Non-Respiratory Sleep Medicine for the Pulmonary Boards

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Disclosures

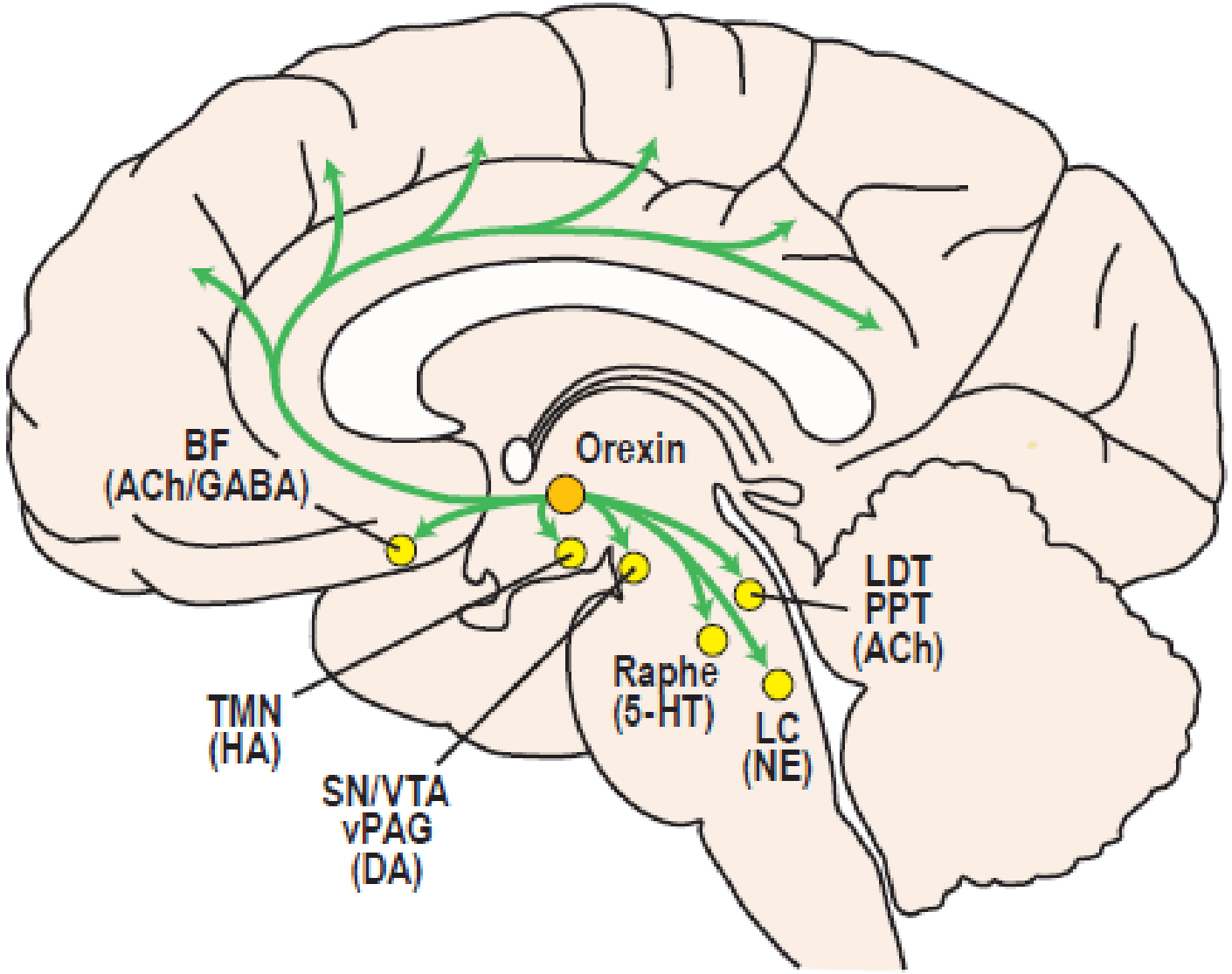
- None

Outline

- Review Basic Sleep Physiology
- Non-Respiratory Sleep Disorders for the Pulmonary Boards
  - Narcolepsy/Hypersomnia disorders
  - Insomnia
  - Parasmonias (NREM/REM)
  - RLS/PLMD
  - Circadian Rhythm Disorders

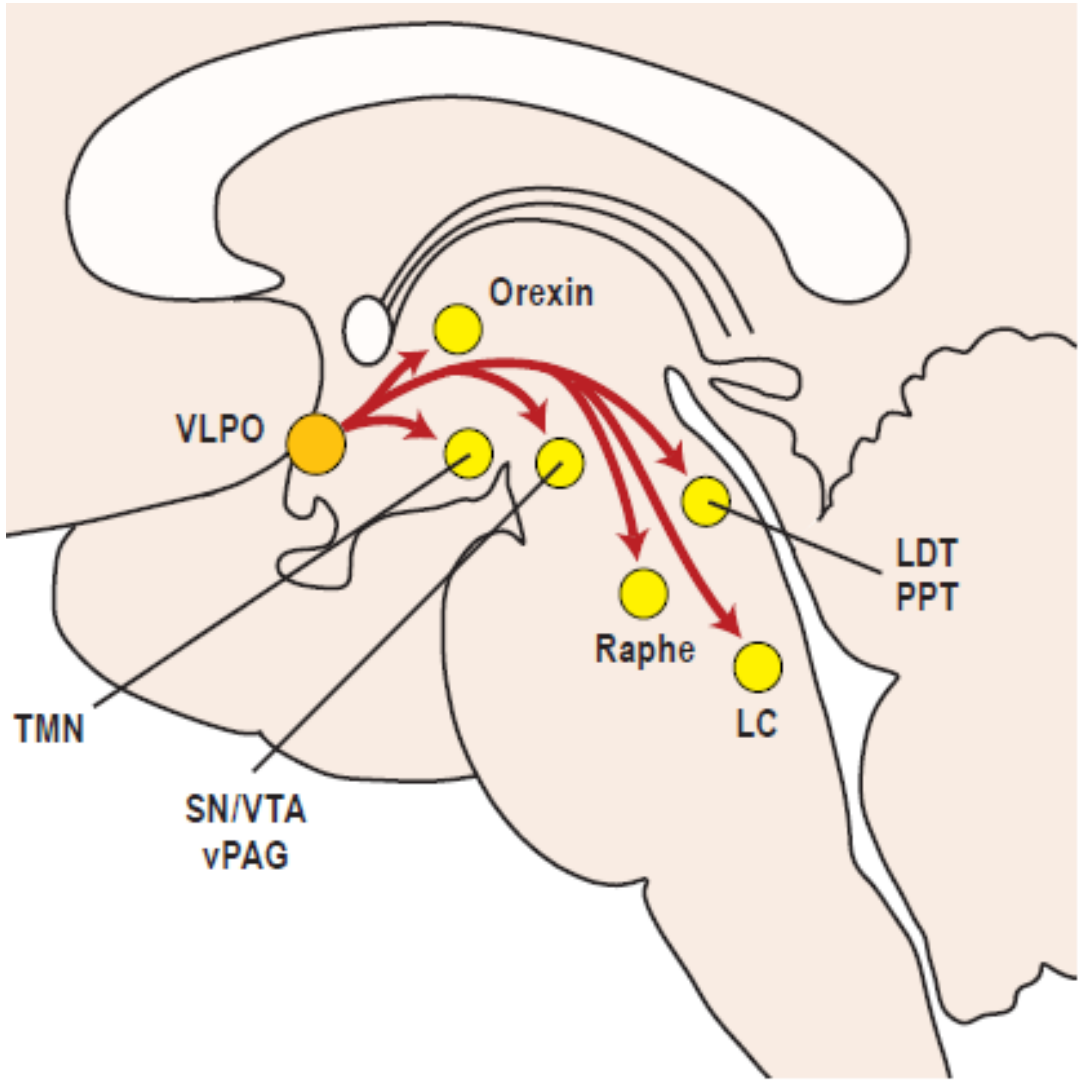
Sleep Physiology- Wake Neurons

- Wake promoting areas of the brain send neurotransmitters to the cortex to activate the brain and keep the “sleep switch” in the off (awake position).
- Raphe-Serotonin,
- LC-Norepinephrine
- TMN –Histamine
- LDT/PPT- Acetylcholine
- PBN- (not shown)- Glutamate
- Orexin- Activate all above neuron systems- sustain wake



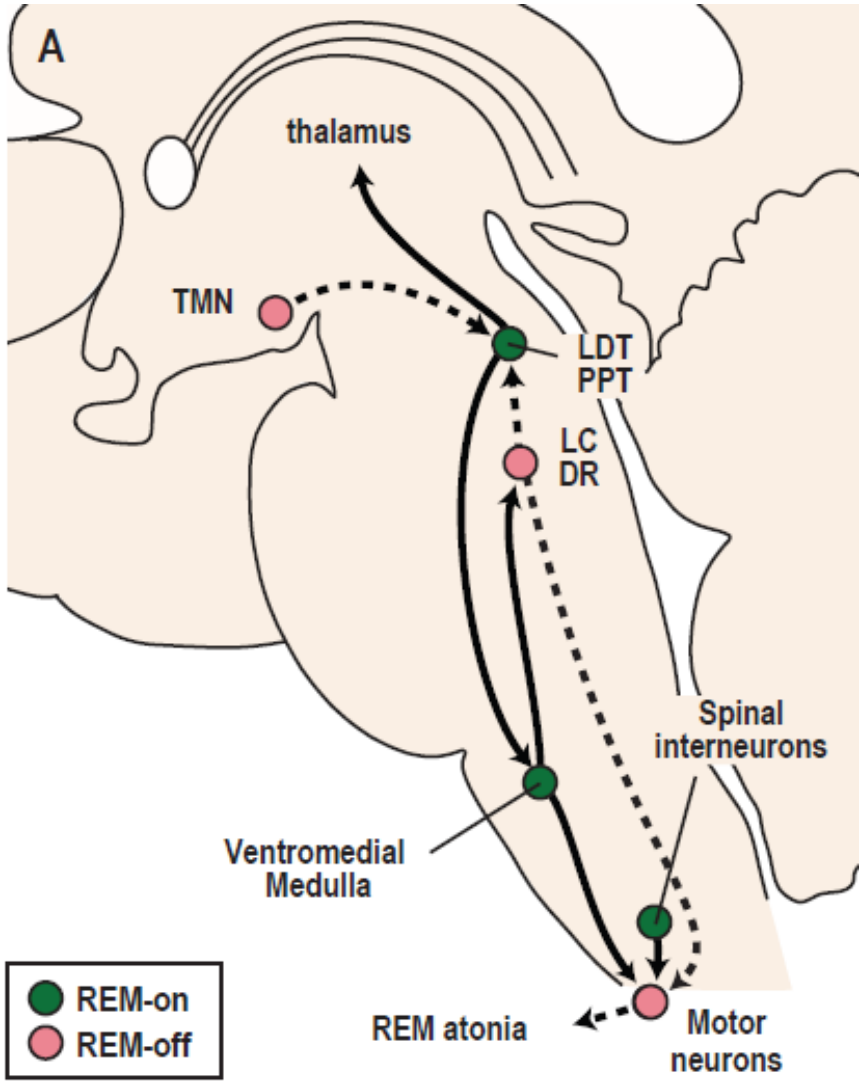
NREM Sleep Promoting Neurons

- Neurons thought to be part of the "sleep switch" are in the ventral lateral pre-optic nucleus (VLPO) and the area median to this fire at the onset and during NREM sleep
- These neurons contain GABA neurotransmitter with Galanin neuropeptide
- These neurons actively suppress all the wake promoting regions in yellow



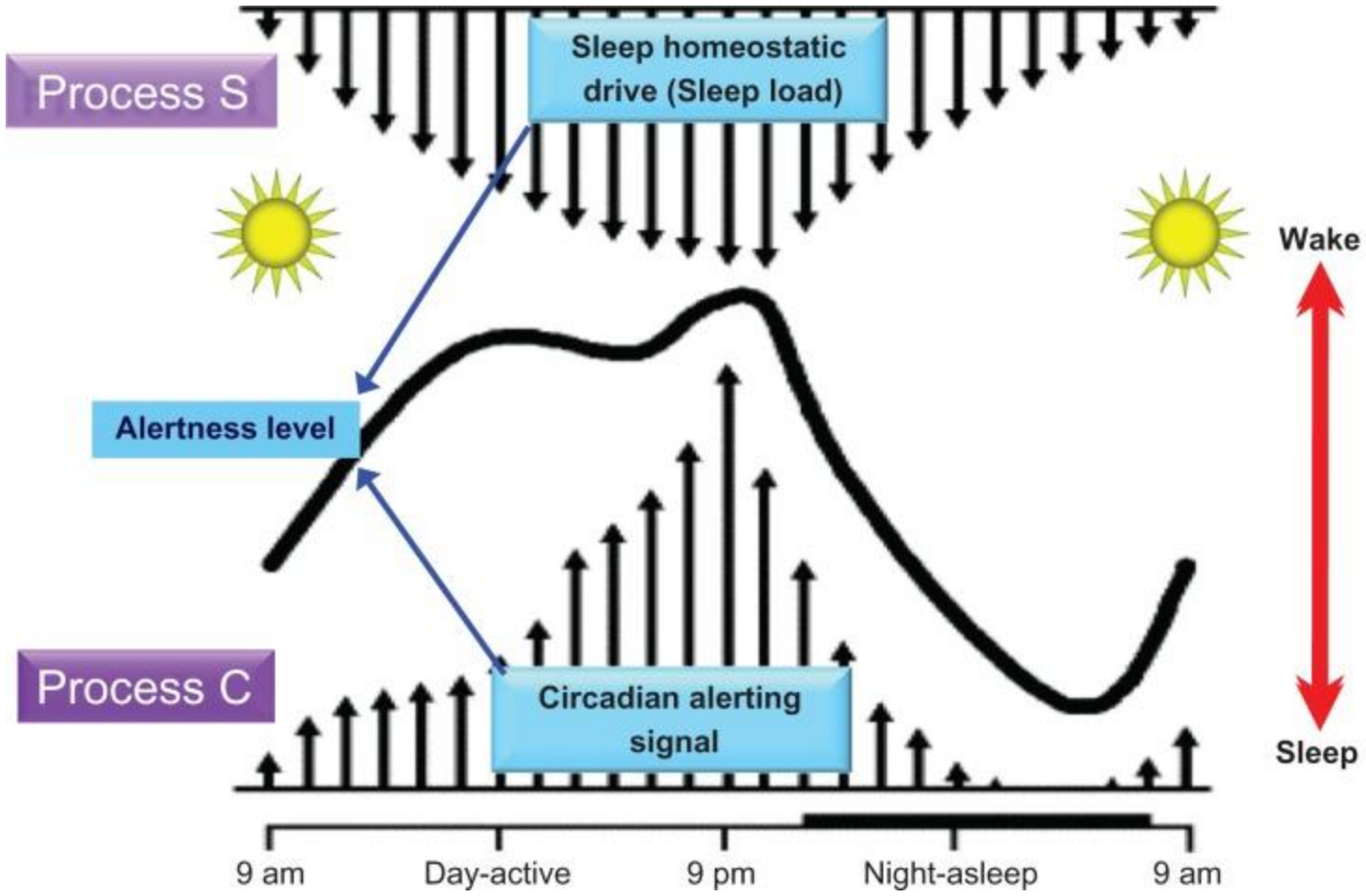
REM Sleep Promoting Neurons

- REM Sleep "On" Neurons become active (by loss of inhibition)
- Activate acetylcholine (Ach) neurons in the brain and brainstem
- REM atonia is induced when these neurons are inhibited in the brainstem (loss of the deep tendon knee reflex, chin tone goes down on PSG)
- Some of the same areas that promote wake also promote REM sleep (LDT/PPT)



Sleep Wake Regulation: Circadian Clock

- Sleep/Wake Neuronal activity is always optimized when it aligns with a persons innate circadian clock
- The longer someone is awake the drive for NREM or REM neurons to activate gets larger (Process S)
- The Circadian clock (Process C) is housed within the SCN - suprachiasmatic nucleus and is very active during the day to help promote wake, then as light of day weans off, its withdrawal signals the pineal gland to release melatonin, promoting sleep
- Activity of the SCN is highest early evening and late am to promote wakefulness



Multiple Sleep Latency Testing (MSLT)

Objective measure of a person's tendency to fall asleep during the day in a quiet situation.

Ensuring as regular a sleep as possible x 7 days prior and having them sleep the night before the MSLT in the sleep lab is important

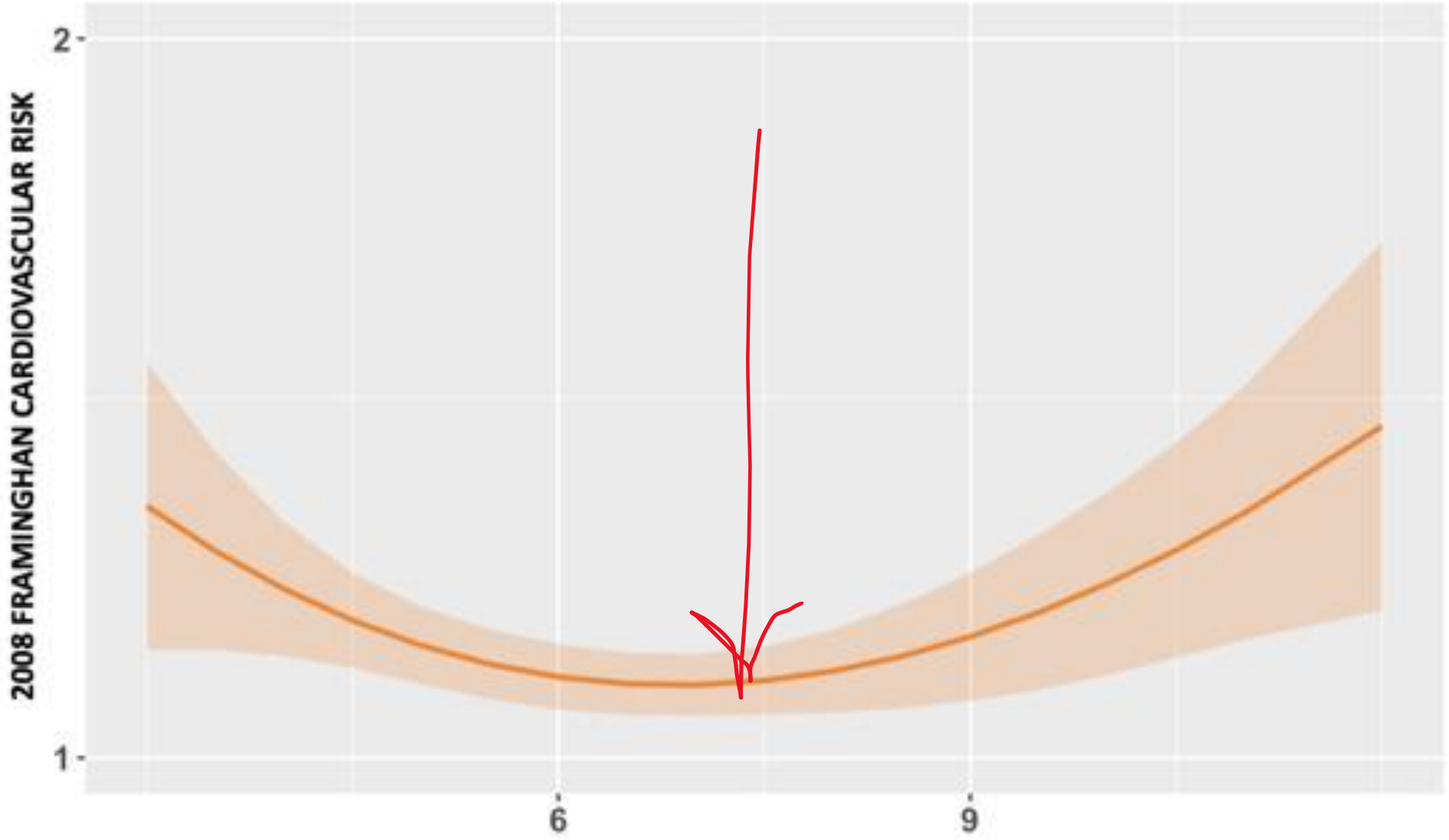
Nicotine is not recommended; Caffeine is not allowed.

5 nap opportunities spaced by 2 hours, with each nap lasting 20 min.

Each nap is terminated at 20 min if no sleep seen or at maximum of 15 minutes from the time of sleep onset if the patient falls asleep.

The mean sleep onset (averaged over 5 naps) is abnormal if <8 min and its abnormal to go into Stage REM during any of these naps.

Sleep Duration- What is normal



Non-Respiratory Sleep Disorders

- Insomia
- Narcolepsy Hypersomnia
- Parasmonias (NREM/REM)
- RLS/PLMD
- Circadian Rhythm Disorders

Insomnia- Defined

- At least one of the following sleep difficulties:
  - Falling asleep (sleep onset insomnia)
  - Staying asleep (sleep maintenance insomnia)
  - Waking up too early
- At least one associated problem:
  - Fatigue, non-refreshing sleep
  - Concerns about or dissatisfaction with sleep
- Physiologic Change
  - Sleep onset latency by PSG >30 min
  - Reduced Sleep efficiency (TST/TIB) <85%, TST total sleep time <6h
  - Increased WASO (wake after sleep onset) >30 min

Insomnia – Risk Factors

- Female gender
- Advancing Age (decreased slow wave sleep as we age, increased arousals)
- Widowed or divorced individuals
- Underemployed (lack of sleep scheduling)
- Concomitant disease (Cardiopulmonary dz- Cheyne-Stokes)

Insomnia- Classification

- Primary insomnia
  - Idiopathic- chronic, hyperaware/hyperarousal (EEG) state at bedtime or after sleep onset, polygenetic
  - Paradoxical -sleep state misperception- pt thinks they don't sleep at all but have near normal sleep studies including total sleep time
  - Psychophysiologic- sleep disruption caused by rumination, maladaptive behavior, intrusive thoughts or anxiety at bedtime

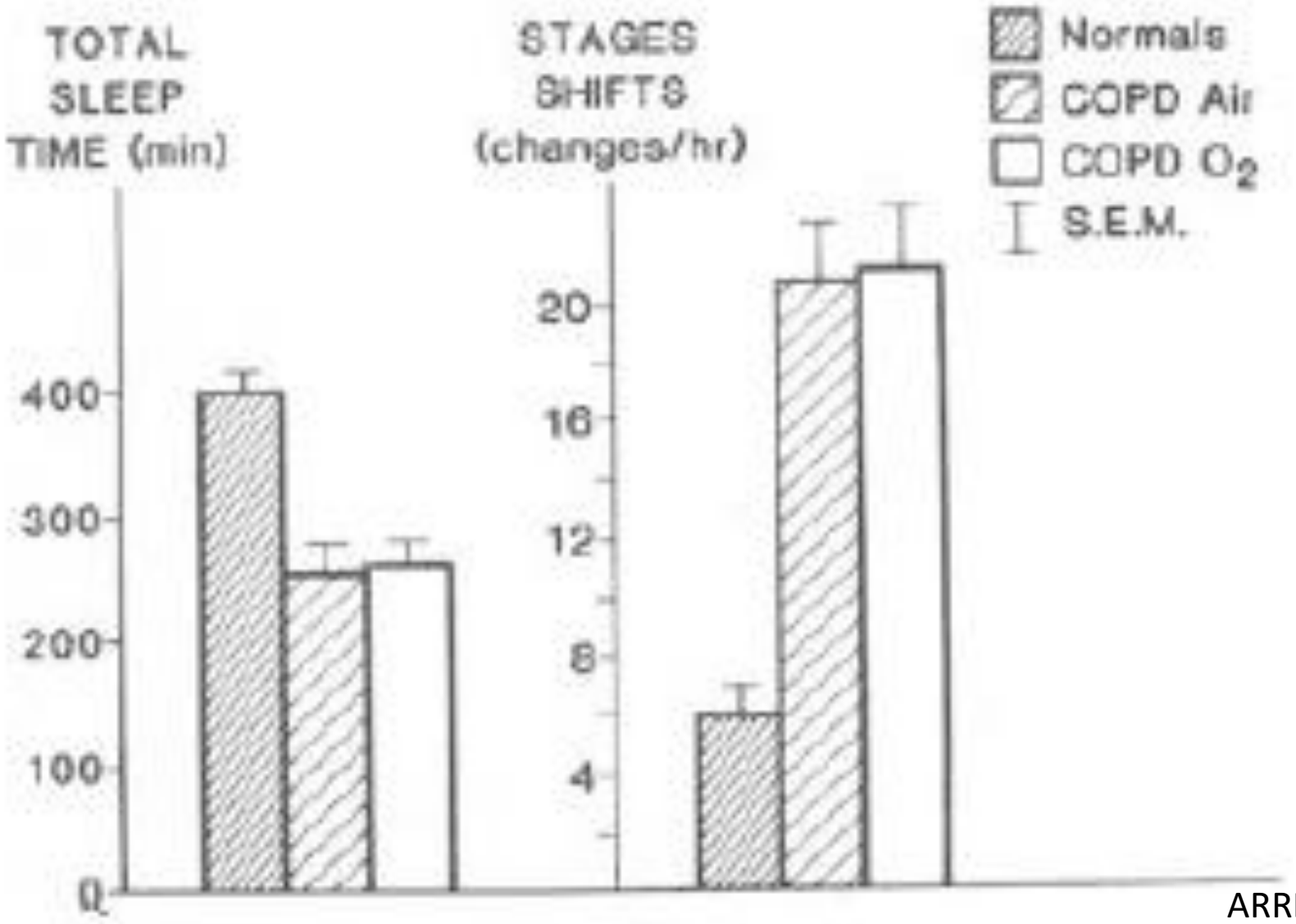
- Comorbid Insomnia
  - Poor sleep associated with comorbid conditions (ie lung disease)

Sleep Fragmentation in IPF pts waiting for lung transplant- no association w nocturnal hypoxemia- worse sleep quality noted

	Patients	Controls	*P*
Cycles/night	2.82 ± 1.13	3.21 ± 0.9	NS
Phase changes per sleep-hour	9.65 ± 2.61	9.11 ± 7	.001
Wakeful periods (%)	25.51 ± 15	8.52 ± 8	.013
Arousals/hour	22.13 ± 7.29	14.09 ± 9	NS
Total sleep time (TST) (min)	257.52 ± 57	316.25 ± 52	NS
Phase 1 + 2 (%)	68.93 ± 15	64 ± 6	.043
Phase 3 + 4 (%)	20.26 ± 11	21.55 ± 8.2	NS
REM (%)	13.17 ± 14	14.67 ± 4	NS

Transplantation Proceedings, 37, 1537–1539 (2005), Pascual et al.

Insomnia and COPD –Poor Sleep Quality - Not Related to Nocturnal Oxygen Levels



ARRD 1982;126(3):429–33

Insomnia- Diagnostic Tools

TWO WEEK SLEEP DIARY

INSTRUCTIONS:

1. Write the date, day of the week, and type of day: Work, School, Day Off, or Vacation.
2. Put the letter "C" in the box when you have coffee, cola or tea. Put "M" when you take any medicine. Put "A" when you drink alcohol. Put "E" when you exercise.
3. Put a line (|) to show when you go to bed. Shade in the box that shows when you think you fell asleep.
4. Shade in all the boxes that show when you are asleep at night or when you take a nap during the day.
5. Leave boxes unshaded to show when you wake up at night and when you are awake during the day.

SAMPLE ENTRY BELOW: On a Monday when I worked, I jogged on my lunch break at 1 PM, had a glass of wine with dinner at 6 PM, fell asleep watching TV from 7 to 8 PM, went to bed at 10:30 PM, fell asleep around Midnight, woke up and couldn't got back to sleep at about 4 AM, went back to sleep from 5 to 7 AM, and had coffee and medicine at 7:00 in the morning.

Today's Date	Day of the week	Type of Day Work, School, Off, Vacation	Noon	1PM	2	3	4	5	6PM	7	8	9	10	11PM	Midnight	1AM	2	3	4	5	6AM	7	8	9	10	11AM
sample	Mon.	Work		E					A				I									C M				

week 1

week 2

Fit Bit Sleep Data Recordings

Insomnia Severity Index

0 - 7	No clinically significant insomnia
8 - 14	Subthreshold insomnia
15 - 21	Clinical insomnia (moderate severity)
22 - 28	Clinical insomnia (severe)

Insomnia Severity Index

Patient's Name _____ Date _____

For each question, make a single selection to check a box. Click the button to clear the form if needed.

Clear

1. Please rate the current (last 2 weeks) SEVERITY of your insomnia problem(s).

	None 0	*Mild* 1	*Moderate* 2	*Severe* 3	*Very* 4	Score
Difficulty falling asleep	☐	☐	☐	☐	☐	0
Difficulty staying asleep	☐	☐	☐	☐	☐	0
Problem waking up too early	☐	☐	☐	☐	☐	0

2. How SATISFIED/dissatisfied are you with your current sleep pattern?

Very Satisfied 0	*Satisfied* 1	*Somewhat Satisfied* 2	*Dissatisfied* 3	*Very Dissatisfied* 4	
☐	☐	☐	☐	☐	0

3. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, ability to function at work/daily chores, concentration, memory, mood, etc.)

Not at all Interfering 0	*A Little Interfering* 1	*Somewhat Interfering* 2	*Much Interfering* 3	*Very Much Interfering* 4	
☐	☐	☐	☐	☐	0

4. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?

Not at all Noticeable 0	*A Little Noticeable* 1	*Somewhat Noticeable* 2	*Much Noticeable* 3	*Very Much Noticeable* 4	
☐	☐	☐	☐	☐	0

5. How WORRIED/distressed are you about your current sleep problem?

Not at all Worried 0	*A Little Worried* 1	*Somewhat Worried* 2	*Much Worried* 3	*Very Much Worried* 4	
☐	☐	☐	☐	☐	0

Guidelines for Scoring/Interpretation:
The total score is the sum of all seven items. Total score ranges from 0-28.

0 - 7	No clinically significant insomnia
8 - 14	Subthreshold insomnia
15 - 21	Clinical insomnia (moderate severity)
22 - 28	Clinical insomnia (severe)

TOTAL Score: 0

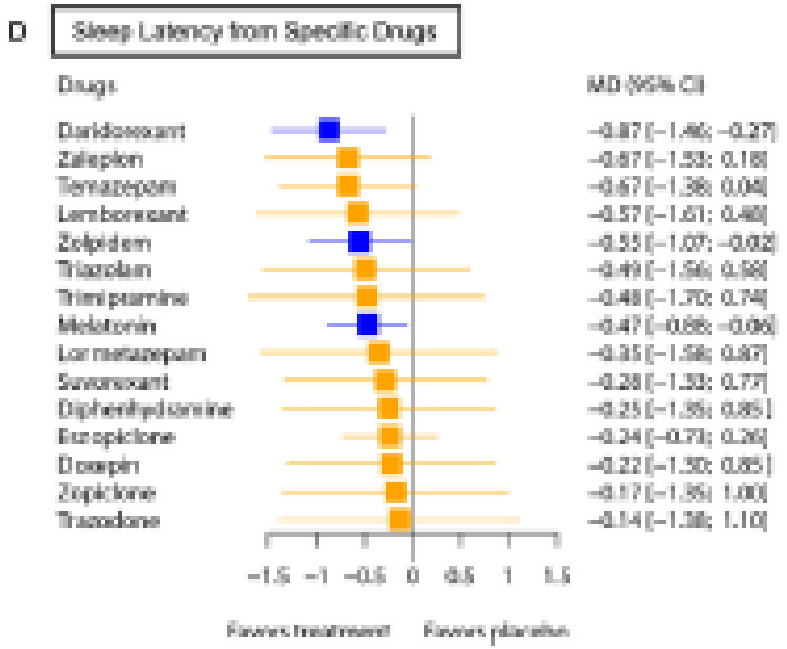
Insomnia Therapy

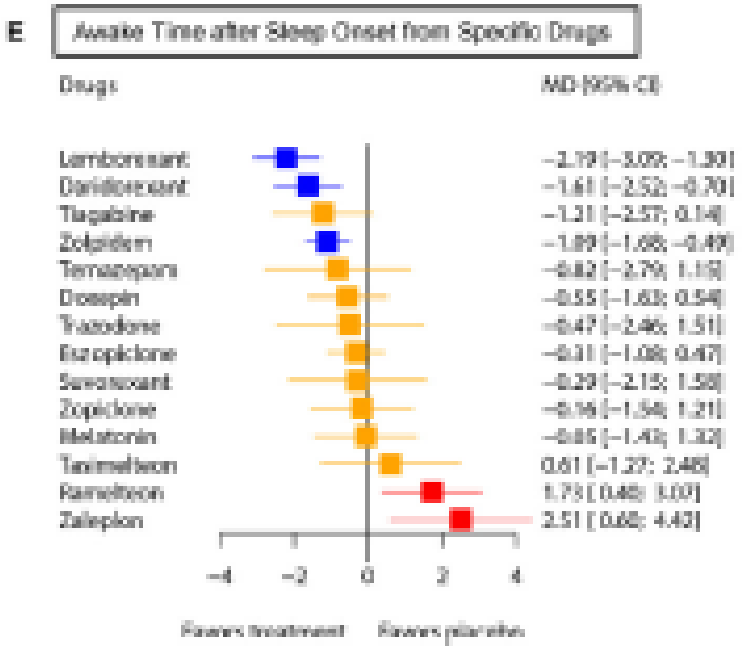
Cognitive Behavioral Therapy –relaxation techniques (early in night), stimulus control (making the bed not a frustrating place to be), sleep restriction (takes advantage of increased sleep drive) works better than meds long term

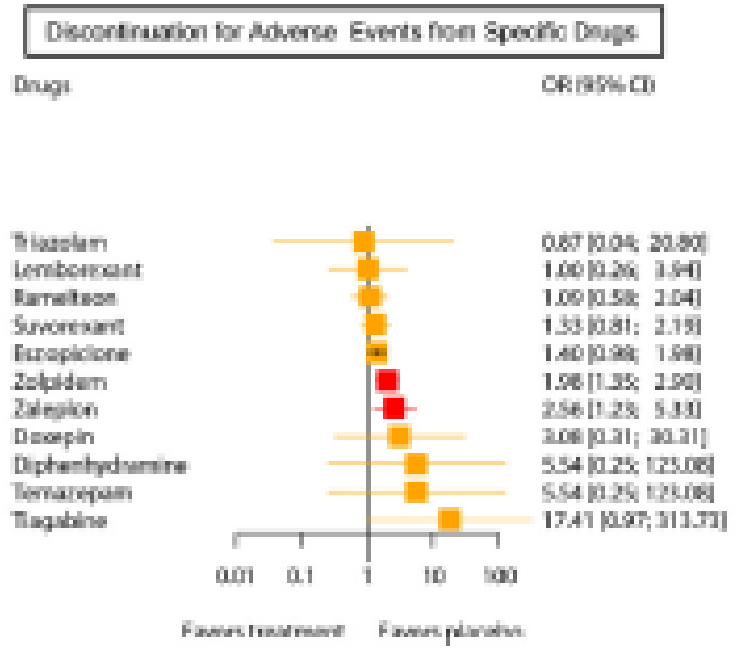
New versions of CBT available digitally (Restful App, Stellar Sleep)

Pharmacotherapy- enhance sleep but often don’t improve daytime performance. These agents can be helpful in comorbid disease (ie lung disease) that does not respond to the above therapies and therapies directed at the lung disease specifically (O2, bronchodilators, NIV)

Impact of specific agents on Sleep Latency, Wake after Sleep Onset and Discontinuation







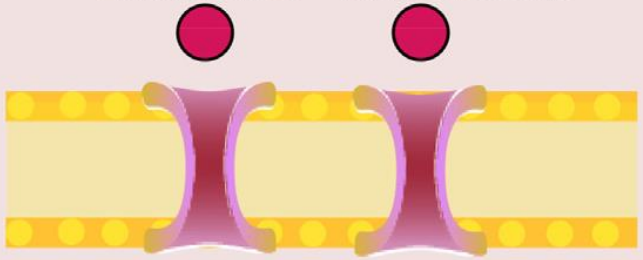
Pharmacotherapy for Insomnia- Metanalysis- 2023

1) ORAs (orexin receptor agonists- Suvorexant, Lamborexant) and Z-drugs (zolpidem, zalaeplon, ezopiclone) were both effective for objective outcomes of
insomnia (including SL, WASO, TST and SE) compared with placebo.

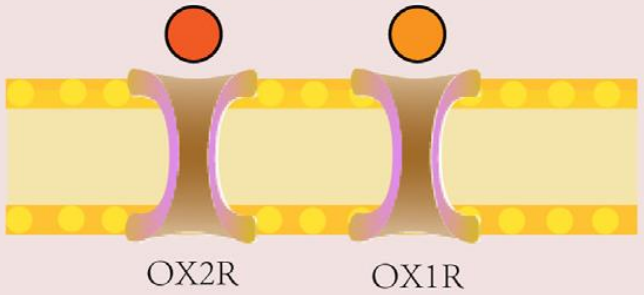
2) ORAs were best recommendation for sleep-maintenance insomnia, combining efficacy and tolerability/safety, while Z-drugs with higher risk to safety profiles.

3) BDZs (Benzodiazepines) were superior to placebo in improving subjective sleep quality; however, with poor safety.

Diphenhydramine Trimipramine
Doxepin
Antihistamines Antidepressants



Daridorexant
Lemborexant
Orexin receptor antagonists

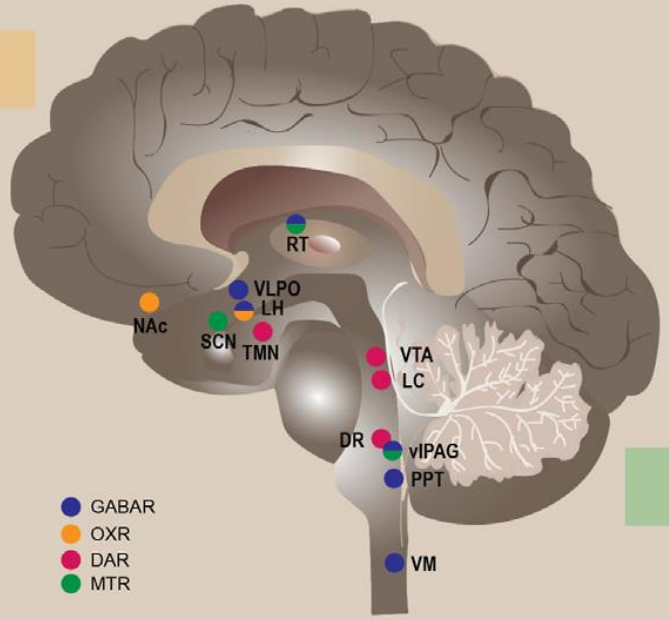


Sleep-maintenance insomnia

Daridorexant
Lemborexant
Zolpidem

INSOMNIA

Wake

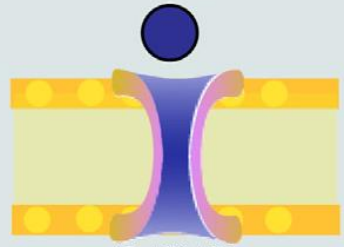


Sleep

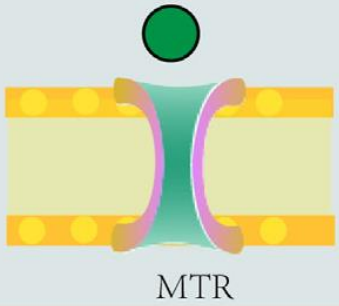
Daridorexant
Zolpidem
Zaleplon

Sleep-onset insomnia

Zolpidem Temazepam
Zaleplon Triazolam
Benzodiazepines
Z-drugs



Tasimeltaon
Ramelteon
Melatonin receptor agonists

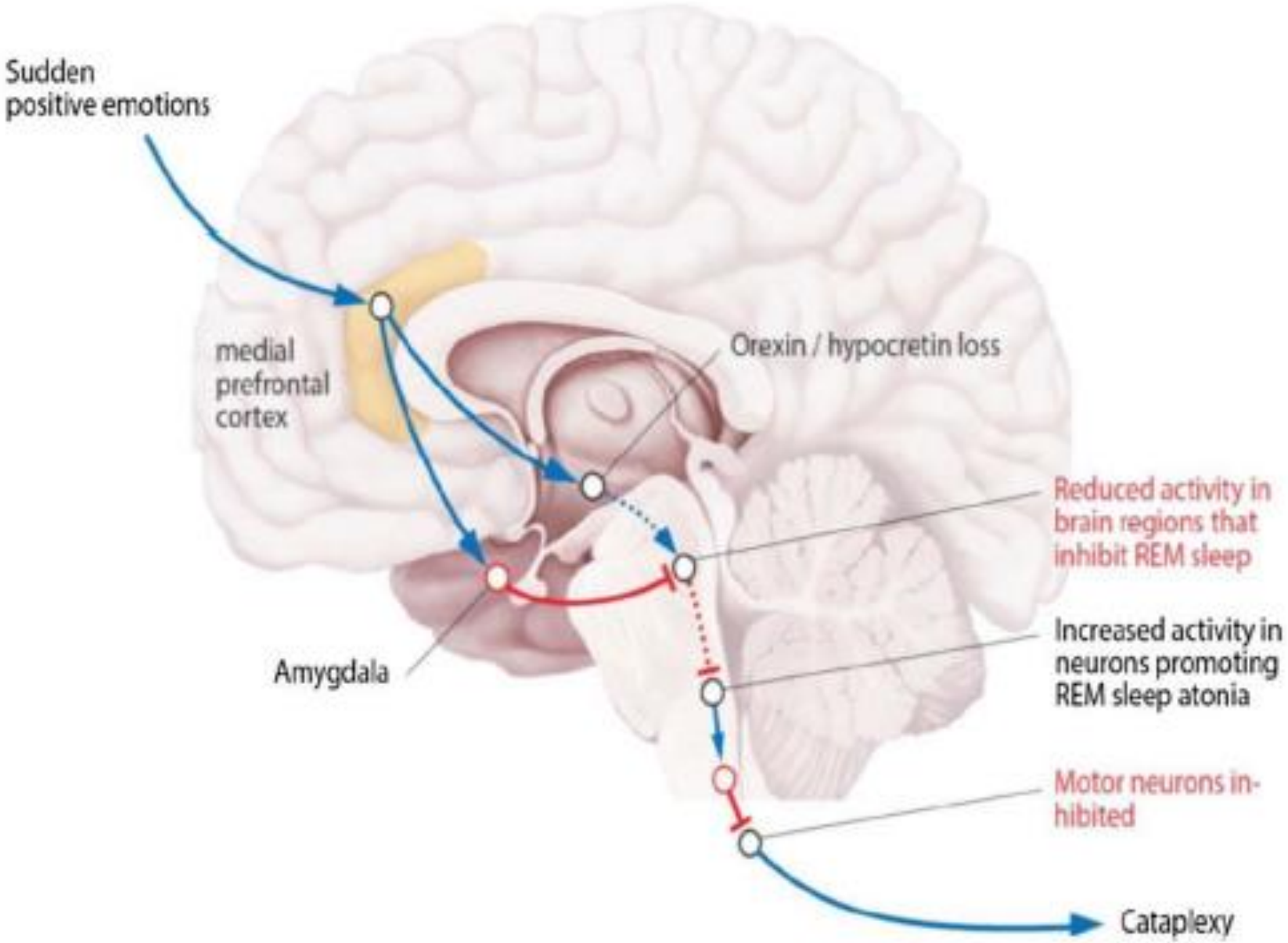


Hypersomnia Disorders- Narcolepsy

REM Sleep Behaviors invading on wakefulness – characterized by "tetrad"

1. Excessive Daytimes Sleepiness
2. Sleep Paralysis
3. Hypnogogic (sleep onset) hallucinations
4. Cataplexy (muscle atonia or weakness w strong emotions- most commonly laughter, anger)- Interestingly, respiratory muscles are spared, as are memory and consciousness

- Type 1 (with Cataplexy); Type 2 (without cataplexy)


Sudden
positive emotions
medial
prefrontal
cortex
Orexin / hypocretin loss
Reduced activity in
brain regions that
inhibit REM sleep
Amygdala
Increased activity in
neurons promoting
REM sleep atonia
Motor neurons in-
hibited
Cataplexy

Narcolepsy- Pathophysiology/Diagnostics

Caused by loss of function of Orexin neurons to activate the normal wake promoting neuron systems

Patients have trouble maintaining wakefulness, but feel refreshed after naps

Pts fall asleep easily when given the chance and will often go into REM sleep easier than those w/o Narcolepsy

Multiple Sleep Latency Testing- MSLT, will show mean sleep onset latency <8 min and pts will go into REM on >2 of the five Nap opportunities during the test

CSF Orexin <110 (typically only Type 1)

Narcolepsy Treatment

Ensure sleep, Naps

Stimulants

- Amine (stimulate DA, NE systems- Methypheidate, Amphetamine Salts, Dexidrine); Non- Amine (DA- Armodafinil, Modafinil, DA, NE-Solriamfetol, Histamine-Pitolisant)
- Venlafaxine/fluoxetine - cataplexy

Sodium Oxybate (Zyrem, Zywav and newer version Lumryz)

(these meds are similar to GHB, increase SWS; reduce EDS and cataplexy)

Parasomnias

- Activities/experiences that happen while asleep
- Associated w wake invading on sleep – considered disorders of arousal
- Characterized by when they happen during the night – NREM, REM

NREM Parasomnias

- Sleepwalking- ambulation in sleep, often from slow wave sleep
  - Often associated w sleep deprivation, febrile states, worsened by ETOH use
- Sleep Terrors- abrupt awakenings w profound fear, often w screaming out, occasionally walking as well
- Confusional Arousals – episodes of complete confusion then waking, often associated w only partial awakening with inappropriate behavior
- Sleep Related Eating Disorder- getting out of bed eating dense foods, cakes, etc. Can be seen as side effect of zolpidem use.

REM Parasomnias

- Nightmares- Frightening or unpleasant dreams, suddenly awaken people from sleep
- REM Behavior disorder- Dream reenactment, loss of REM associated muscle atonia (i.e. acting out violent dreams), associated w Lewy body dementia, Parkinson's- may be the best biomarker for these synucleopathies – has given researchers options for RCTs of neuroprotective therapies as well
- Catathrenia- expiratory groaning during sleep w/o respiratory distress and no oxygen desaturation, normal upper airway exam, no stridor
- Enuresis- urination during sleep; low ADH levels, prostate issues, concurrent OSA

Parasomnia – Diagnosis and Treatment

- PSG to r/o other sleep disorders (OSA) or to assess for movements- r/o seizures etc.
- Ensure no sleep deprivation- increase total sleep time
- Benzodiazepines (for severe sleepwalking and for reducing symptoms in severe RBD)
- Melatonin (for RBD)- may be neuroprotective RCT underway – higher doses 6-15 mg
- Safeguard pts apartment/house- keys in drawer, lock door- MOST IMPORTANT

Restless Legs Syndrome RLS (insomnia)
Periodic Limb Movement PLMD (daytime sleepiness)

- RLS
  - Irresistible urge to move or creepy crawly feeling in legs while AWAKE, most commonly in evening hours and may lead to insomnia
  - Sensory component relieved by getting up walking (motor component)
  - Treatments aimed at improving sleep onset insomnia
  - Related to Fe stores in motor strip, pre-frontal cortex

- PLMD
  - Repetitive, patterned, leg kicks at NIGHT seen o PSG
  - Disorder of sleep fragmentation
  - Treatments aimed at improving sleep fragmentation/disruption

RLS/PLMD Therapy

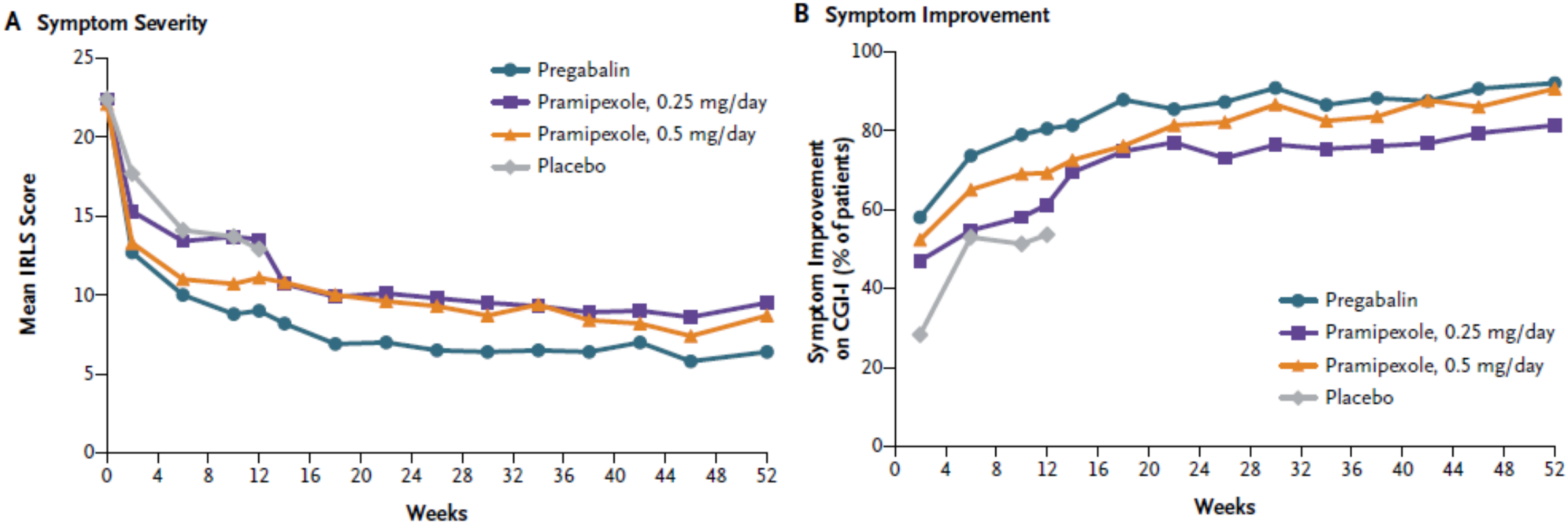
- Conservative therapy
- IV Iron- multiple preparations now, reasonable long-term success when Ferritin <50 ug/L
- **Gabapentin/Pregabalin- NEJM – optimal therapy and less augmentation**
- Dopaminergic agonists (pramipexole, ropinirole)- augmentation (side effect of more intense RLS, happening earlier in the day in other limbs)
- Opiates- short and longer acting (Methodone)- second, 3rd line
- Benzodiazepines- some symptomatic relief, but have a high side effect profile

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Comparison of Pregabalin with Pramipexole for Restless Legs Syndrome

Richard P. Allen, Ph.D., Crystal Chen, M.D., Diego Garcia-Borreguero, M.D., Ph.D., Olli Polo, M.D., Sarah DuBrava, M.S., Jeffrey Miceli, Ph.D., Lloyd Knapp, Pharm.D., and John W. Winkelman, M.D., Ph.D.


A Symptom Severity
Mean IRLS Score
25
20
15
10
5
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52
Weeks
Pregabalin
Pramipexole, 0.25 mg/day
Pramipexole, 0.5 mg/day
Placebo
B Symptom Improvement
Symptom Improvement on CGI-I (% of patients)
100
80
60
40
20
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52
Weeks
Pregabalin
Pramipexole, 0.25 mg/day
Pramipexole, 0.5 mg/day
Placebo

NEJM, 2014

Circadian Rhythm Sleep Disorders

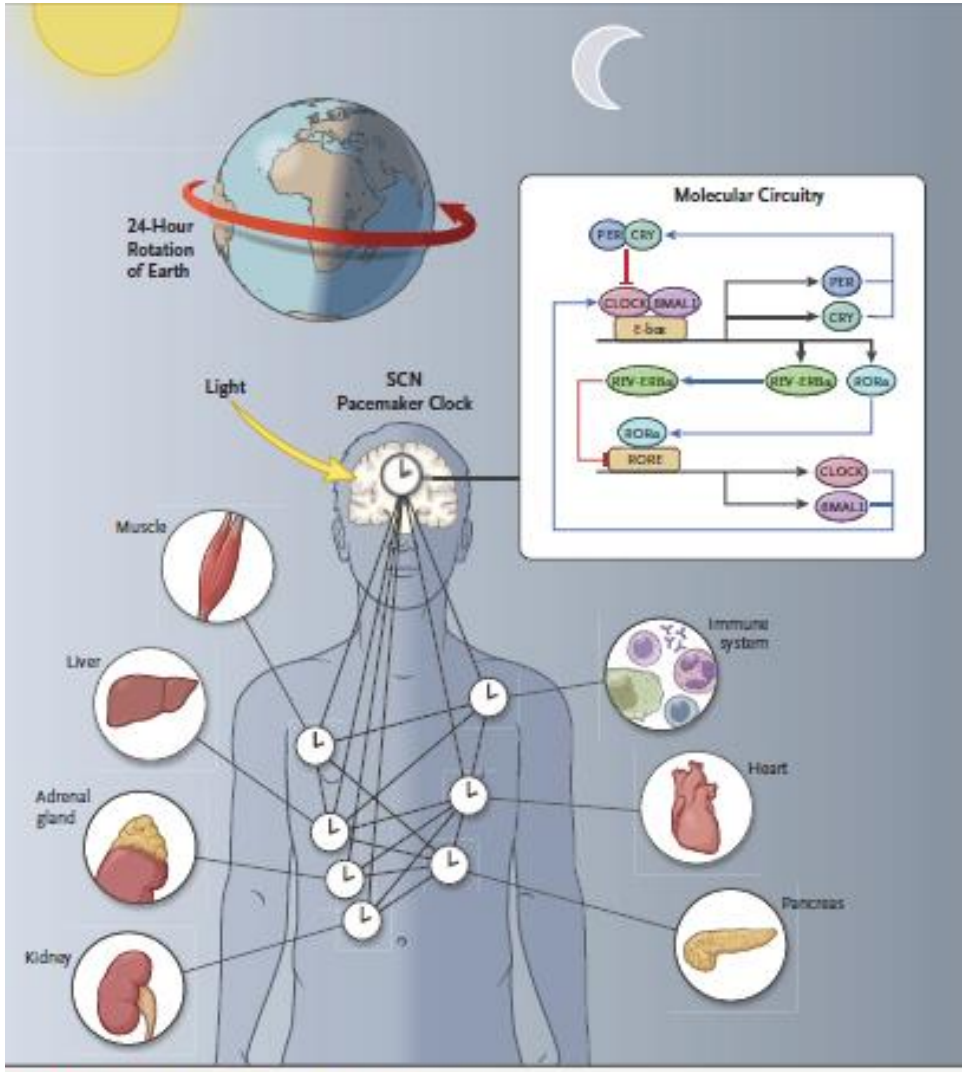
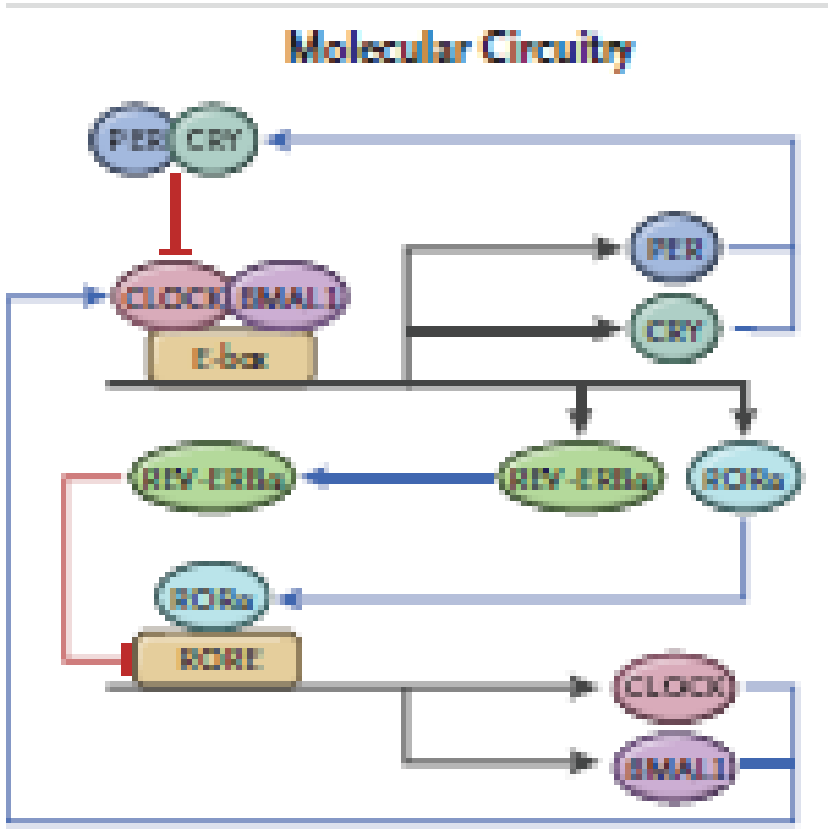


Figure 1. Circadian Networks and Geophysical Time.



Circadian Rhythm Disorders

Delayed Sleep Phase Disorder

- Night Owls, pts go to bed late, no issues falling asleep late, diff waking, have normal late wake times, treated w am light, avoiding late night light, melatonin rx Common in high school

Advanced Sleep Phase Disorder

- Morning larks, prefer early bedtime and have early rise time 2-5 am. Common in mid-age. Rx Light in late night

Non-24 Sleep Disorder

- Lack of retinal connections to the suprachiasmatic nucleus (SCN), pts cannot entrain to the 24 hour day, go to bed 10 min later each day (tasimelteon-melatonin receptor agonist)

Jet Lag Syndrome

- Transient insomnia or sleepiness after westward or eastward air travel across multiple time zones, melatonin or light to reset the clock

Shift Worker Sleep Disorder

- Sleep disturbance related ot no-traditional work hours; associated w sleepiness on shifts (i.e. 3rd shift) and difficulty sleeping in daytime.

The New England Journal of Medicine

ENTRAINMENT OF FREE-RUNNING CIRCADIAN RHYTHMS BY MELATONIN IN BLIND PEOPLE

ROBERT L. SACK, M.D., RICHARD W. BRANDES, B.S., ADAM R. KENDALL, B.S., AND ALFRED J. LEWY, M.D., PH.D.

Board Questions

Which therapy has been shown to be most effective improving sleep maintenance insomnia long term

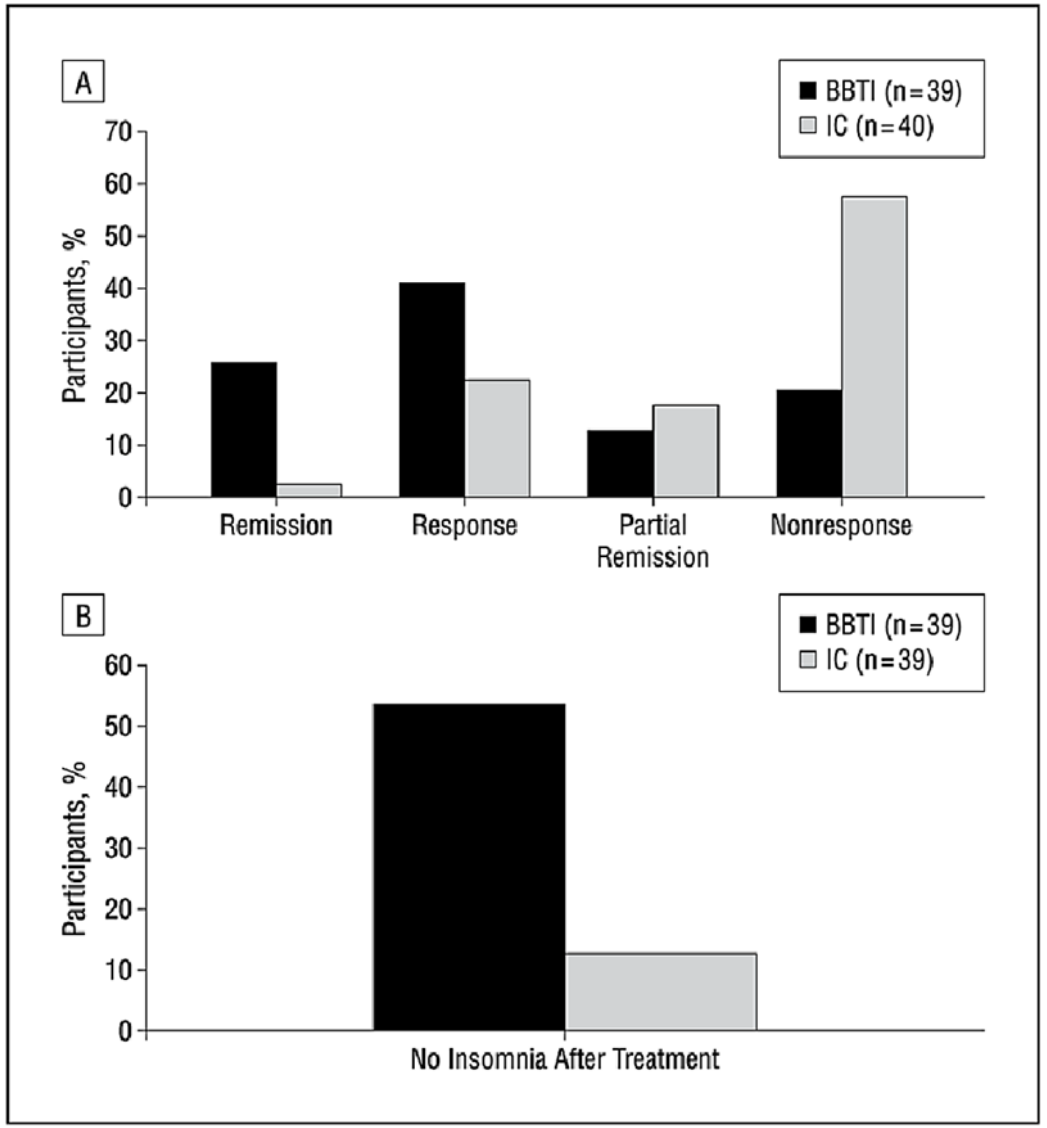
a) Orexin Receptor Antagonists

b) Benzodiazepine Receptor Agonists

c) Melatonin Receptor Agonists

d) Cognitive Behavioral Therapy

d) Cognitive Behavioral Therapy



Brief CBT (BBTi) vs controls in Insomnia pts
Buysse, D, JAMA 2011

What is the most optimal therapy for both cataplexy and daytime sleepiness in Narcolepsy patients?

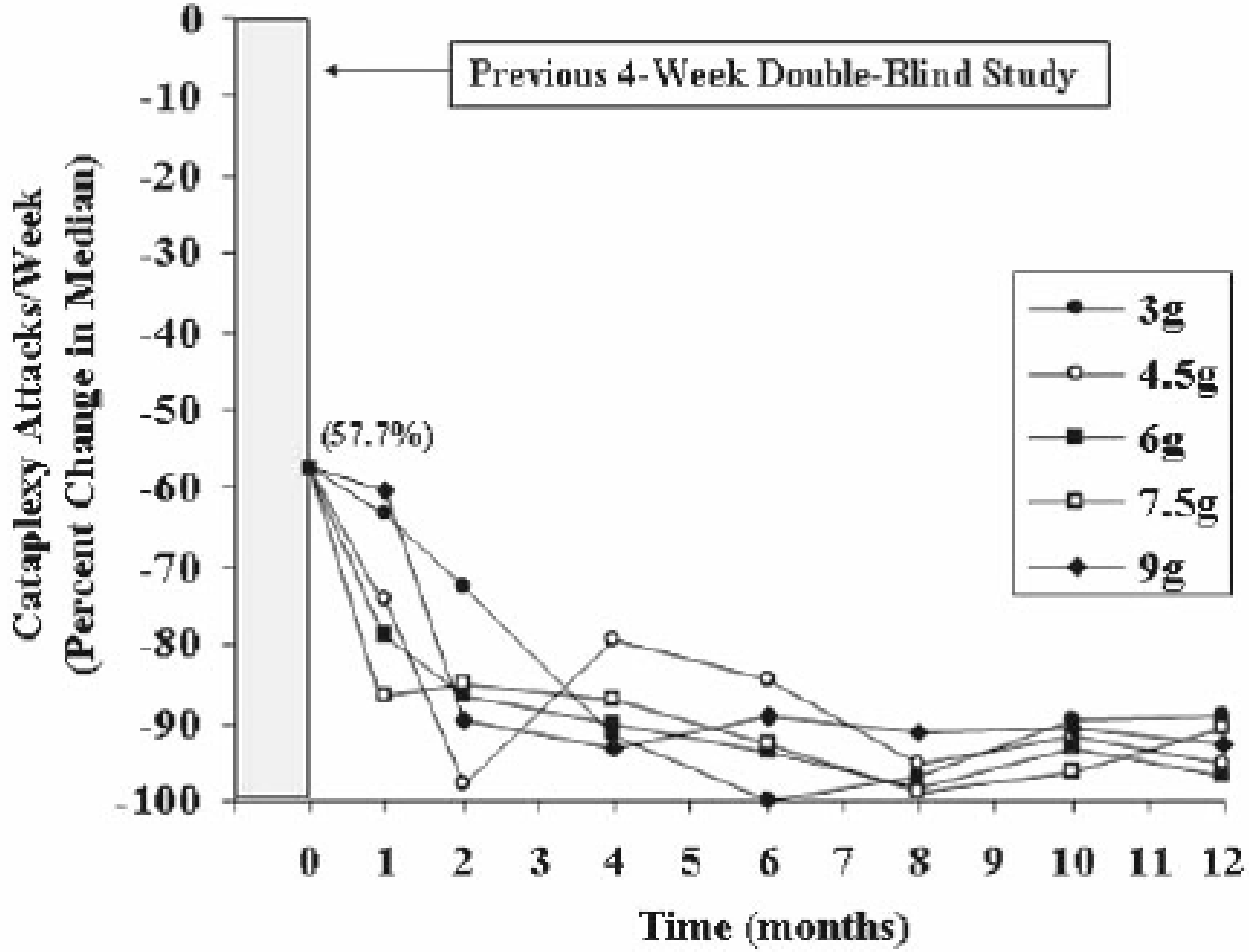
a) Amphetamine salts

b) Orexin receptor antagonists

c) Amitriptyline

d) Sodium Oxybate

d)Sodium Oxybate

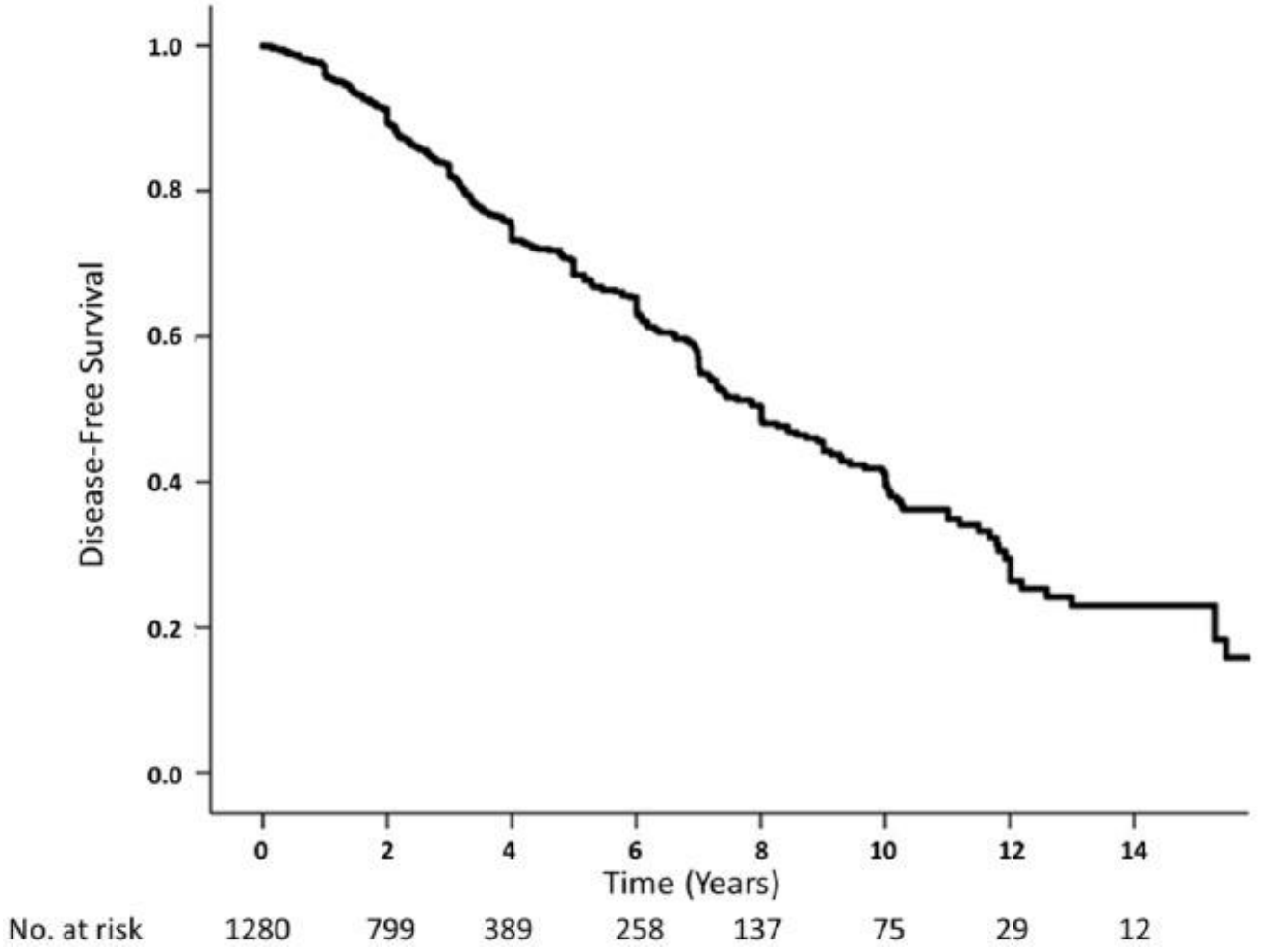


SLEEP 2002

You are reviewing your pt with COPD and complaints of violently acting out his dreams, punching his wife at times at 4 am and has evidence of lack of REM Atonia on a sleep study but no OSA and you diagnose him with REM behavior disorder (RBD). Which of the following is true about REM Behavior disorder?

- 1) RBD is linked to Huntington's disease
- 2) RBD is linked to ALS
- 3) Concurrent OSA is not common with this disorder
- 4) RBD may be considered a biomarker for risk of Lewy body dementia and Parkinson's disease

4) RBD may be considered a biomarker for risk of Lewy body dementia and Parkinson's disease



Kaplan-Meier plot of disease-free survival (i.e. free of parkinsonism or dementia) among patients with iRBD..