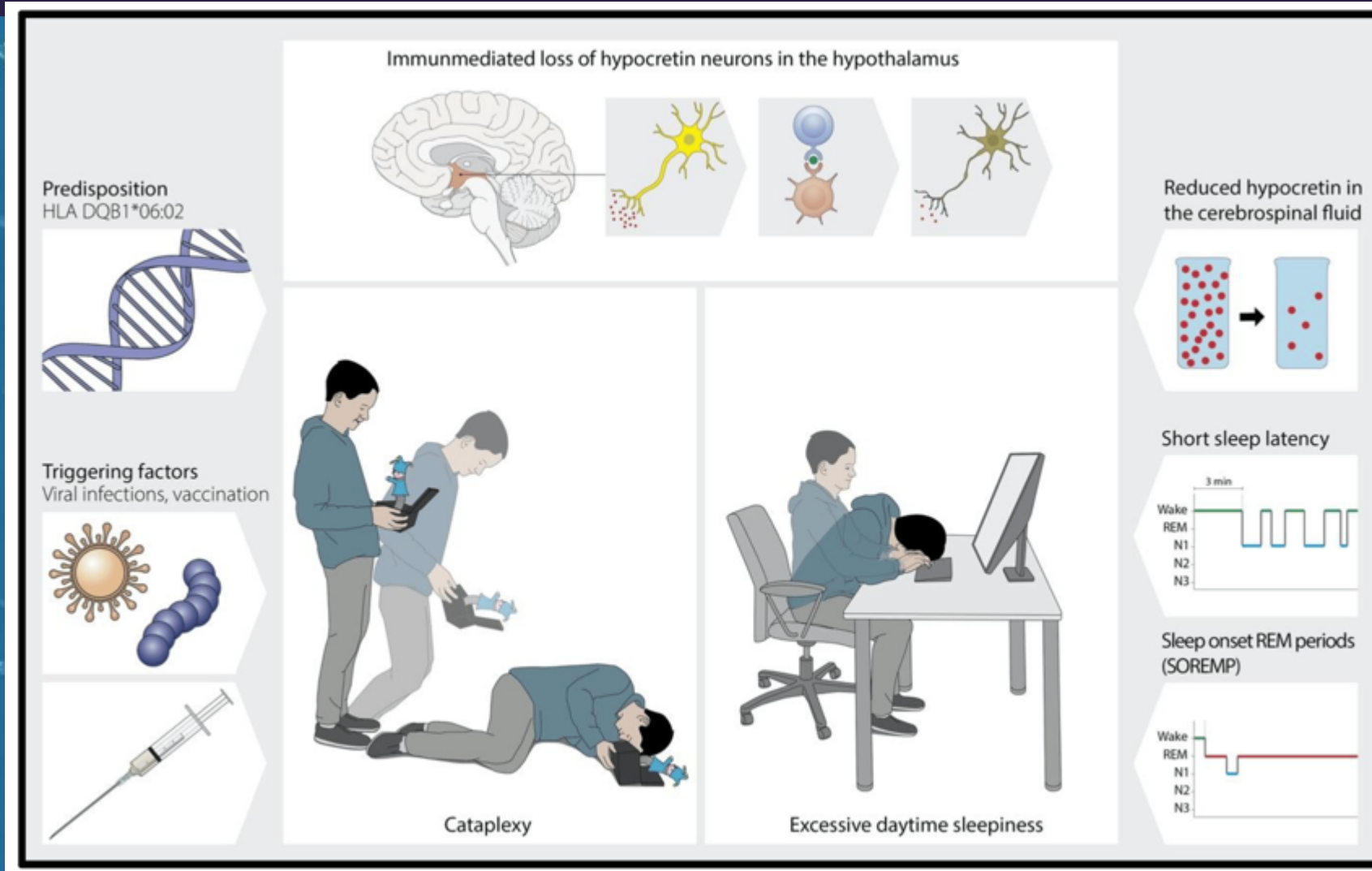
Caused by a **lack of orexins** (hypocretins)

Orexin : Neuropeptides that help sustain **alertness** & **prevent REM sleep** from occurring at the wrong times.

Genetics, & triggering infections or inflammation

Play important roles in the development of narcolepsy.

Patient with Narcolepsy



Chronic Neurological disorder with Impaired SLEEP-WAKE STABILITY

NARCOLEPSY TYPE 1 (With Cataplexy)

+++ Excessive Daytime Sleepiness
+++ Cataplexy (Present)

+/- Hallucinations
+/- Sleep Paralysis
+/- Automatic Behaviors

Upto 95 % of Hypocretin Neurons lost
Low CSF Hypocretin - (<110 pg/mL)

NARCOLEPSY TYPE 2 (Without Cataplexy)

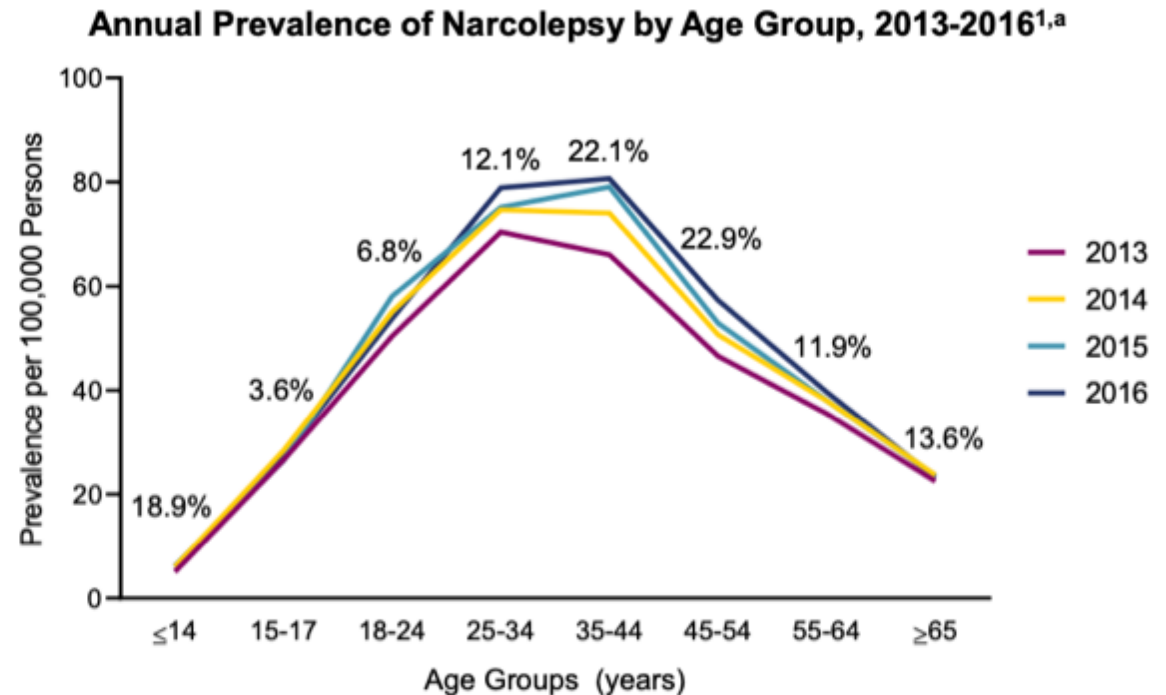
+++ Excessive Daytime Sleepiness
Cataplexy (Absent)

+/- Hallucinations
+/- Sleep Paralysis
+/- Automatic Behaviors

Etiology – Unclear
Only 24 % may show reduced Hypocretin
Conversion to Type 1 Possible

US Prevalence of Narcolepsy : ~ 1 in 2000

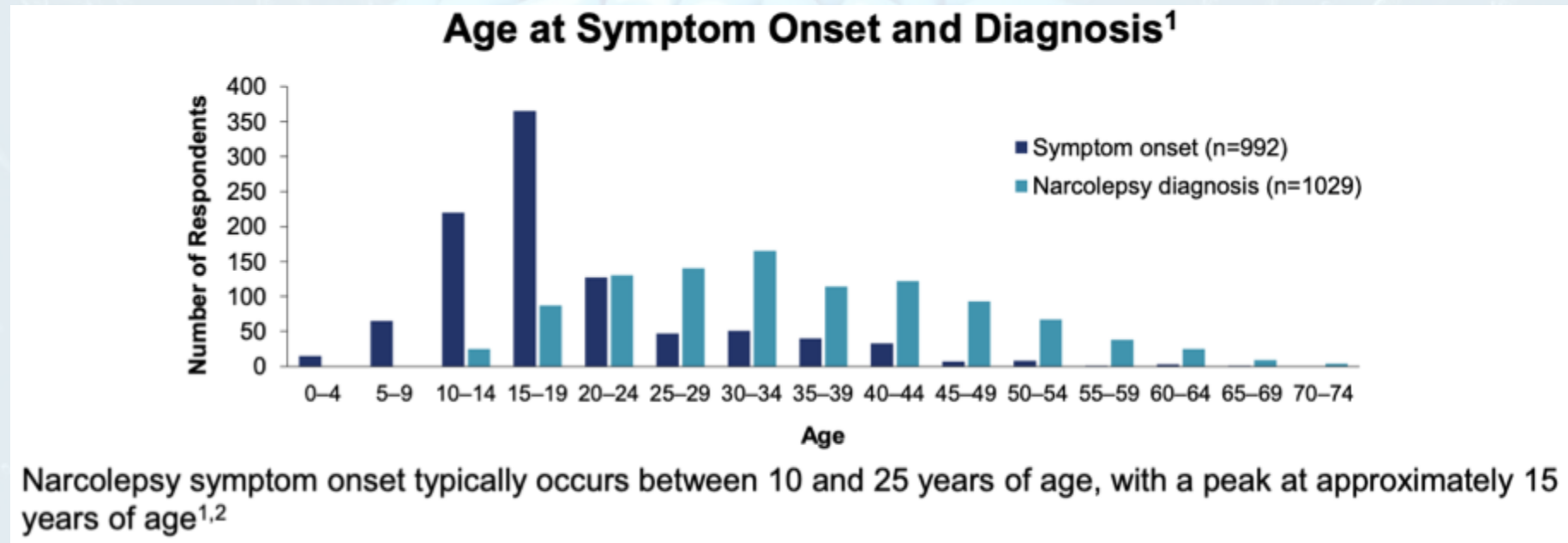
- Estimated annual US prevalence of narcolepsy was 38.9 per 100,000 persons in 2013 and 44.3 per 100,000 persons in 2016 (per US insurance claims 2013–2016)¹
 - This represents an increase of 13.9% over the study period
 - It is unclear whether this increase reflects increasing prevalence of narcolepsy or increased awareness of narcolepsy among healthcare providers



The estimated national estimate for 2016 was approximately 142,000 prevalent cases¹

^aPercentages are change in prevalence from 2013 to 2016.
1. Acquavella J, et al. *J Clin Sleep Med*. 2020;16:1255-1263.

Age at Symptom Onset & Diagnosis



- Symptom onset **10- 25** yrs of age
- Symptoms going **unrecognized**, particularly in children, can cause **delays** in **diagnosis and treatment**

1. Thorpy MJ, Krieger AC. Sleep Med. 2014;15(5):502-507. 2. American Academy of Sleep Medicine. Narcolepsy type 1.



05

DIAGNOSIS of NARCOLEPSY

Do Patients with Narcolepsy Sleep well ?

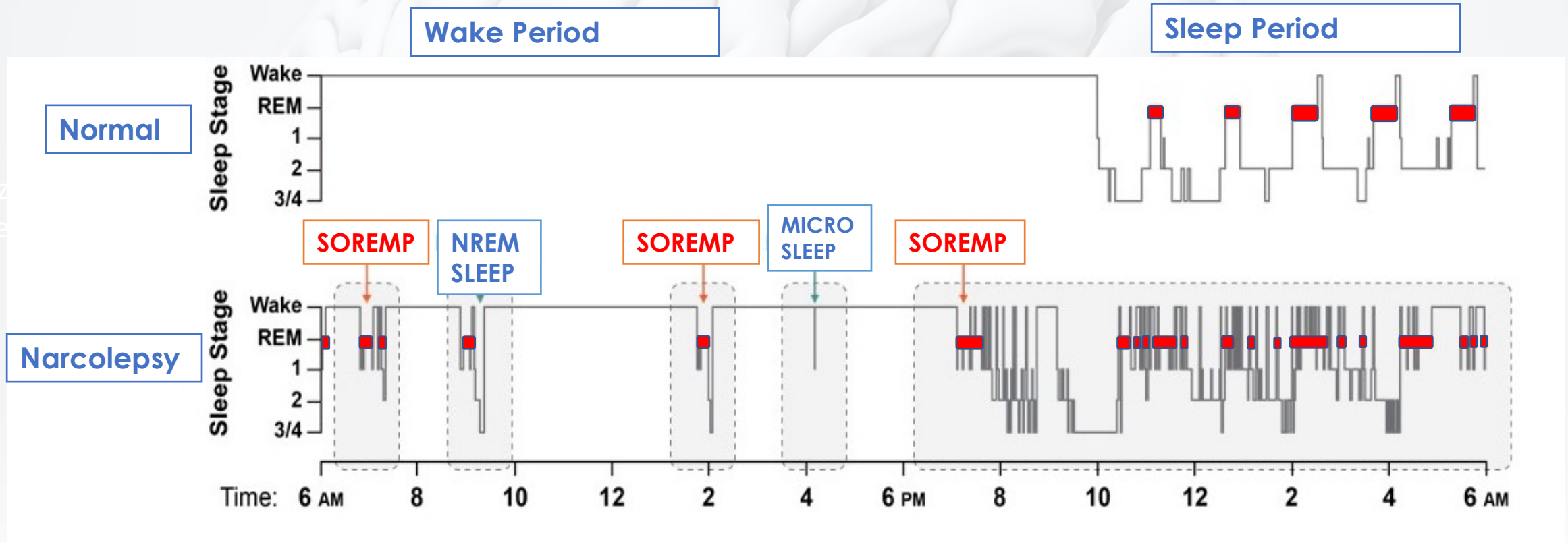


SLEEP VIGILANTE



Narcolepsy: Chronic Neurological Disorder

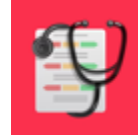
Sleep wake instability



Piazzì G et al , Sleep Med Rev 2008
Rogers et al Sleep, 1994

DIAGNOSTIC TOOLS

- History & Physical



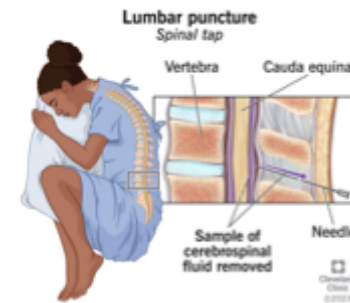
- Excessive Sleepiness (ESS) +/- Cataplexy

- Sleep Studies



- Spinal Fluid testing- Hypocretin

- HLA testing



Polysomnography & Multiple Sleep Latency Test

PSG – Overnight

Sleep Latency	Shorter than normal
REM Latency	Shorter than normal
<u>SOREMPs</u>	Present within 15 min of sleep onset
Other	<ul style="list-style-type: none">- Fragmented REM sleep- Frequent awakenings- HIGH Sleep stage transitions

MSLT- Daytime Nap Test

Mean Sleep Latency	< 8 minutes
On 4 or 5; 20 min Naps	
SOREMPs	2 or more during MSLT

CSF- Hypocretin

CSF Hypocretin-1 Level	Interpretation	Clinical Significance
≤ 110 pg/mL	Low/Deficient	Diagnostic for narcolepsy type 1 (NT1)
111-200 pg/mL	Intermediate	May indicate NT1; requires further clinical evaluation
> 200 pg/mL	Normal	Typical for healthy controls; does not rule out narcolepsy

Test Characteristics	Value
Sensitivity for NT1 (≤ 110 pg/mL cutoff)	60%-88 %
Specificity for NT1 (≤ 110 pg/mL cutoff)	98%
Best cutoff for NT2 diagnosis	~200 pg/mL



HLA- DQB*0602 or DR2 Test

HLA typing can be used since there is a strong correlation of narcolepsy in individuals with cataplexy when human leukocyte antigen typing is positive for DQB*0602 or DR2.

Table 1 - Prevalence rates of HLA and hypocretin-1 in the CSF

Diagnosis	HLA-DQB1*0602 positive	Hypocretin - 1 \leq 110pg/mL
Narcolepsy with cataplexy	> 90%	85 -90% > 90% HLA positive
Narcolepsy without cataplexy	40-60%	10-20% (almost all HLA positive)
General population	12-34%	-

Narcolepsy Types 1 & 2 & Idiopathic Hypersomnia

Y. Dauvilliers, R.K. Bogan, I. Arnulf et al.

Sleep Medicine Reviews 66 (2022) 101709

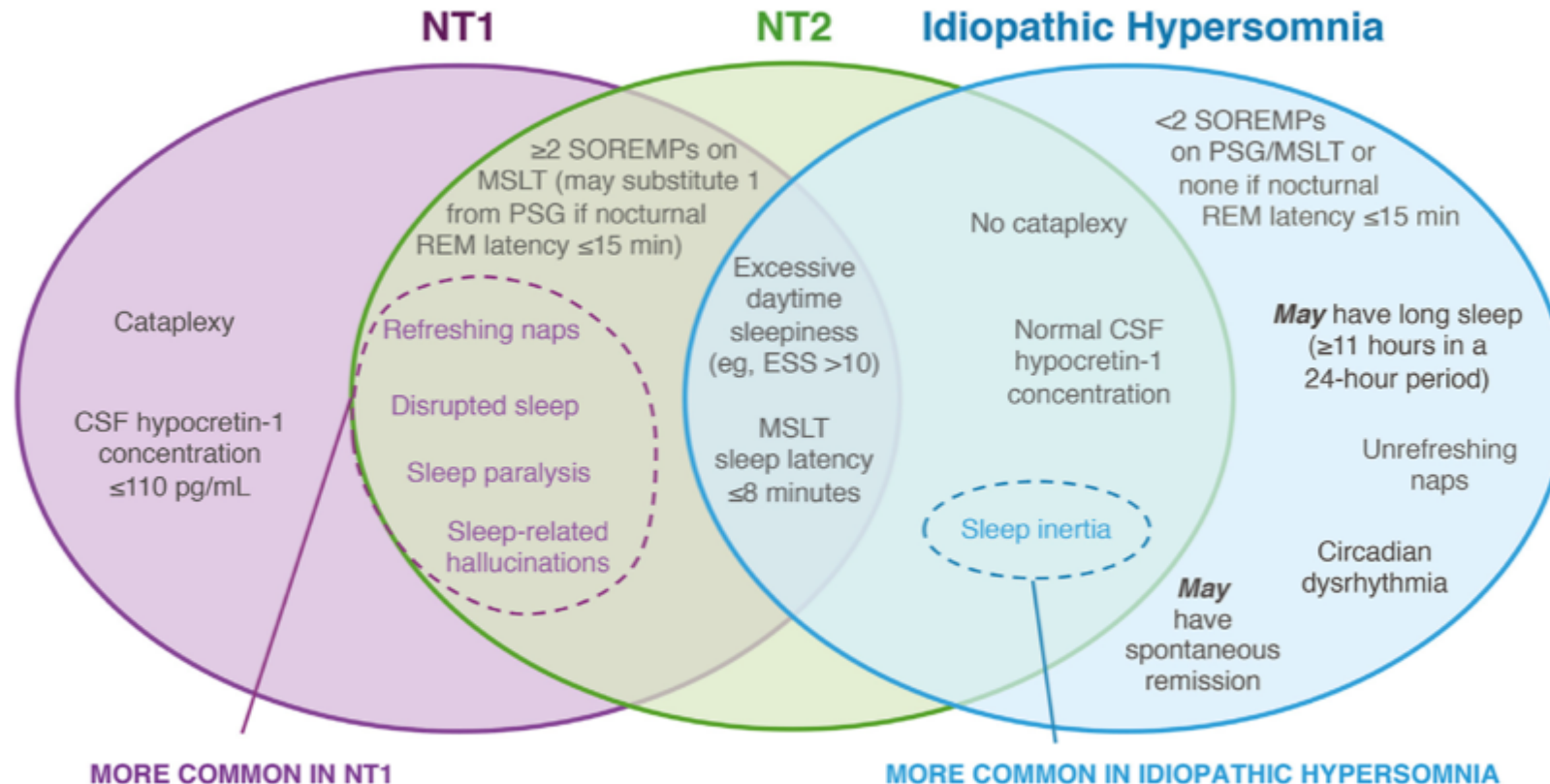


Fig. 2. Diagnostic Features of NT1, NT2, and Idiopathic Hypersomnia [2,12,27,105,106]

CSF, cerebrospinal fluid; ESS, Epworth Sleepiness Scale; MSLT, multiple sleep latency test; NT1, narcolepsy type 1; NT2, narcolepsy type 2; PSG, polysomnography; REM, rapid eye movement; SOREMP, sleep onset rapid eye movement period.

OVERLAP OF SYMPTOMS

INITIAL COMPLAINT of Excessive Daytime Sleepiness

		Possible Cause	IH	NT1	NT2	OSA	ISS	MDD or BPD
Screening	Demographics							
	Age of onset		Often in adolescence or early adulthood	Usually in childhood or early adulthood	Typically in adolescence	Usually in middle age or older	Any	Usually in adolescence or early adulthood
	Sex		♀ > ♂	♀ ≈ ♂	♀ ≈ ♂	♀ < ♂	♀ ≈ ♂	♀ > ♂
	BMI		Average	Often high	Average	Usually high	Average to high	Often high
	Daytime symptoms							
	Sleep attacks		Rarely or sometimes	Yes	Often	Rarely	Rarely	Rarely
	Cataplexy		No	Usually	No	No	No	No
	Sleep inertia		Often (severe)	Sometimes	Sometimes to often	Sometimes to often	Sometimes to often	Sometimes to often
	Naps		Unrefreshing	Refreshing	Refreshing	Unrefreshing	Refreshing	Unrefreshing
	Depressive symptoms		Sometimes	Common	Common	Sometimes	Sometimes	Yes
	Nighttime symptoms							
	Nocturnal TST		Often long (≥10 hours)	Often disrupted	Often disrupted	Normal	Reduced (weekdays)	Variable
	Snoring		Rarely	Sometimes (obesity)	Sometimes (obesity)	Usually	Rarely	Rarely
	Nightmares, hallucinations		Sometimes	Frequent	Frequent	Rarely	Sometimes	Rarely
	Lifestyle, work, and school							
	Planned sleep period		Long or normal	Normal	Normal	Long or normal	Short	Long or normal
	Electronic devices at bedtime		Rarely	Rarely	Rarely	Rarely	Often	Sometimes
Diagnostic Testing								
			PSG + MSLT (including extended sleep recording)	PSG + MSLT	PSG + MSLT	PSG or OCST	Trial of Behavior Modification	Trial of Psychiatric Treatment
			Hypocretin Normal	Hypocretin Low	Hypocretin Not Low	Trial of CPAP	PSG + MSLT (if required)	PSG + MSLT (if required)



06

TREATMENT OF NARCOLEPSY

TREATMENTS of NARCOLEPSY

01

➤ BEHAVIORAL

02

➤ Stimulants

03

➤ Modafinil, Armodafinil

04

➤ Sodium Oxybate

05

➤ Pitolisant

06

➤ Solriamfetol

07

➤ Newer Treatments

BEHAVIOURAL TREATMENTS

- Consistent Sleep Wake Pattern to align with Circadian Sleep Wake Schedule



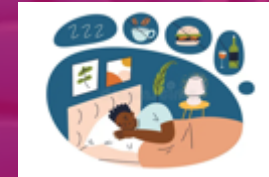
- Naps, Strategic short naps can be helpful.



- Driving safety (Avoid 4 Ds)



- Limit Caffeine , heavy meals and Alcohol close to bedtime



- Exercise regularly



- Medic Alert Bracelet



Excessive Sleepiness: Stimulants

Drug	Dose	Mechanisms of Action	Efficacy	Side Effects
Methylphenidate IR, ER (e.g. Ritalin, Focalin, Concerta) Schedule II <i>Pediatric Narcolepsy</i>	-10-30 mg/day IR BID, TID -ER (18- 54 mg) -Appx 1 mg/kg/d ay	DAT inhibitor (inhibits DA reuptake) Duration of action: 3-5hours(IR); 6-12 hours (ER); 2-8 hours (SR)	ESS: no data MWT: 2.9 min improvement (95% CI: -2.9 to 7.8) Observational Study	irritability, headaches, insomnia, GI upset, hypertension, arrhythmias, anxiety, psychosis
Mixed amphetamine salts (Adderall) Schedule II <i>Pediatric Narcolepsy</i>	5-40 mg/day BID-TID or ER -Appx 0.5 mg/kg/d ay	<ul style="list-style-type: none"> •DAT inhibitor (inhibits DA reuptake); increases DA from presynaptic cleft •Duration of action: 4-6 hours (IR); 8-12 hours (XR) 	ESS: 5 points improvement (95% CI: 3.4 to 6.6) Observational Study	same, reduced appetite, weight loss, psychosis (2x higher than MP)* <small>*Moran LV NEJM 2019</small>
Lisdexamphetamine (Vyvanse _{Per}) Schedule II	20-70 mg/day	Duration of action: 8-12 hours	ESS: 8 points improvement; Case series	Same, hyperhidrosis, skin rash, dry mouth

Excessive Sleepiness: Wake Promoting Agents

Name & Dose	Mechanisms of Action	Efficacy	Side Effects
Modafinil (Provigil) 50-200 mg BID (morning & afternoon)	R,S, enantiomer Weak DAT Inhibitor, inhibit DA reuptake Tmax: 2-4 hrs; T1/2: 15 hrs	ESS: 2.8 (95% CI:1.7- 3.8) improvement MWT: 4.1 min (3.4-4.8) 7 RCTs	Headache, nausea, nervousness, HTN , insomnia, rash, psychosis**, SJS**, dyspepsia, OCP interaction
Armodafinil (Nuvigil) 50-250 mg qAM	Longer acting R- enantiomer, Weak DAT Inhibitor, inhibit DA reuptake Tmax: 2 hrs; T1/2: 15 hrs. Higher [plasma] in afternoon*	ESS: 4.7 (95% CI 7.4- 1.9) improvement MWT: 3.3 min (1.1-5.5) Observational studies	Same
Solriamfetol (Sunosi) 75-150 mg qAM	DAT and NET Inhibitor , Inhibit DA & NE reuptake Tmax 2-3 hours; T1/2: 7 hours	ESS: 3.8 (95% CI 5.1-2) Improvement MWT: 9.5 min (6.3-12.7) 3 RCTs	
Atomoxetine (Strattera) 10-50 mg qAM (Unscheduled)	Inhibits NE reuptake Tmax 1-2 hours; T1/2: 5- 8 hours	NA	Similar to stimulants but lower frequencies

DAT = Dopamine Transporter, NET = Norepinep

Maski, K, Sleep 2024

EDS & Cataplexy

Name & Dose	Mechanisms of Action	Efficacy	Side Effects
Sodium Oxybate (Xyrem , generic) 2.25-4.5 g twice nightly	?; GABA-B agonist	ESS (3-9 g): 1.5-3.3 point improvement on <u>RCT</u> & ESS : 5.9 point improvement (7.2 to 4.5) on <u>observational</u> MWT : 3.8 min (1.2 to 6.4) Weekly cataplexy : 9-86% reduction 5 RCTs, multiple obs	REMS : OSA/hypoventilation, depression, SI, psychosis, driving safety, Dizzy, nausea, enuresis, headache, weight loss
Sodium Oxybate Once nightly (Lumryz) 4.5-9 g bedtime	?; GABA-B agonist	ESS (6-9 g): 2.1-3.9 point improvement MWT (6-9 g): 5-6.1min improvement Weekly cataplexy (4.5-9 g): 2.7- 6.7 reduction - 1 RCT	REMS: Similar AE profile Meskill G et al. Abstract SLEEP 2024. Reason for switch 38% not awake for second dose;
Low-salt Oxybate (Xywav) 2.25-4.5 g twice nightly	?; GABA-B agonist <u>131 mg vs 1640 mg SALT @ 9 Gm</u>	ESS : Placebo 3 point worsening VS no change in LXB Weekly Cataplexy : 11.5 increase on cataplexy vs 0.1 LXB - 1 withdrawal RCT,	REMS : Similar AE profile,
Pitolisant (Wakix) 4.45-35.6 mg q AM 8 Week	H3-receptor antagonist/inverse agonist	ESS : 3.8 - 5.8 point improvement MWT : 2.1 to 4.3 minutes improvement Cataplexy : 37- 75% improvement -	HAs, insomnia, irritability, anxiety, nausea (all <10%); potential for QTc prolongation with SSRI/SNRIs

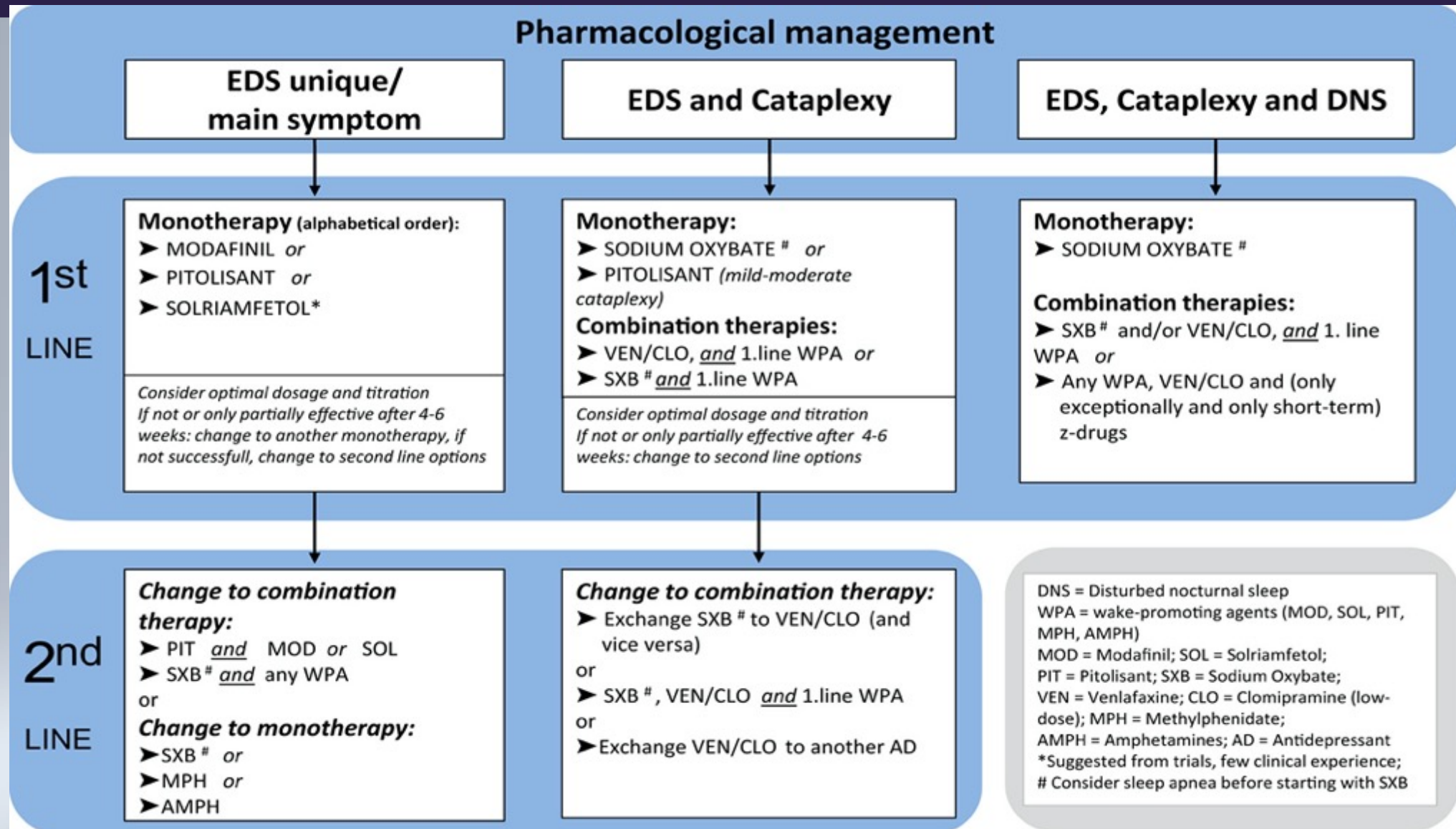
Other agents: Cataplexy

Drug	Typical dose	Mechanism of Action	Side effects
Venlafaxine (Effexor)	37.5-325 mg XR q AM (IR formulation BID)	Inhibits 5-HT & NE reuptake	Serotonin syndrome, SI risks, Weight gain, nausea
Fluoxetine (Prozac)	20-60 mg q AM	Inhibits 5HT reuptake	Same, dry mouth, sexual dysfunction
Protriptyline (Vivactyl)	2.5-5 mg TID (max 60 mg/day)	Monoamine Reuptake Inhibitor (5HT, NE, DA)	Anticholinergic effects, Cardiac arrhythmia, abnormal LFTs
Clomipramine	25-75 mg q day	Monoamine Reuptake Inhibitor (5HT, NE, DA)	Anticholinergic effects (>10% constipation, dry mouth). Cardiac arrhythmia,

NEWER TREATMENTS

- **Mazindol** (likely DA) for EDS treatment
- **Reboxetine** (Selective inhibits NE reuptake, DA modulator) for treatment EDS and cataplexy
- **Samelisant** H3 inverse agonists/antagonists
- **Orexin – 2 receptor agonists** (Takeda / Merck)

Management of Narcolepsy in adults: European Guidelines



Hypersomnias: NARCOLEPSY & IDIOPATHIC HYPERSOMNIA

HALLMARK FEATURES

- KEY COMMON FEATURE ☾
- **Excessive daytime sleepiness (EDS)**
- **Narcolepsy** can involve cataplexy (sudden muscle weakness), sleep paralysis, & hallucinations (**visual**) around sleep onset/offset.
- **IH** often involves severe difficulty waking up after sleeping (**Profound sleep inertia**) and LONG unrefreshing naps

DIAGNOSIS

- ▶ **DIAGNOSIS**
- ▶ Polysomnography (overnight sleep study) & multiple sleep latency test (MSLT).
- ▶ **Both have < 8 min Mean Sleep Latency**
- ▶ **Narcolepsy** has ≥ 2 sleep onset REM periods on MSLT, IH has < 2
- ▶ Diagnosis is often **delayed**, taking 8-22 years on average



07

Common Medications & Sleep Impact

COMMON MEDICATIONS & SLEEP IMPACT

SLEEP VIGILANTE



Medication Class

Selective Serotonin Reuptake Inhibitors (**SSRIs**)

Serotonin-Norepinephrine Reuptake Inhibitors (**SNRIs**)

Monoamine Oxidase Inhibitors (**MAOIs**)

Mood Stabilizers

Stimulants

Common Medications

Fluoxetine (Prozac), Sertraline (Zoloft), Escitalopram (Lexapro)

Venlafaxine (Effexor), Duloxetine (Cymbalta), Desvenlafaxine (Pristiq)

Phenelzine (Nardil), Isocarboxazid (Marplan), Tranylcypromine

Lithium, Lamotrigine (Lamictal), Valproic Acid (Depakote)

Methylphenidate (Ritalin), Amphetamine salts (Adderall),

Adverse Effects on Sleep

Insomnia, vivid dreams or nightmares, drowsiness or fatigue, **REM sleep disruption**

Insomnia, **night sweats**, **REM sleep disruption**, daytime drowsiness or fatigue

Insomnia, vivid dreams or nightmares, **daytime drowsiness** or fatigue

Insomnia, daytime drowsiness or fatigue, **REM sleep disruption**, nightmares or vivid dreams

Insomnia, delayed sleep onset, **shortened** total sleep time

COMMON MEDS & SLEEP IMPACT

Medication Class

Benzodiazepines

Tricyclic Antidepressants (TCAs)

Atypical Antipsychotics

Common Medications

Alprazolam (Xanax), Diazepam (Valium), Lorazepam (Ativan)

Amitriptyline, Nortriptyline, Imipramine

Quetiapine (Seroquel), Olanzapine (Zyprexa), Risperidone (Risperdal)

Adverse Effects on Sleep

Sedation (may aid sleep), Hangover effect, rebound Insomnia
REM & Slow wave reduction

Sedation (may aid sleep), daytime drowsiness or fatigue, nightmares or vivid dreams, **REM sleep disruption**

Sedation (may aid sleep), daytime drowsiness or fatigue, **restless legs syndrome**

MEDS WITH RELATIVELY FAVORABLE SLEEP PROFILES

Buspirone (Buspar) , Bupropion (Wellbutrin) , Vortioxetine (Trintellix)



08 Pearls

Pearls : Narcolepsy



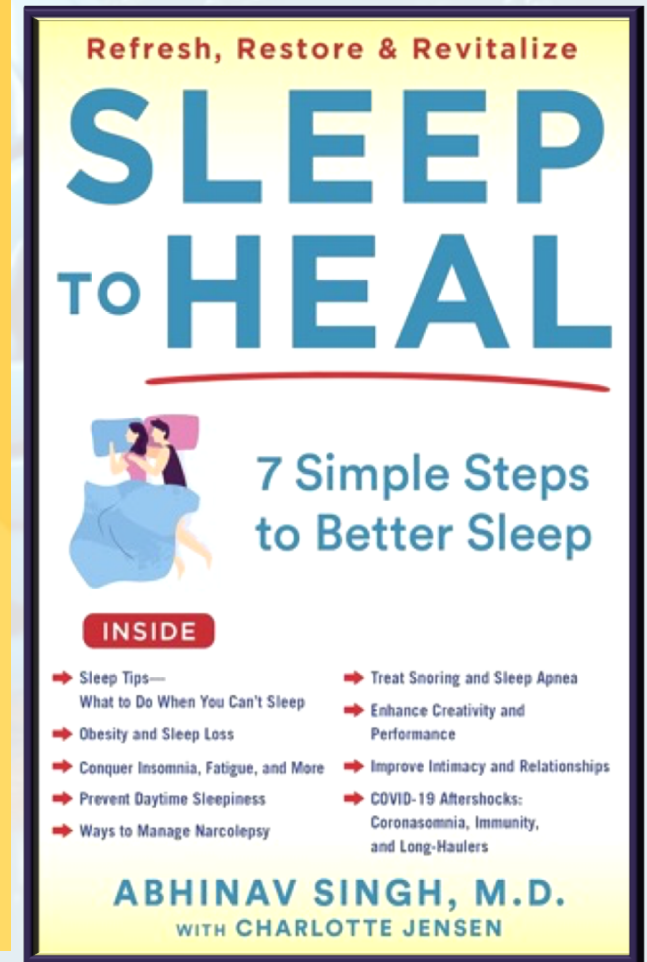
- **N** - **Neurological condition**: Chronic disorder affecting the brain's regulation of **sleep-wake states**.
- **A** - **Associated comorbidities**: Often coexists with other health issues, impacting overall well-being.
- **R** - **Regulation of sleep-wake**: The brain struggles to maintain both **Sleep & Wake State Stability**.
- **C** - **Cataplexy**: Sudden loss of muscle tone triggered by strong emotions; specific- **Narcolepsy Type 1**.
- **O** - **OSA**: Narcolepsy is the **2nd** most common diagnosis in sleep centers after (OSA).
- **L** - **Loss** of **hypocretin** neurons: Narcolepsy Type 1 → **85-95%** loss of these neurons.
- **E** - **Excessive** Daytime Sleepiness (EDS): The **cardinal symptom** that significantly impacts daily life.
- **P** - **Prevalence**: Estimated at approximately 30-40 per 100,000 people (**1 in 2000**).
- **S** - **Sleep** diagnostic testing: **PSG /MSLT** or **CSF Hypocretin**
- **Y** - **You** can manage it!: Various Rx options available, research is promising for future therapies.

THANK YOU

All that is Sleepy May not Snore !



☾ ☾ ☾ ● ☾ ☾
SLEEP VIGILANTE



Refresh, Restore & Revitalize

SLEEP TO HEAL



7 Simple Steps
to Better Sleep

INSIDE

- Sleep Tips—
What to Do When You Can't Sleep
- Obesity and Sleep Loss
- Conquer Insomnia, Fatigue, and More
- Prevent Daytime Sleepiness
- Ways to Manage Narcolepsy
- Treat Snoring and Sleep Apnea
- Enhance Creativity and Performance
- Improve Intimacy and Relationships
- COVID-19 Aftershocks:
Coronasomnia, Immunity,
and Long-Haulers

ABHINAV SINGH, M.D.
WITH CHARLOTTE JENSEN

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Pearls : Narcolepsy



- Chronic neurologic condition that affects the brain's ability to properly regulate **sleep-wake states** (**SLEEP & WAKE are affected**)
- **2nd most common** diagnosis in SLEEP CENTERS after OSA.
- Prevalence of narcolepsy is estimated at **≈30 -40 /100,000-----1 in 2000**
- **NT 1** is associated with selective loss **of hypocretin** neurons (85% to 95%);
- Narcolepsy type 2 is **unclear**, ? partial loss of hypocretin neurons
- **EDS** is the cardinal symptom & **cataplexy** is the most specific
- **Associated with comorbid conditions** and negatively impacts general health and social, academic, and work performance
- Diagnosis of narcolepsy involves **clinical evaluation** and **sleep diagnostic testing**
- **Many treatment options** are available and more coming !