Utilizing New Tools to Regulate the Sleep-Wake Mode and Better Treat Insomnia

Supported by an educational grant from Merck & Co., Inc.

Jointly provided by Center for Independent Healthcare Education and Vemco MedEd

Activity Description

Target Audience

This continuing medical education activity is planned to meet the needs of sleep specialists who are involved in the diagnosis, evaluation, and treatment of patients with insomnia. These include physicians, researchers, sleep technologists, and other professionals who specialize in sleep medicine, neurology, psychology, psychiatry, and neurophysiology.

Learning Objectives

Upon completing this activity, participants will be able to:

- Understand the latest advancements in the pathophysiology of sleep disorders
- Recognize the latest non-pharmacologic and pharmacologic approaches in controlling the sleep-wake cycle
- Evaluate the use of orexin receptor antagonists in the management of insomnia

Normal Sleep Physiology and Its Implications in Insomnia Pathophysiology

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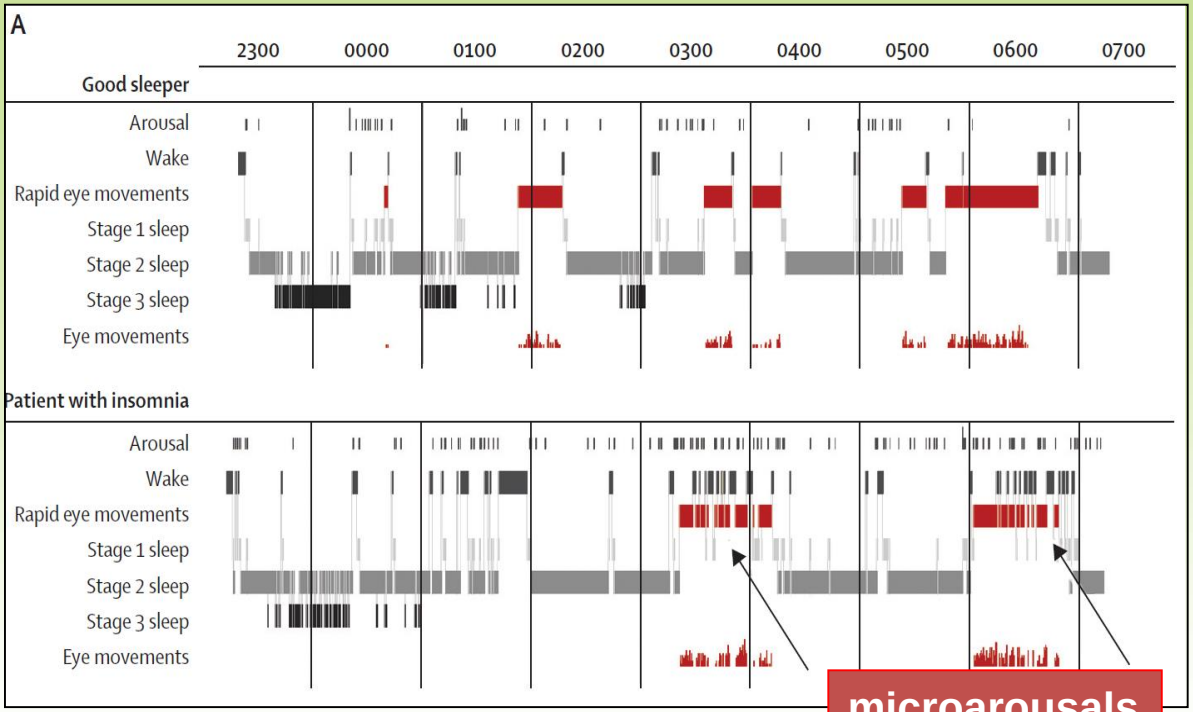
Director Center for Circadian and Sleep Medicine
Northwestern University Feinberg School of Medicine
Chicago, IL

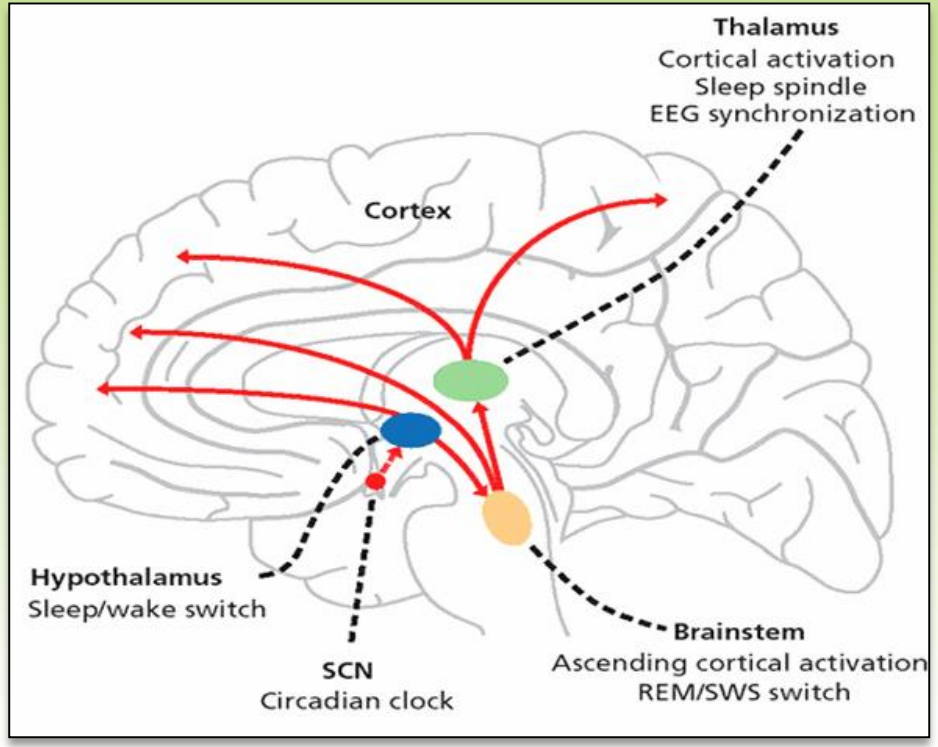
Sleepless Patient

- 34-year-old female with difficulty falling asleep (1–2 hours) and staying asleep (wakes up for 1–2 hours) for past 8 months
- She feels tired, down and irritable
- Just can't seem to shut her mind down at bedtime
- It's affecting her work and personal life



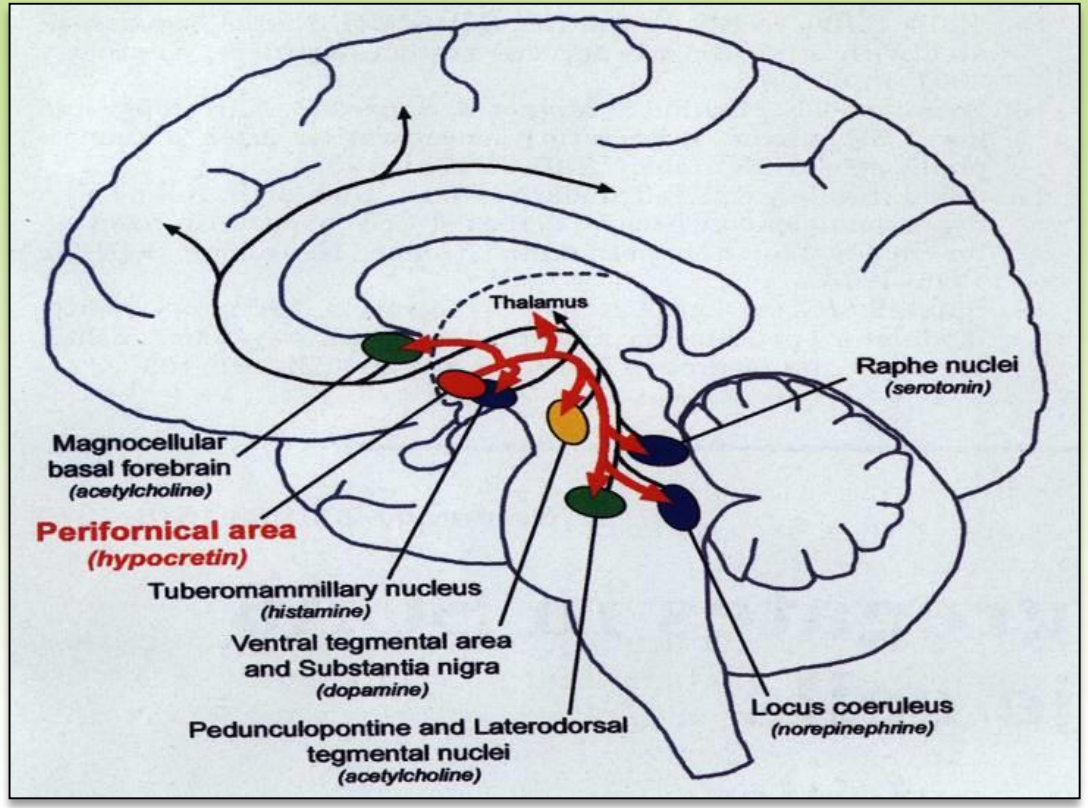
Riemann D, et al. *Lancet Neurol*. 2015;14:547-58.

Sleep-Wake Regulation: Interacting Homeostatic and Circadian Systems



SCN, suprachiasmatic nucleus; REM, rapid eye movement; SWS, slow-wave sleep.
Mignot E, et al. *Nat Neurosci*. 2002;5(suppl):1071-1075.

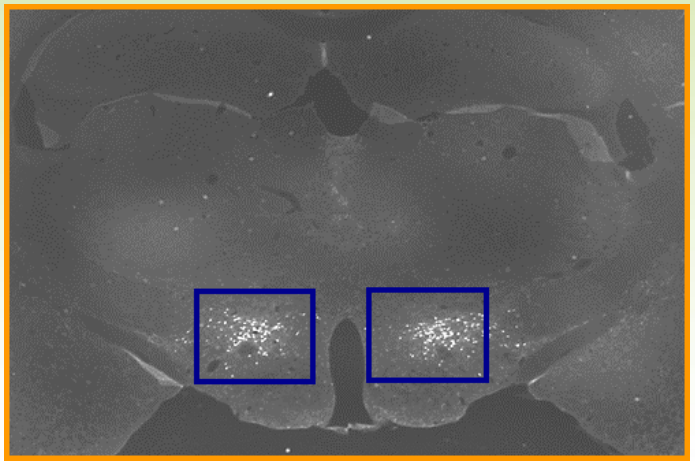
Regulation of Wakefulness



Silber MH, Rye DB. *Neurology*. 2001;56:1616-8.

Hypocretin/Orexin

- Maintenance of arousal/wakefulness
- Hypothalamic peptides
  - Localized in the dorsolateral hypothalamus
  - Wide projections throughout the brain
  - Projections found in the spinal column
- Dense, excitatory projections to brain areas that influence
  - Wakefulness
  - Appetite
  - Thermoregulation
  - Autonomic control



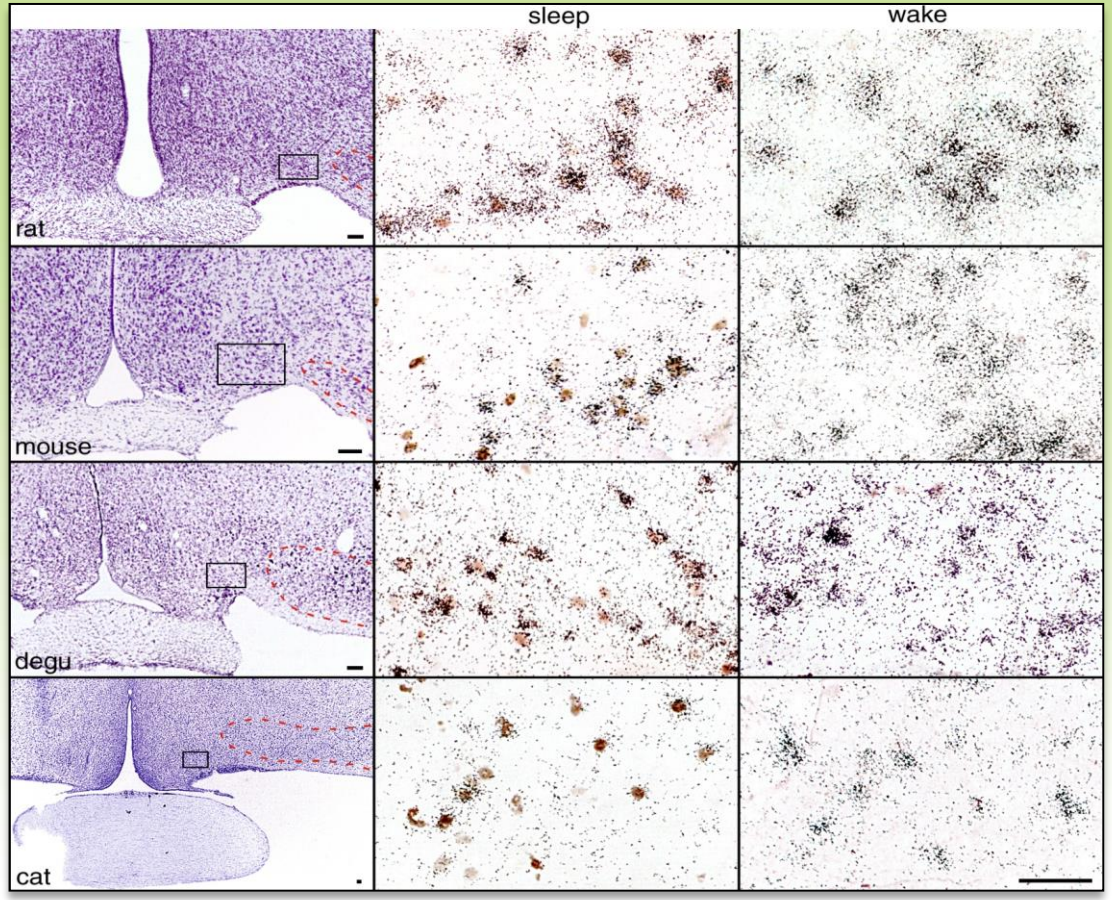
Peyron C, et al. *J Neurosci*. 1998;18:9996-10015.
Moore RY, et al. *Arch Ital Biol*. 2001;139:195-205.
Silber MH, Rye DB. *Neurology*. 2001;56:1616-8.

Control of NREM Sleep

GABA, γ-aminobutyrate; VLPO, ventrolateral preoptic area; TMN, tuberomammillary nucleus; VTA, ventral tegmental area; PPT, pedunculopontine nucleus; LDT, laterodorsal tegmental nucleus; LC, locus coeruleus.

Adapted with permission from Espana RA, Scammell TE. *Sleep*. 2004;27:811-20.

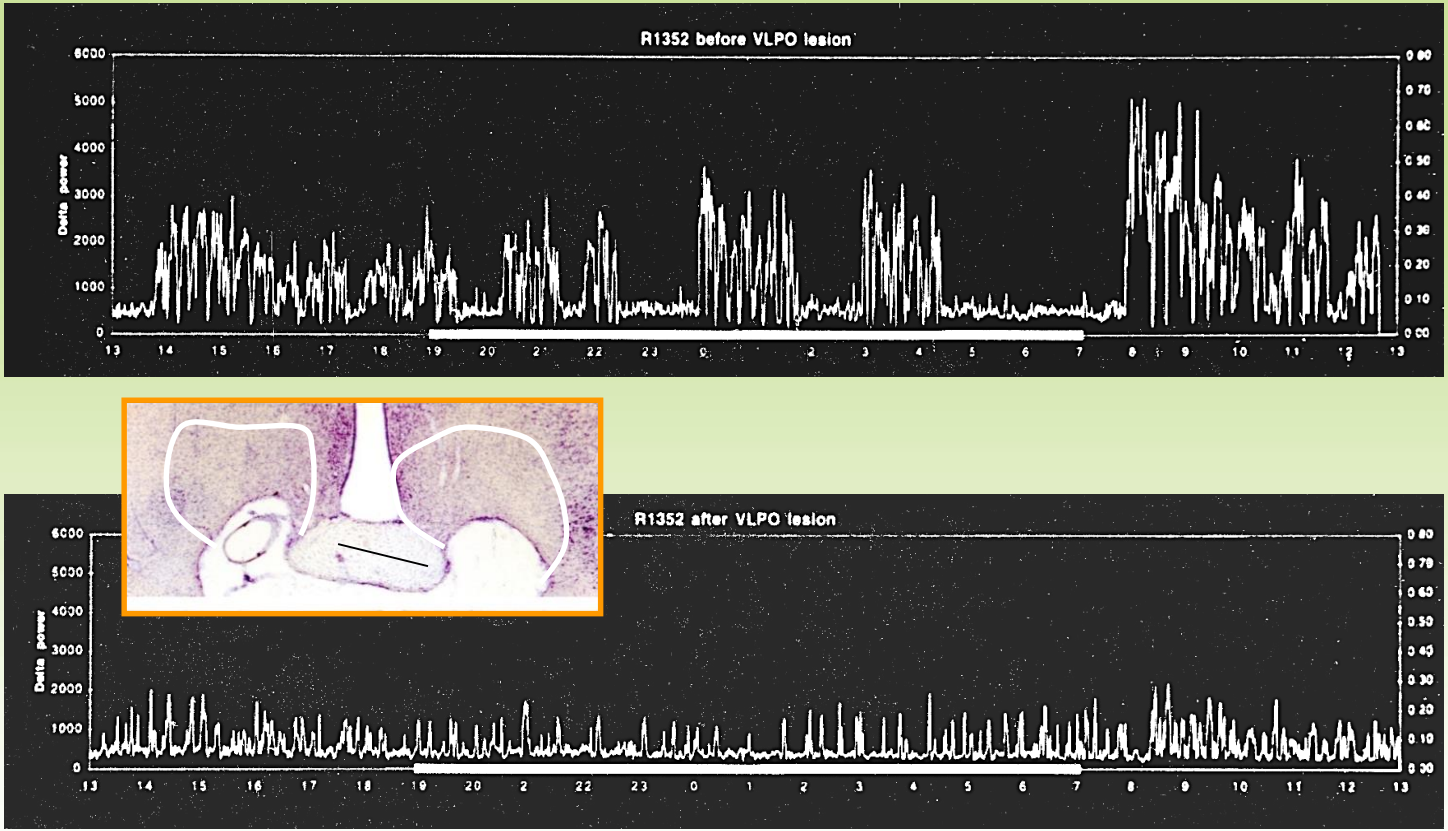
The VLPO is Sleep-active in Mammals



VLPO, ventrolateral preoptic area.

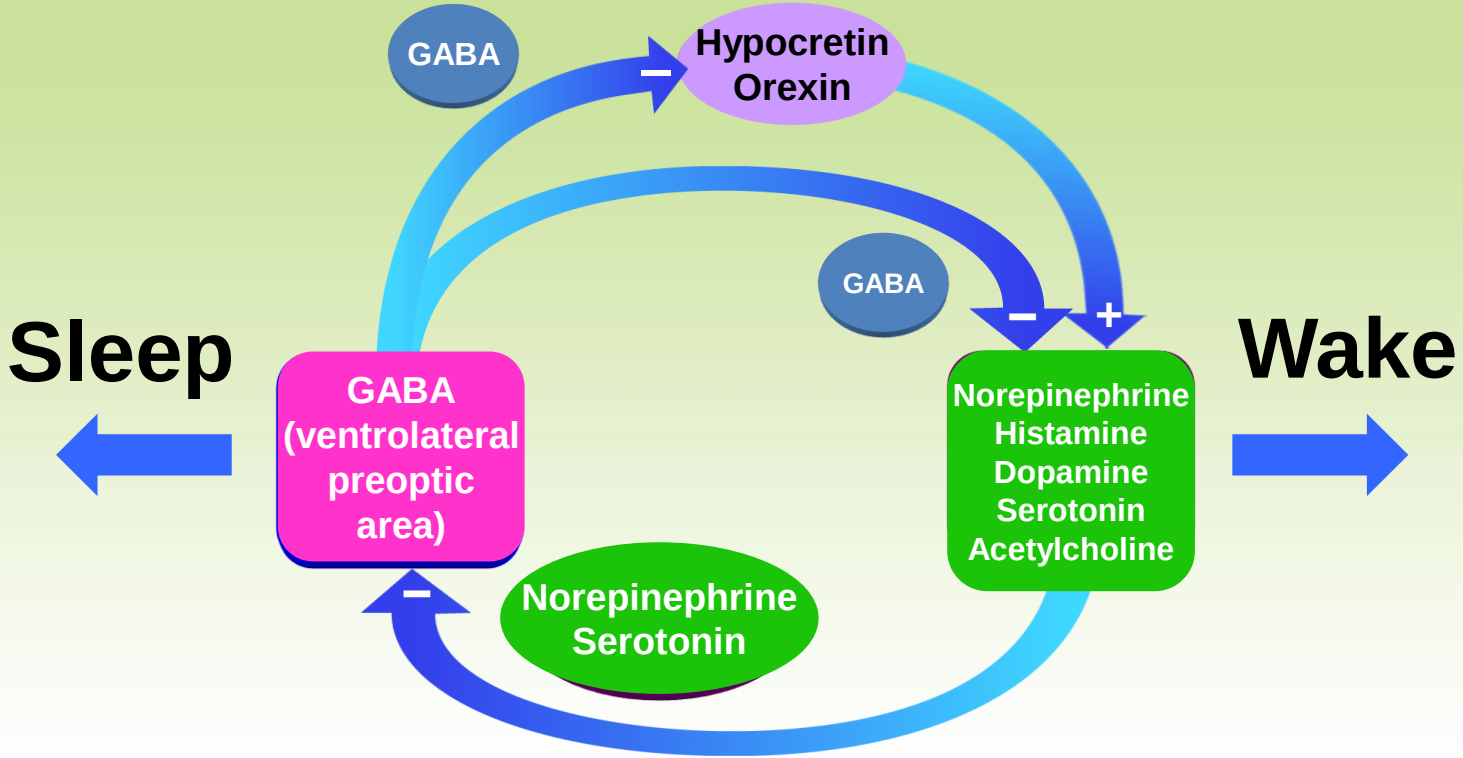
Modified from Gaus SE, et al. *Neuroscience*. 2002;115:285-94.

Lesions of the VLPO in Rats Produce Insomnia



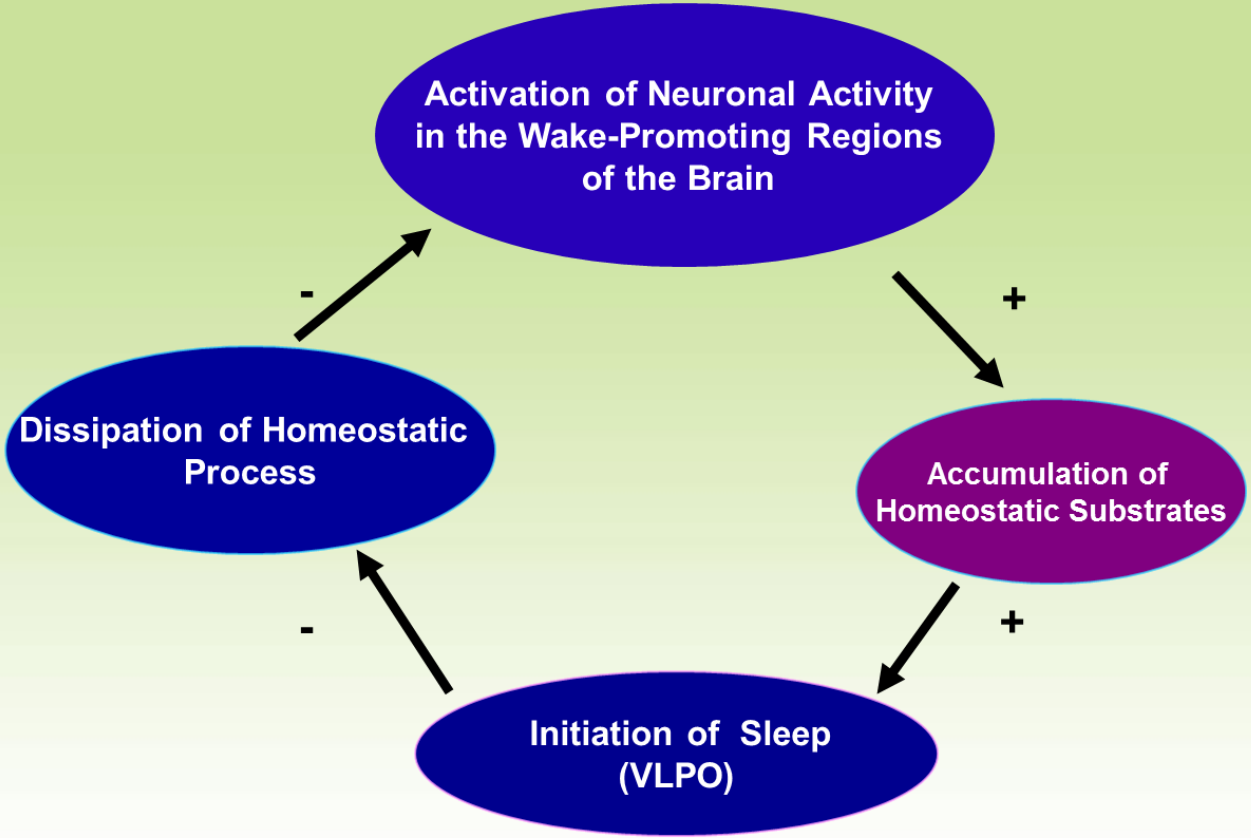
Modified from Lu J, et al. *J Neurosci*. 2000;20:3830-42.

The Sleep-Wake Switch



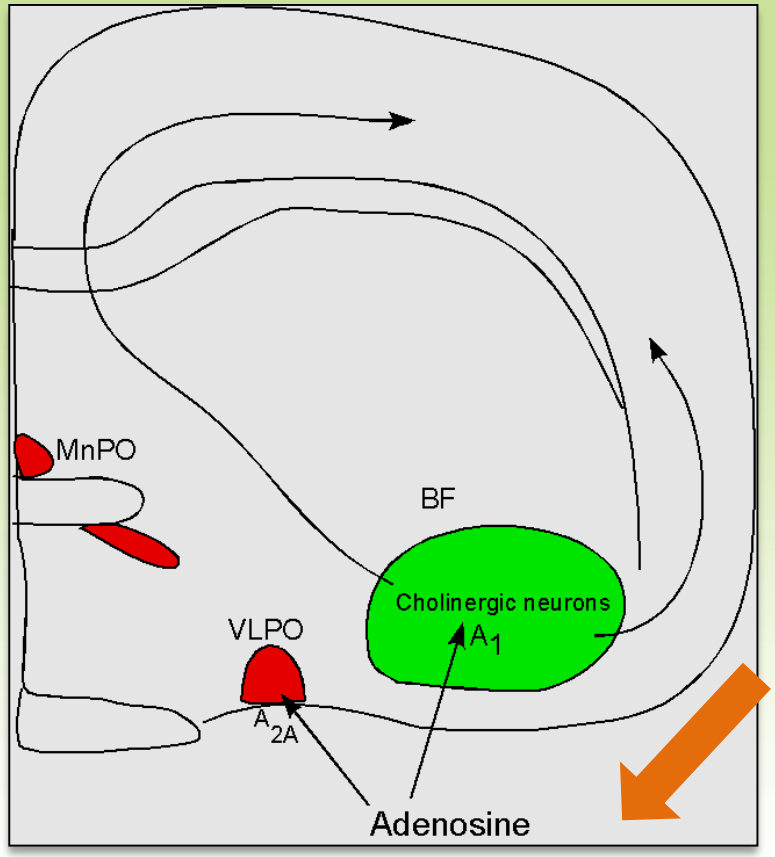
Adapted from Saper CB, et al. *Trends Neurosci*. 2001;24:726-31.

Homeostatic Regulation of Sleep



Datta S, MacLean RR. *Neurosci Biobehavioral Rev.* 2007;31:775-824.
Lorton D, et al. *Neuroimmunomodulation.* 2006;13:357-374.

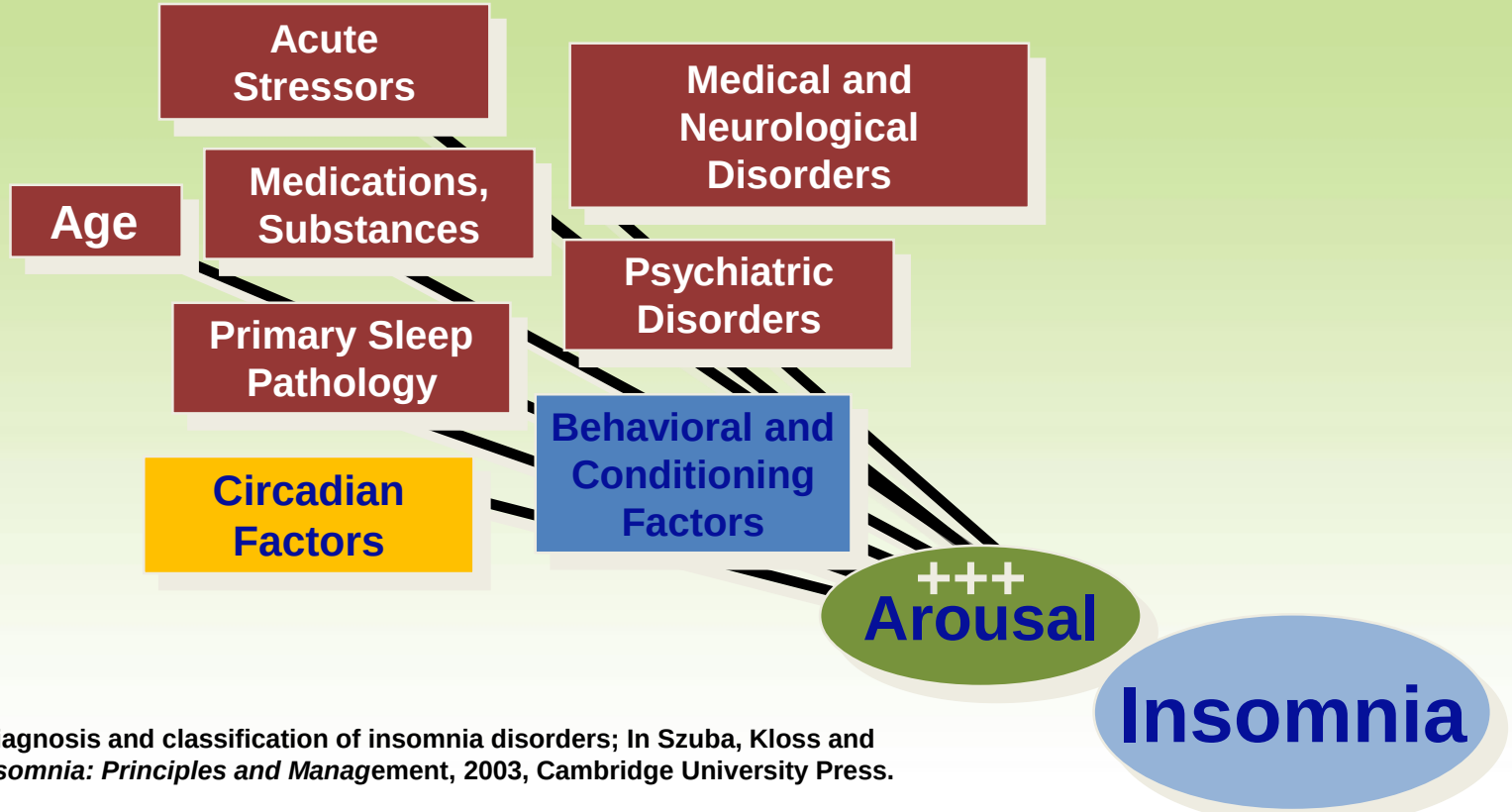
What Determines Homeostatic Sleep Drive?



Caffeine

Modified from Basheer R, et al. *Prog Neurobiol.* 2004;73:379-96.

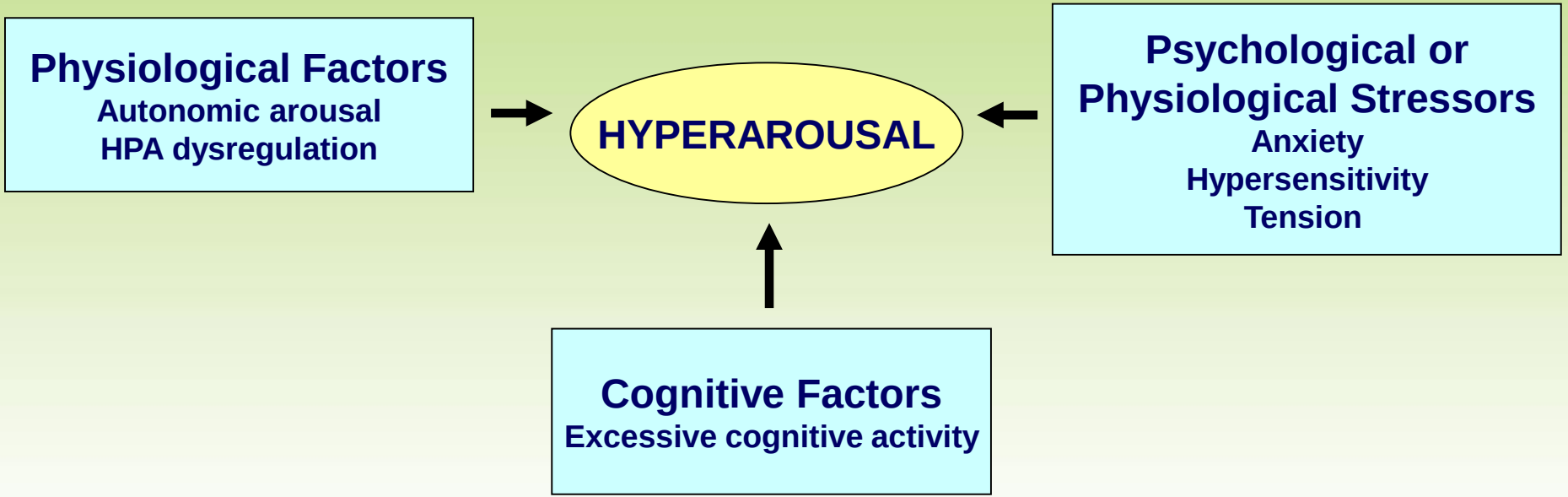
Model of Insomnia: Implications for Treatment



Buysse, Diagnosis and classification of insomnia disorders; In Szuba, Kloss and Dinges, *Insomnia: Principles and Manage*ment, 2003, Cambridge University Press.

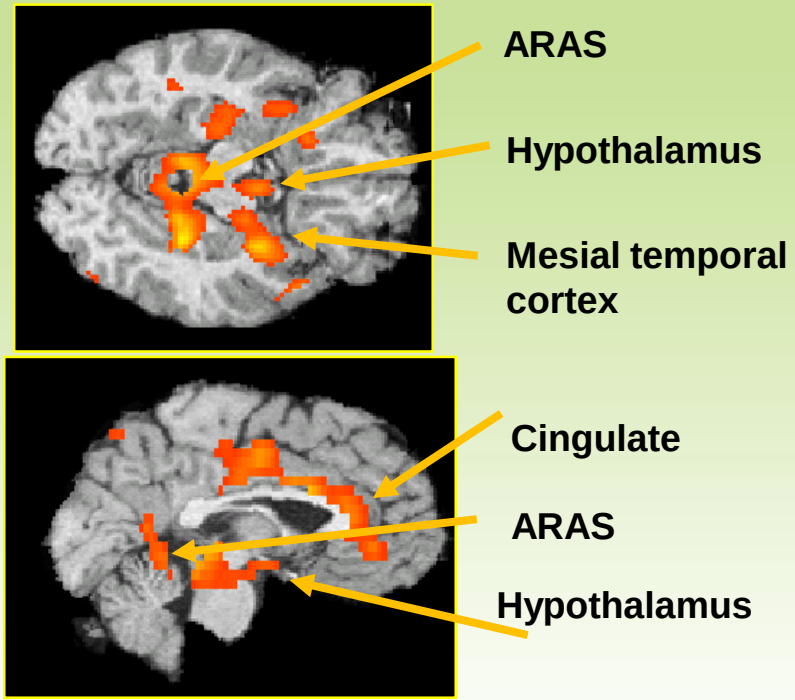
Neurobiology of Insomnia

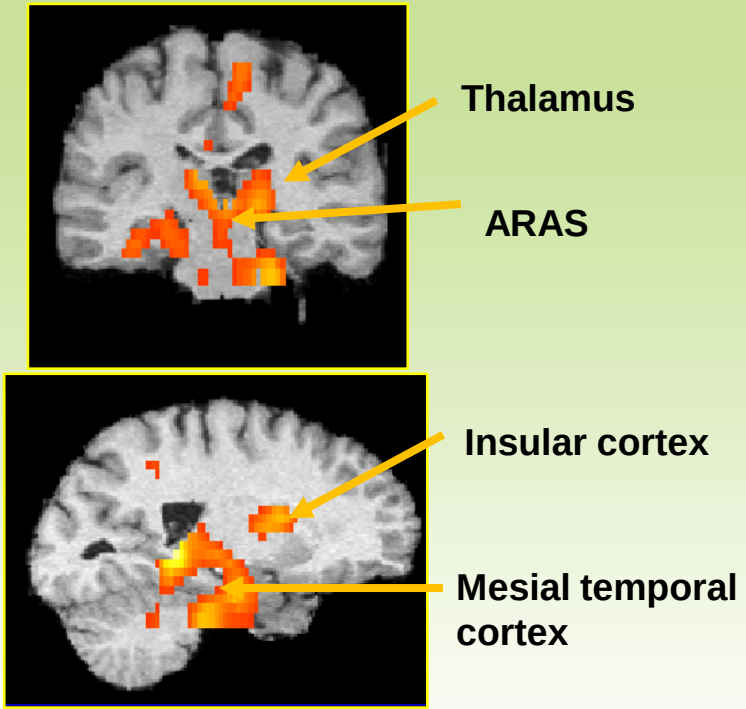
Increased physiological arousal day and night



Nofzinger EA, et al. *Am J Psychiatry* 2004;161:2126-8.
Billiard M, et al. *Sleep Medicine*. 2004;5(Suppl 1):S35-S40.

Arousal Systems in Insomnia Patients That Deactivate Less from Waking to Sleep Compared to Good Sleepers

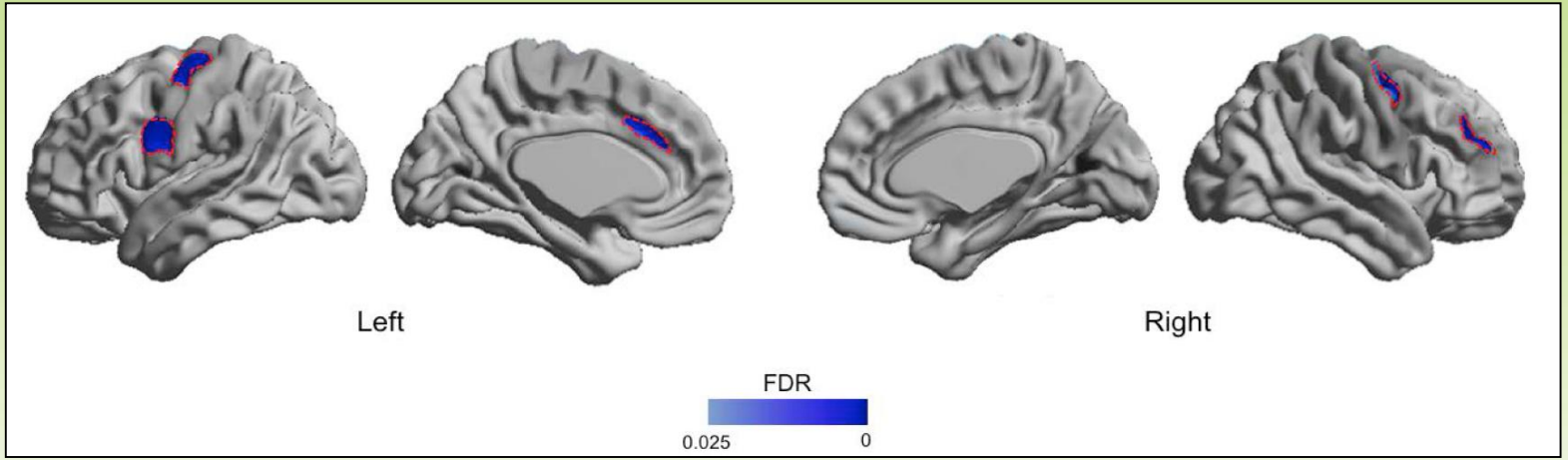




ARAS, ascending reticular activating system.

Nofzinger EA,et al. *Am J Psychiatry*. 2004;161:2126-8.

Insomnia: Functional Neuroanatomical Changes

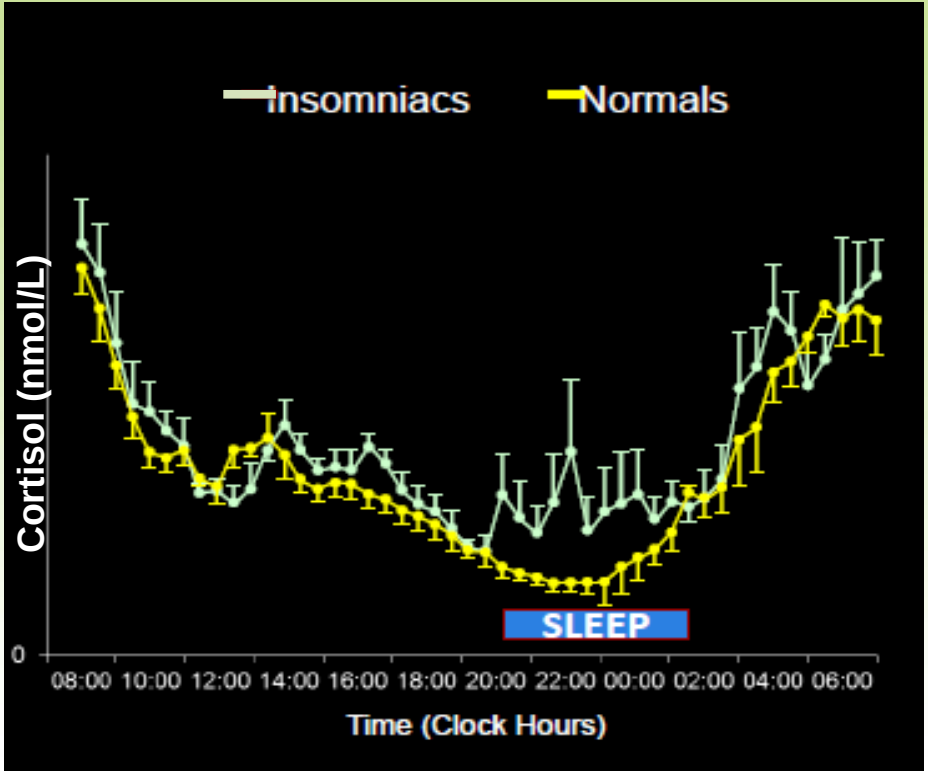


- Cortical thinning of anterior cingulate, precentral, lateral prefrontal regions
- Decreased structural connectivity of anterior and posterior regions of the default mode network

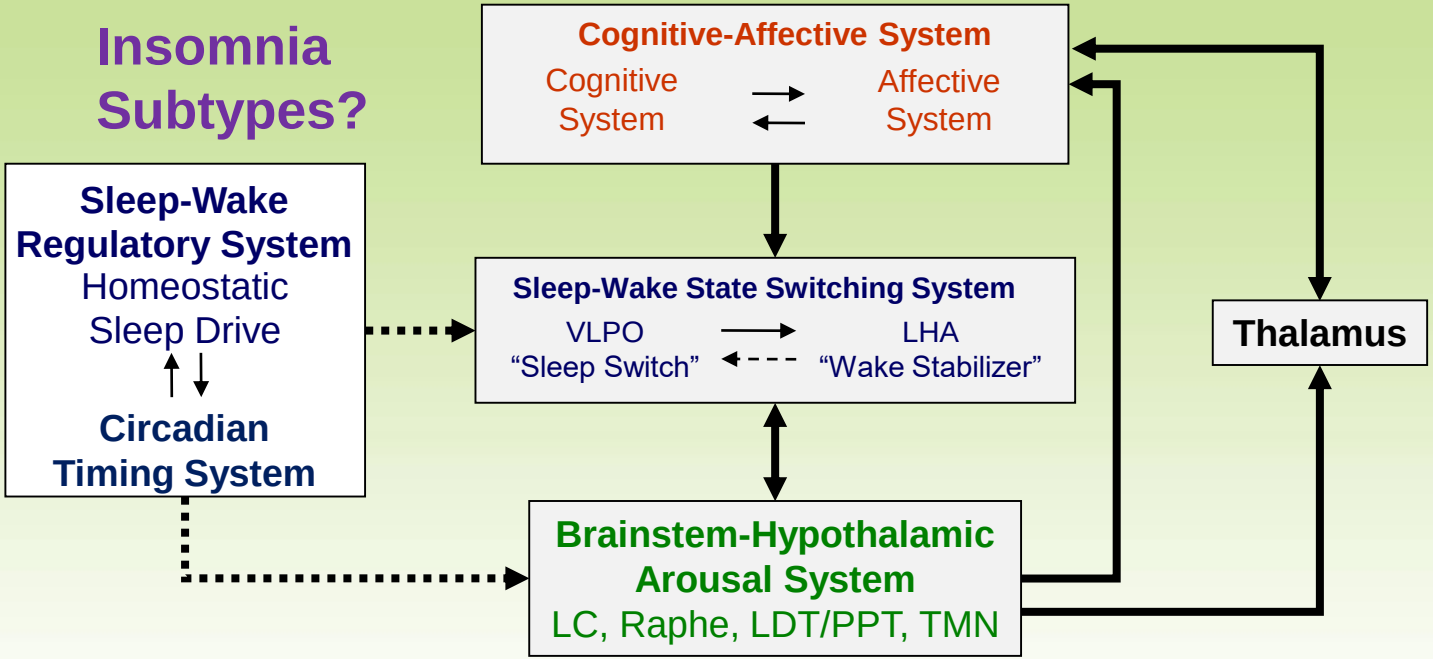
Suh S, et al. *Sleep*. 2016;39:161-71.

CNS and Peripheral Overactivity in Insomnia

- Significant 24-hour increase in cortisol
  (Vgontzas. *J Clin Endocrinol Metab*. 2001;86:3787-94.)
- Increased metabolic rate
  (Bonnet. *Sleep*. 1995;18:581-8; Bonnet and Arand. *Sleep Med Rev*. 2010;14:9-15.)
- Increased sympathetic activity
  (Lushington. *Sleep*. 2000;23:504-10.)
- Increased EEG high frequency/low frequency ratio
  (Bonnet. *Psychosom Med*. 1998;60:610-5.; Perlis. *Sleep Med Rev*. 2001;5:363-74.)

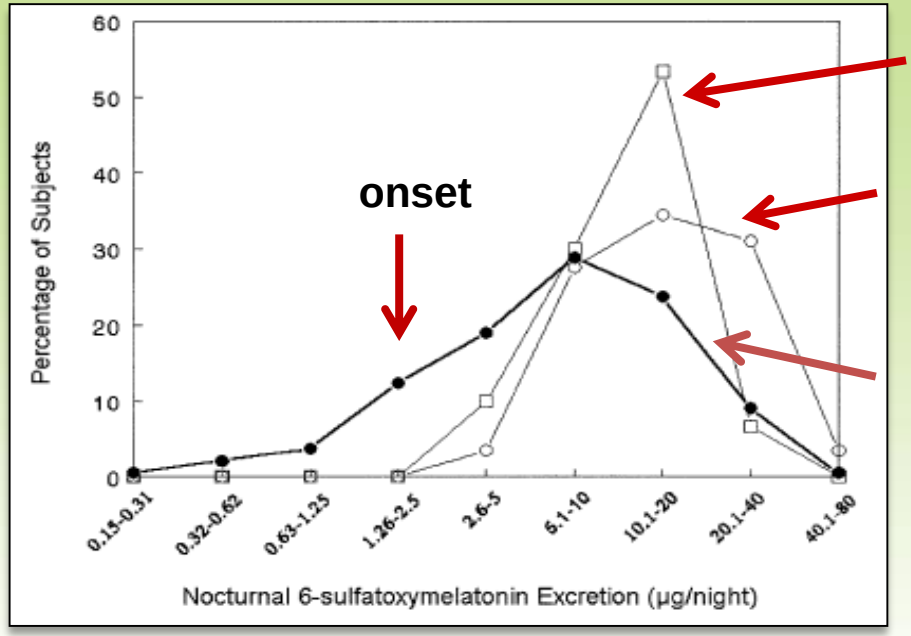


Conceptual Model of Sleep-Wake Regulation Relevant to Insomnia Disorder



Solid arrows indicate direct anatomic or physiologic pathways. Dotted arrows indicate indirect pathways. VLPO, Ventrolateral preoptic area. LHA, Lateral hypothalamus peri-fornical area. LC, locus coeruleus. LDT, Laterodorsal pontine tegmentum. PPT, Pedunculopontine tegmentum. TMN, Tuberomamillary nucleus of the posterior hypothalamus.
Courtesy: D. Buysse (modified)

Evidence for Circadian Disturbance in Insomnia Disorder



Young control (30)

55 years and older control (29)

55 years and older insomnia (517)

Decreased amplitude and earlier phase of melatonin rhythm in older adults with insomnia

Leger D, et al. *Am J Med*. 2004;116:91-5.

Circadian Melatonin and Insomnia in Older Women

- Melatonin level and core body temperature (CBT) were intact in young and older poor sleepers.
- However, older poor sleepers showed:
  - Weaker evening increase in melatonin level
  - DLMO was a significant predictor of SOL in the older women ($R(2)=0.64$, $p<.001$), but not in younger women.
- Suggests that amplitude and timing of the circadian rhythm might contribute to disturbances in insomnia of older adults.

DLMO, dim light melatonin onset; SOL, sleep-onset latency.
Olbrich D, et al. *Chronobiol Int*. 2011;28:681-9.

Differential Sleep, Sleepiness, and Neurophysiology in the Insomnia Phenotypes of Shift Work Disorder

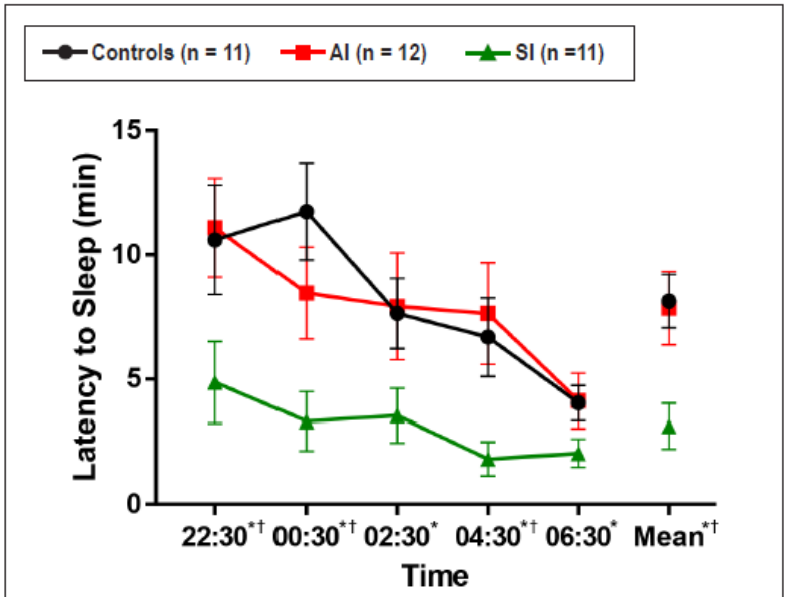


Figure 2—MSLT scores by SWD phenotype (mean latency ± SD). * SI vs. Controls, P < 0.05. † SI vs. AI, P < 0.05. AI vs. Controls, all n/s.

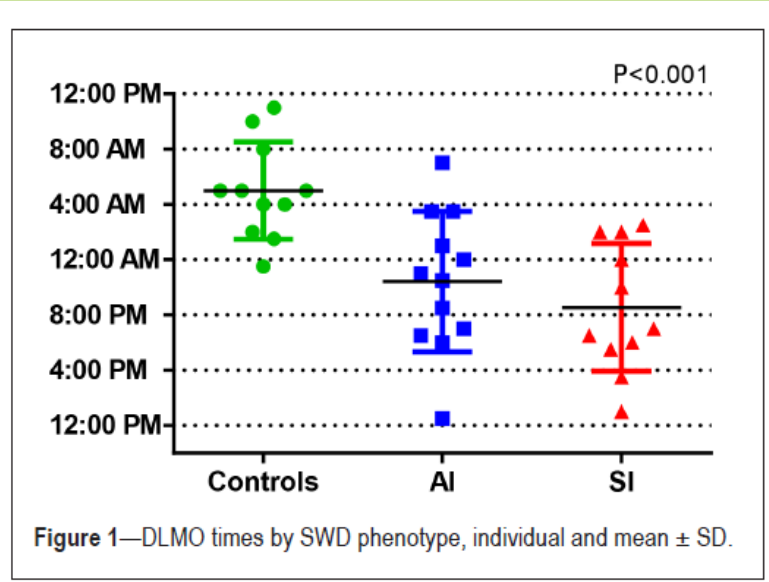


Figure 1—DLMO times by SWD phenotype, individual and mean ± SD.

MSLT, multiple sleep latency test; AI, alert insomniacs; SI, sleepy insomniacs; DLMO, dim light salivary melatonin onset.

Gumenyuk V, et al. *Sleep*. 2015;38:119-26.

Circadian Insomnia Subtypes

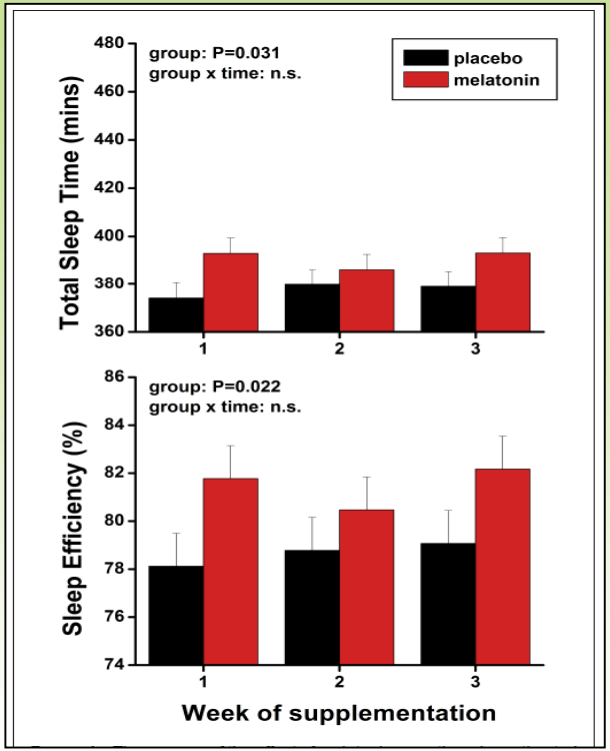
Low levels of melatonin associated with insomnia in middle to older age.

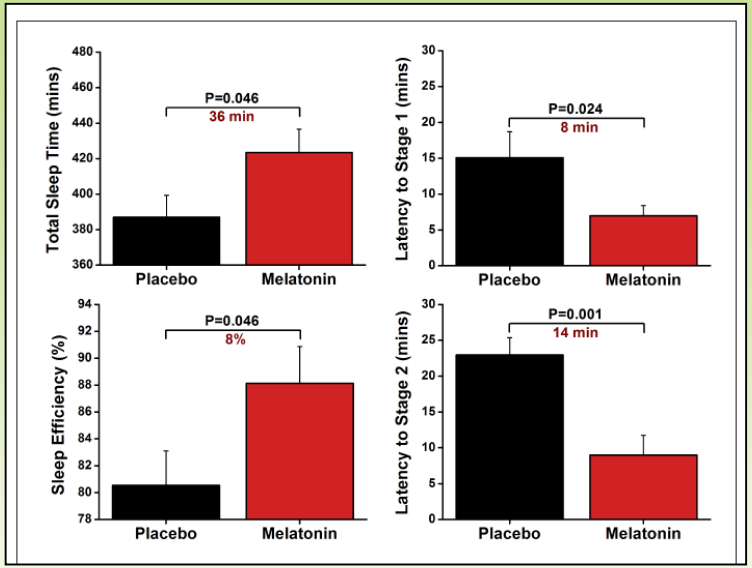
- Melatonin deficiency may be marker of risk for insomnia subtype.
- Represents an insomnia subtype that may be responsive to adjunctive treatment with melatonin.

Insomnia associated with circadian alignment

- Late chronotype insomnia
  - Sleep-onset insomnia
  - Risk for severity and non-remission of depression
- Early chronotype, earlier phase
  - Sleep-maintenance insomnia
- SWD insomnia subtype
  - **Sleepy** vs. alert

Melatonin at Bedtime Improves Sleep in Patients on Beta Blockers (Atenolol or Metoprolol)



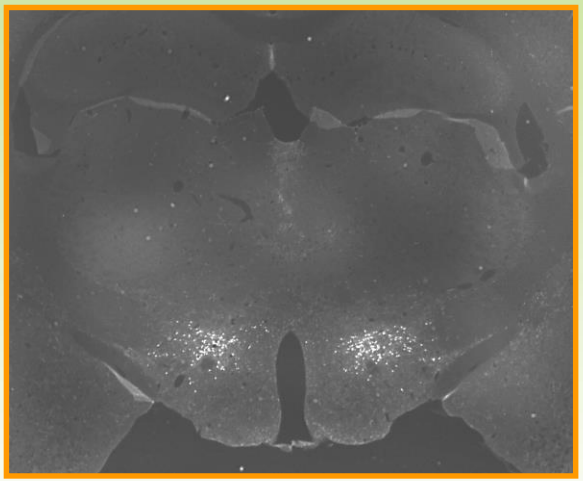


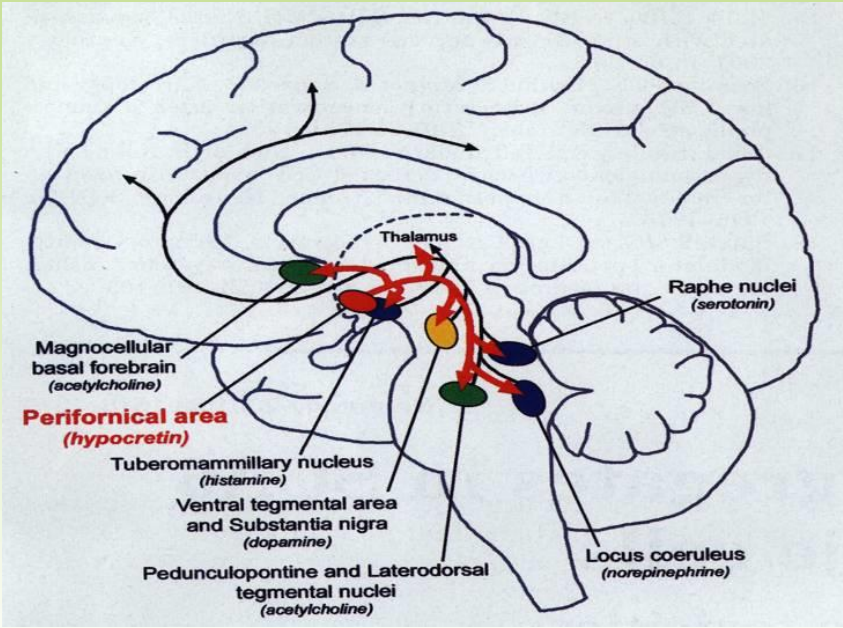
Beta blockers can decrease melatonin secretion and are associated with sleep and circadian disruption.

Scheer FA, et al. *Sleep*. 2012;35:1395-402.

How and Why Orexin-Receptor Antagonists for Insomnia Treatment

Orexin: Central Regulator of Wake-Promoting System





Silber MH, Rye DB. *Neurology*. 2001;56:1616-8.

Distribution of Orexin Receptors and Multiple Other CNS Effects

	OX_1	OX_2
Gene	*HCRTR1*	*HCRTR2*
Main ligand	Orexin A (Hcrt1)	Orexin A, Orexin B (Hcrt2)
Distribution	Prefrontal cortex	Tuberomammillary nucleus
	Insular cortex	Lateral hypothalamus
	Locus ceruleus	Paraventricular nucleus
	LDT/PPT	VTA
	Dorsal raphe	Dorsal raphe
	VTA	
Functions	REM sleep modulation?	Arousal
	Feeding	Stress responses
	Drug-seeking behavior	

Grimaldi D, et al. *Neurology*. 2014;82:271-8.

Diurnal Rhythm of Orexin Levels (Rise During Wake and Decline During Sleep)

Zeitzer J, et al. *J Neurosci*. 2003;23:3555–3560.
Salomon RM, et al. *Biol Psychiatry*. 2003;54:96–104.
Grady SP, et al. *Sleep*. 2006;29:295–297.

A temporal pattern of orexin concentration in human CSF samples has also been observed

Inhibition of Orexin Activity Promotes Sleep

No clear evidence that orexin levels are higher in patients with insomnia but there is evidence for “hyperarousal”

Sleep

VLPO
(GABA, galanin)

Orexin

X

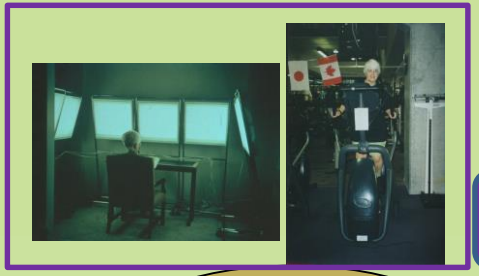
Monoaminergic
neurons

Wake

Suppression of the wake-promoting system is considered necessary for sleep onset and maintenance to occur.

Sakurai T. *Nat Rev Neurosci*. 2007;8:171–181. Saper CB, et al. *Nature*. 2005;437:1257–1263.; Szymusiak R, et al. *Brain Res*. 1998;803:178–188. Chou TC, et al. *J Neurosci.* 2002;22:977–990.

Conceptual Model of Treatment Approaches Relevant to Insomnia



CBT-I

BzRA

Melatonin, receptor agonists

Cognitive-Affective Circuits (Cortex, Limbic System)

Homeostatic Sleep Drive

Circadian Timing System

Sleep-Wake State Switching System (Hypothalamus)

Thalamus

Antidepressants, antihistamines

Orexin antagonists

Brainstem-Hypothalamic Arousal System

Modified and courtesy of D. Buysse.

Personalization of Insomnia Therapy: Matching Treatment with Patient Needs

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Vice Chair of Research
University of California San Francisco School of Medicine
San Francisco, CA
Professor of Psychiatry and Behavioral Sciences
Duke University School of Medicine
Durham, NC

Introduction – “One Size Fits All”

- Insomnia therapy has long been a one-size-fits-all endeavor
  - Clinicians have tended to use one medication to treat all of their patients with insomnia
- The opportunity to improve treatment through personalization has been limited to matching the time of night of sleep problem with drug duration of action
  - Example: Zolpidem
- There was no evidence that mechanism of action of insomnia therapy mattered
  - It was assumed that clinical effects were determined only by pharmacokinetics

Introduction – "Mechanism Matters"

- There are several relatively recently emerging insomnia medications with high pharmacologic specificity
  - Mechanism of action affects the nature of clinical effects
- Such agents pave the way for a new paradigm for insomnia therapy where specific interventions are selected to target a specific type of sleep difficulty for each patient
  - Advantage: improved risk/benefit ratio over non-specific agents that have global effects and impact many areas of the brain other than those needed to improve a patient's particular sleep problem

Introduction – Towards Personalization

- This requires characterizing the specific effects of each of the targeted therapies and identifying key phenotypes of insomnia patients who will optimally benefit from each type of therapy
  - This is a work in progress
- We will review the existing insomnia treatments in this forward-looking context, discussing rationale for patient subtype matching

Overview

- Existing insomnia treatments
- Specificity of insomnia treatments
- Review of each insomnia treatment, identifying considerations for matching mechanism to insomnia subtype

Current Primary Options

- Cognitive Behavioral Therapy (CBT)
- Medications

Insomnia Medications

- **Hypocretin/Orexin Antagonists**
  - Suvorexant
- **Selective H1 Antihistamines**
  - Doxepin 3–6 mg
- **Melatonin Agonists**
  - Ramelteon
- **Antihypertensives**
  - Prazosin
- **Benzodiazepines**
  - Triazolam, flurazepam, temazepam, clonazepam, alprazolam, diazepam, lorazepam
- **“Non-benzodiazepines”**
  - Zolpidem, zaleplon, eszopiclone
- **Antidepressants**
  - Trazodone, doxepin, mirtazapine, amitriptyline...
- **Antipsychotics**
  - Quetiapine, risperidone, olanzapine…
- **OTC Agents (Antihistamines)**
  - Diphenhydramine, doxylamine, chlorpheniramine

Krystal AD. *Sleep Med Rev*. 2009;13:265-74.

Treatment Specificity

Treatment	Treatment Specificity	Target
CBT-I	Highly Specific	Specific maladaptive behaviors and cognitions that perpetuate insomnia
Suvorexant	Highly Specific	Antagonism of orexin receptors
Doxepin 3–6 mg	Highly Specific	Antagonism of H1 histamine receptors
Prazosin	Highly Specific	Antagonism of α_1 adrenergic receptors
Ramelteon	Highly Specific	Agonism of melatonin M1/M2 receptors
Benzodiazepines	Non-Specific	Binding to benzo binding site on GABA-A receptor complex leads to broad CNS inhibition
Non-Benzodiazepines	Non-Specific	Binding to benzo binding site on GABA-A receptor complex leads to broad CNS inhibition
Antidepressants	Non-Specific	Antagonism of 5HT and NE transporters, 5HT2, α_1, adrenergic, H1 histaminergic, and muscarinic cholinergic antagonism
Antipsychotics	Non-Specific	Dopamine D2, Dopamine D1, 5HT2, α_1, adrenergic, H1 histaminergic, and muscarinic cholinergic antagonism
OTC “Antihistamines”	Non-Specific	Antagonism of H1 histamine receptors and cholinergic receptors

Cognitive Behavioral Therapy – Insomnia (CBT-I)

- Cognitive/Behavioral Targets
  - Individuals with maladaptive behaviors/cognitions that perpetuate insomnia
    - Spending excessive time in bed, napping, worrying in bed, etc., etc.
- Physiologic Targets
  - Diminished homeostatic sleep drive
  - Elevated arousal

PSG Predictors of the Response to CBT-I

We evaluated the relationship between Spectral Analysis Derived Indices (all night averaged Beta Power and Delta Power Dynamics) in primary insomnia patients treated with CBT-I.

PSG, polysomnography.

Krystal AD, Edinger JD. *Sleep*. 2010;33:669-77.

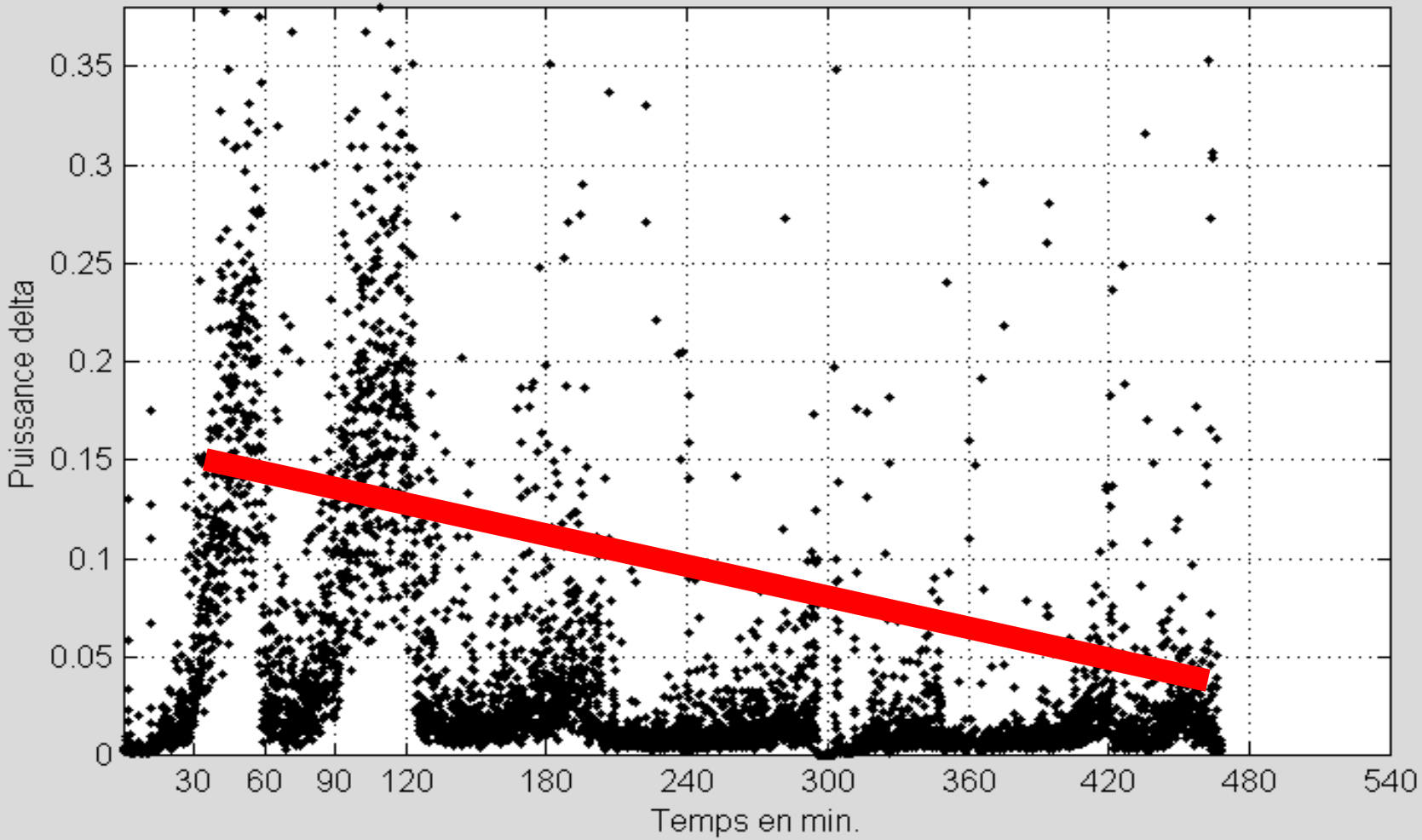
PSG Predictors of the Response to CBT-I

Correlations of non-REM Delta Power Indices and Improvement in Sleep with CBT

EEG Variable	Correlation with Improvement in Sleep
Baseline Peak Delta	-0.57**
Baseline Peak Slope	0.51**
Baseline Average Beta	0.56**
Change in Peak Delta with CBT	0.81**
Change in Delta Slope with CBT	-0.46**
Change in Average Beta with CBT	0.76**

**$p<0.05

Krystal AD, Edinger JD. *Sleep*. 2010;33:669-77.


Puissance delta
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
30
60
90
120
180
240
300
360
420
480
540
Temps en min.

Cognitive Behavioral Therapy – Insomnia

This work supports the hypothesis that individuals with diminished homeostatic sleep drive or elevated arousal are appropriate candidates for CBT-I.

Orexin Antagonists

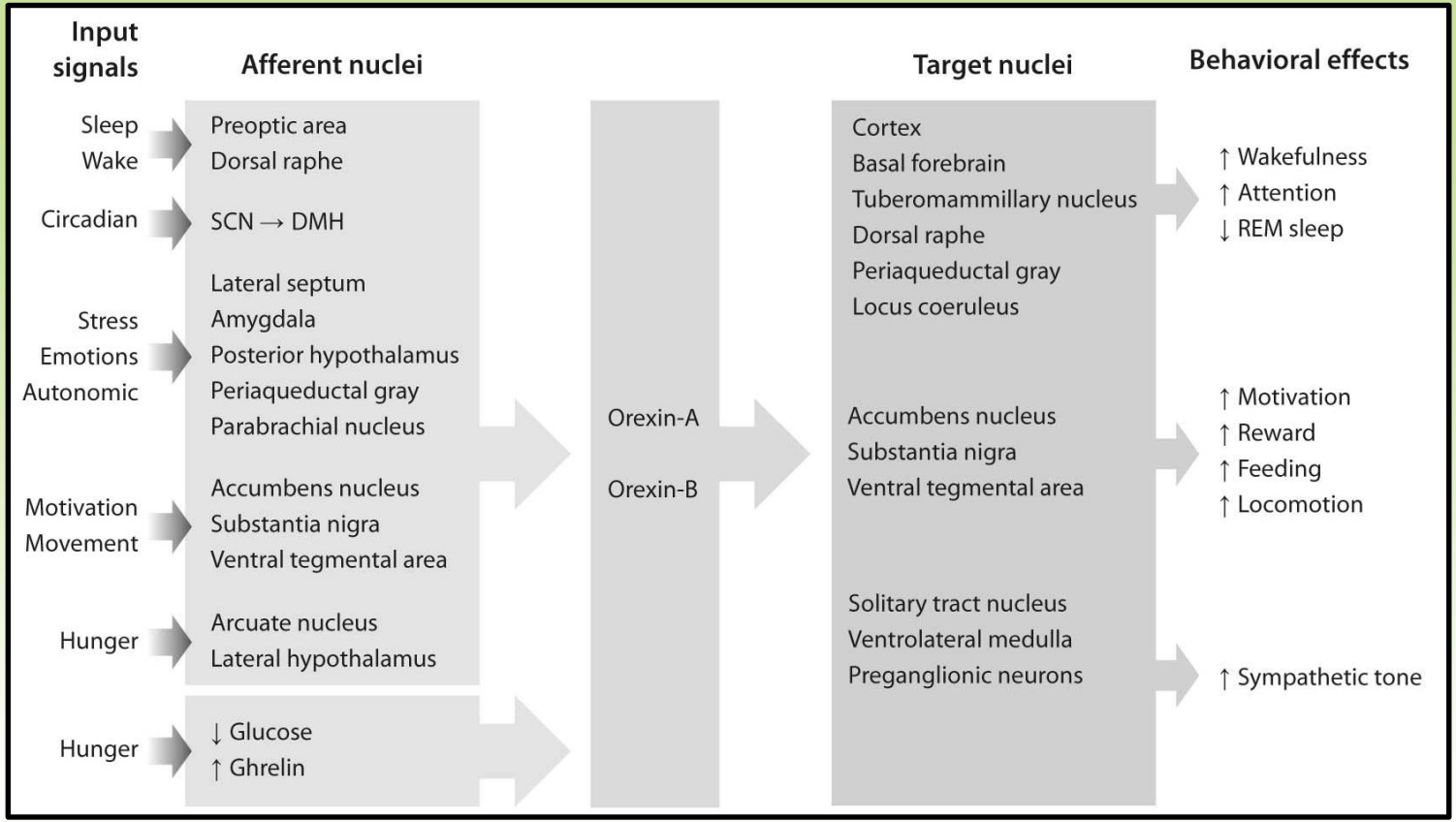
- Specific effect: they block receptors targeted by only the 10–20,000 neurons in the entire brain that produce orexin
- Can attempt to infer insomnia subgroups likely to improve with treatment from known anatomy/physiology of orexin system

Role of Orexin in Sleep-Wake

- Best understood orexin role: maintenance of long, consolidated awake periods. Suggested by:
  - Orexin neuron loss, and deficiencies in OX2R associated with narcolepsy in mice, dogs, and humans
  - Diurnal variation of orexin activity in normal animals, with increased activity during wakefulness and reduced activity during sleep
    - Activity increases over the course of the day counteracting increasing homeostatic drive

Sakurai T. *Nat Rev Neurosci*. 2014;15:719-731.

Orexin System Pathways Related to Arousal



Krystal AD, et al. *J Clin Psychiatry*. 2013;74(suppl 1):3–20.

Contexts in Which Orexin Antagonists Likely to Be Particularly Effective

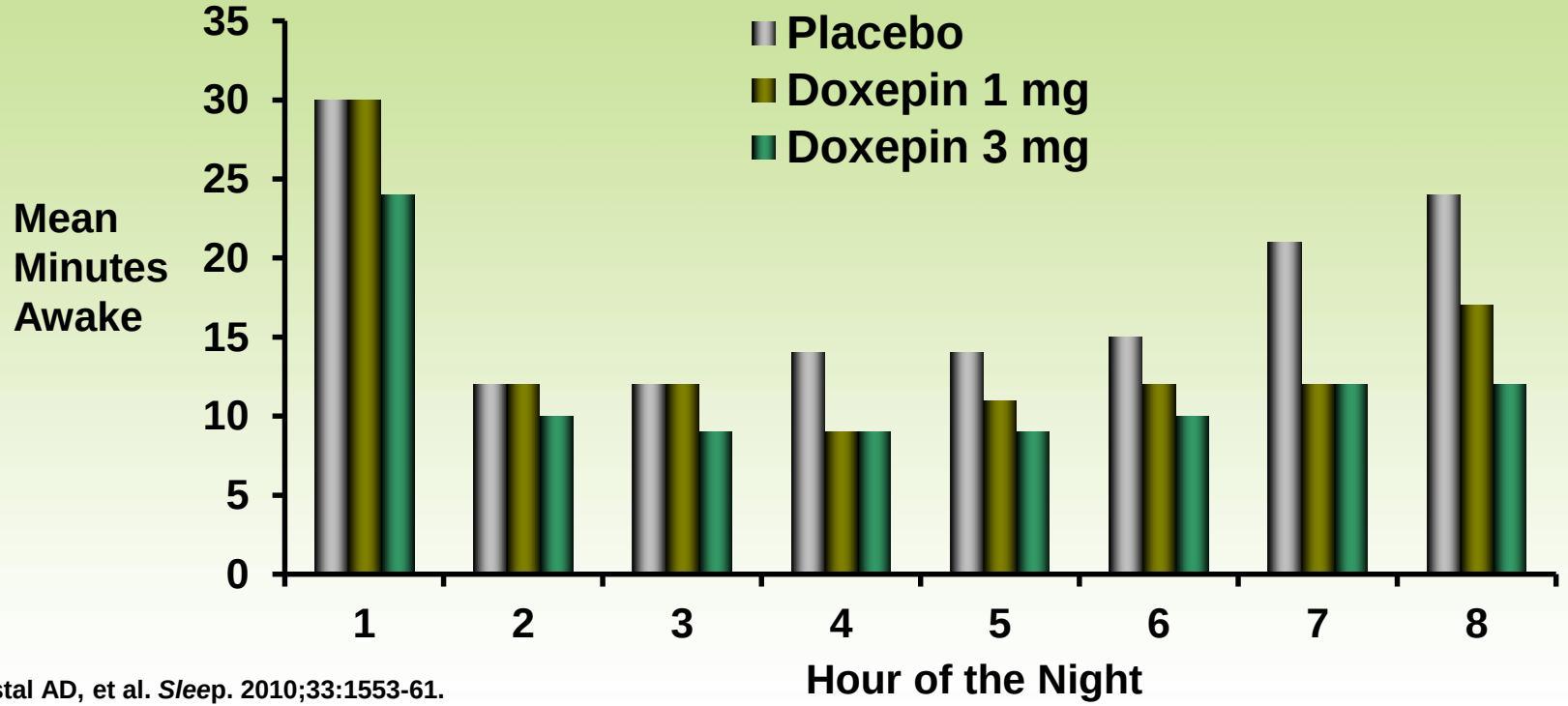
- Based on role in maintaining prolonged periods of wakefulness in face of rising sleep drive
  - Those who can't seem to shut down at bedtime; get "second wind"
  - People attempting to sleep at adverse circadian time?
- Based on Inputs/Outputs of Orexin Neurons
  - Stress/anxiety-related arousal (e.g., trauma-related insomnia)
  - Arousal in setting of loss of rewarding stimuli including substances of abuse

Selective H1 Antagonist

- Doxepin’s strongest effect is H1 antagonism
- At 3–6 mg, it has essentially only H1 antagonism
  - Specificity -> relatively benign adverse effects profile
- Novel effects suggest PK\PD Dissociation
  - Peak blood level in 3–4 hours, but peak sleep effect 7–8 hours after dosing, with minimal effects after waking 9 hours after dosing
  - Decreases WASO but not awakenings

Krystal AD, et al. *Slee*p. 2010;33:1553-61.
Krystal AD, et al. *Sleep*. 2011;34:1433-42.
Krystal AD, et al. *Sleep Med R*ev. 2013;17:263-72.

Wake Time by Hour Night 1 in Elderly With Primary Insomnia: Doxepin 1–3 mg



Krystal AD, et al. *Slee*p. 2010;33:1553-61.

Histamine Overactivity Subtype?

- There appear to be individuals, especially the elderly, who have histamine overactivity underlying their insomnia
- The hallmark of this problem is sleep disturbance predominantly in the last 3rd of the night or early morning awakening
- Best treated with selective H1 antagonist
- Also useful in abuse-prone individuals with sleep maintenance problems

Selective NE Antagonism

- Norepinephrine (NE) plays an important role in wake promotion
- Blocking NE receptors has the potential to enhance sleep
- Increased peripheral NE activity has been identified in insomnia patients
- Prazosin is a selective alpha-1 antagonist
  - No controlled trials in primary insomnia
  - Improves nightmares and sleep maintenance problems in PTSD in 4 placebo-controlled trials

Raskind MA, et al*. Biol Psychiatry*. 2007;61:928-34.

Animal Model of Insomnia Has Increased NE Activity

- Cage Change Model – Causes acute stress response
  - Associated with longer sleep-onset latency and sleep fragmentation
- Evidence for a role of increased NE release
  - Lesioning locus coeruleus and a pharmacologic intervention that decreases HA and NE release decreased manifestations of disturbed sleep

Cano G, et al. *J Neurosci*. 2008;28:10167-84.

Elevated Nocturnal Circulating Levels of Norepinephrine in Insomnia

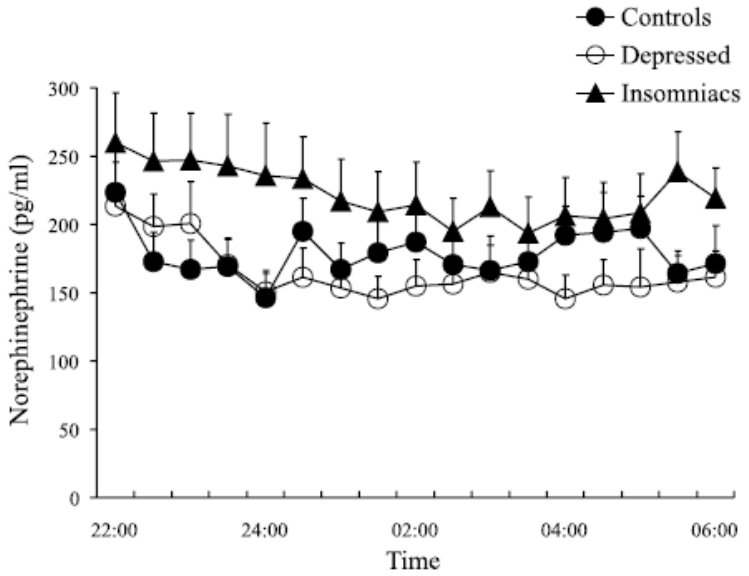


Fig. 1. Circulating levels of norepinpehrine during the nocturnal period in insomniacs, depressed patients, and controls. The bars represent the *SEM*.

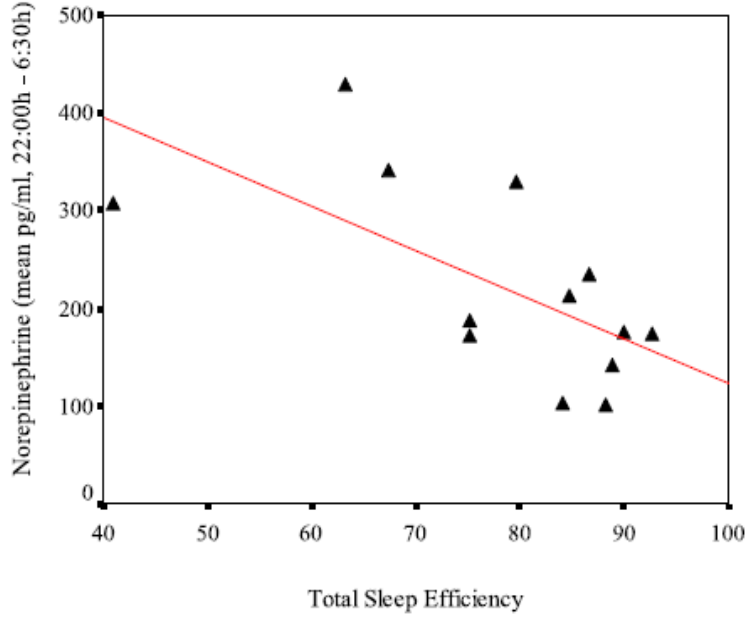


Fig. 2. Correlation between average nocturnal level of norepinephrine and sleep efficiency in the insomniacs.

Irwin M, et al. ***Brain Behav Immun*. 2003;17:365-72.**

Increased NE Insomnia Subtype?

- There may be some individuals who have NE overactivity underlying their insomnia
  - Serum vs. CNS?
- The hallmark of this problem may be association with Novelty/Stress/Trauma
  - Best evidence in PTSD
- Best treated with agent that specifically blocks NE activity such as prazosin to optimize risk/benefit
  - Relatively benign side effect profile
    - Orthostatic hypotension, sedation

Selective Melatoninergic Agonism

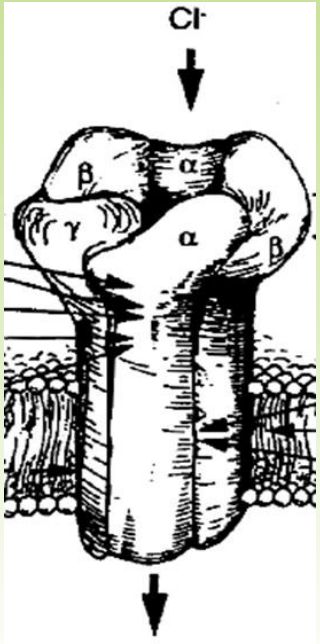
- Promote sleep onset by binding to neuronal membrane-bound MT1 receptors
  - Melatonin
    - Very modest effect on sleep-onset latency
    - More consistent effect on sleep phase
  - Ramelteon
    - Effective for sleep-onset insomnia only
    - Consistent effect on PSG
    - Effect on self-reported outcomes less consistent

Johnson MW, et al. *Arch Gen Psychiatry*. 2006;63:1149-57.
Roth T, et al. *Sleep Med*. 2006;7:312-8.
Erman M, et al. *Sleep Med*. 2006;7:17-24.

Target Subtype

- Patients with only sleep-onset difficulty
  - Those who have been treated with benzodiazepines or non-benzodiazepines don’t tend to improve as much
  - Relatively benign adverse effect profile
  - Useful for those with insomnia in setting of substance use disorders or in substance abuse-prone patients

Medications That Enhance GABA-ergic Inhibition: Non-Selective CNS Inhibition



- **Benzodiazepines** (Temazepam, Flurazepam, Triazolam etc.)
  - Group of compounds with related chemical structure
  - Mechanism of action:
    - GABA-A receptor complex is comprised of 5 peptides that form a channel which controls the flow of chloride ions in and out of the neuron.
    - Generally, Cl is greater outside than inside neurons. GABA binding opens the channel and the resulting inward flux of Cl hyperpolarizes the membrane resulting in inhibition
    - Benzos bind to a site on α subunit of GABA receptor complex and enhance this GABA-mediated inhibition
- **"Non-Benzodiazepines"** (Zolpidem, Zaleplon, Eszopiclone)
  - A group of compounds not related to benzos
  - Mechanism of action:
    - Same as benzos, though they have relatively greater α subunit binding specificity

Dose-Dependent Effects of Benzos and Non-Benzos

- Effects are non-specific reflecting global inhibition due to increase in GABA activity in various brain regions
  - Possibly therapeutic
    - Sleep enhancing, myorelaxant, anxiolytic, anti-seizure effect
  - Adverse effects:
    - Cognitive impairment, psychomotor impairment, abuse potential

Roehrs T, et al. *Psychopharmacology (Berl).* 1996;127:150-4.; Roehrs T, et al. *Sleep Med*. 2001;2:323-332.; Roehrs T, et al. *Psychopharmacology (Berl).* 2002;161:137-42.; Oswald LM, et al. *Exp Clin Psychopharmacol*. 1999;7:379-90.; Hajak G. *Drug Saf*. 1999;21:457-69.; Soyka M, et al. *Pharmacopsychiatry*. 2000;33:138-41.

Target Subtype

- Most efficacious sleep-onset therapies in common use
- Efficacy for maintenance depends on half-life/dose
- Particularly useful where non-specific effects are advantageous:
  - Co-morbidities such as anxiety, pain, treatment-resistant patients, etc.

Roehrs T, et al. *Psychopharmacology (Berl).* 1996;127:150-4.; Roehrs T, et al. *Sleep Med*. 2001;2:323-332.; Roehrs T, et al. *Psychopharmacology (Berl).* 2002;161:137-42.; Oswald LM, et al. *Exp Clin Psychopharmacol*. 1999;7:379-90.; Hajak G. *Drug Saf*. 1999;21:457-69.; Soyka M, et al. *Pharmacopsychiatry*. 2000;33:138-41.

Antidepressants

- Non-selective agents with varying degrees of antagonism of 5HT and NE transporters, and 5HT2, α1, adrenergic, histaminergic, and muscarinic cholinergic antagonism
  - Trazodone, mirtazapine, amitriptyline, doxepin (>6 mg), etc.
  - Minimal data on efficacy/safety in the treatment of insomnia
  - Side effect profile inferred from use in depression, anxiety, etc.
    - May include sedation, weight gain, orthostatic hypotension, dry mouth, constipation, blurred vision, etc.

Target Subtype

- Particularly useful where non-specific effects are advantageous:
  - Co-morbidities such as depression, anxiety, pain, and treatment-resistant patients where it is advantageous to block multiple wake-promoting systems, etc.

Antipsychotics

- Non-selective agents with varying degrees of antagonism of D1, D2, 5HT2, 5HT7, α1, adrenergic, histaminergic, and muscarinic cholinergic receptors
  - Quetiapine, olanzapine, risperidone, lurasidone
  - Minimal data on efficacy/safety in the treatment of insomnia
  - Side effect profile inferred from use in schizophrenia, mania, depression, etc.
    - May include extrapyramidal side effects, sedation, weight gain, insulin resistance, orthostatic hypotension, dry mouth, constipation, blurred vision, etc.

Target Subtype

- Particularly useful where non-specific effects are advantageous:
  - Co-morbidities such as psychotic conditions, mania, depression, anxiety, pain, and treatment-resistant patients where it is advantageous to block multiple wake-promoting systems, etc.

The Future

- There are now several insomnia medications with high pharmacologic specificity
- Such agents pave the way for a new paradigm for insomnia therapy where specific interventions are selected to target a specific type of sleep difficulty
  - Promises improved risk/benefit
  - Problem: We have only limited understanding about how to best match specific treatments to specific patient subgroups
    - Once “pie in the sky”, this approach is increasingly becoming a reality as new data emerge and new specific agents become available
      - Promising methods for personalization
        - » Type/Time of Night Sleep Problem
        - » The context in terms of co-occurring conditions
          - Depression, anxiety, substance abuse-prone individual, psychosis, pain, PTSD, etc.
        - » Physiologic markers of homeostasis and arousal
        - » Genotype?

Case Exercise: What would you choose?

A 42-year-old with a history of alcohol use disorder with chronic difficulty falling asleep.

A. Doxepin 3-6 mg

B. Eszopiclone

C. Ramelteon

D. Zolpidem

Case Exercise: What would you choose?

A 70-year-old with a history of alcohol use disorder with chronic difficulty waking up too early in the morning and not being able to return to sleep.

A. Doxepin 3-6 mg

B. Eszopiclone

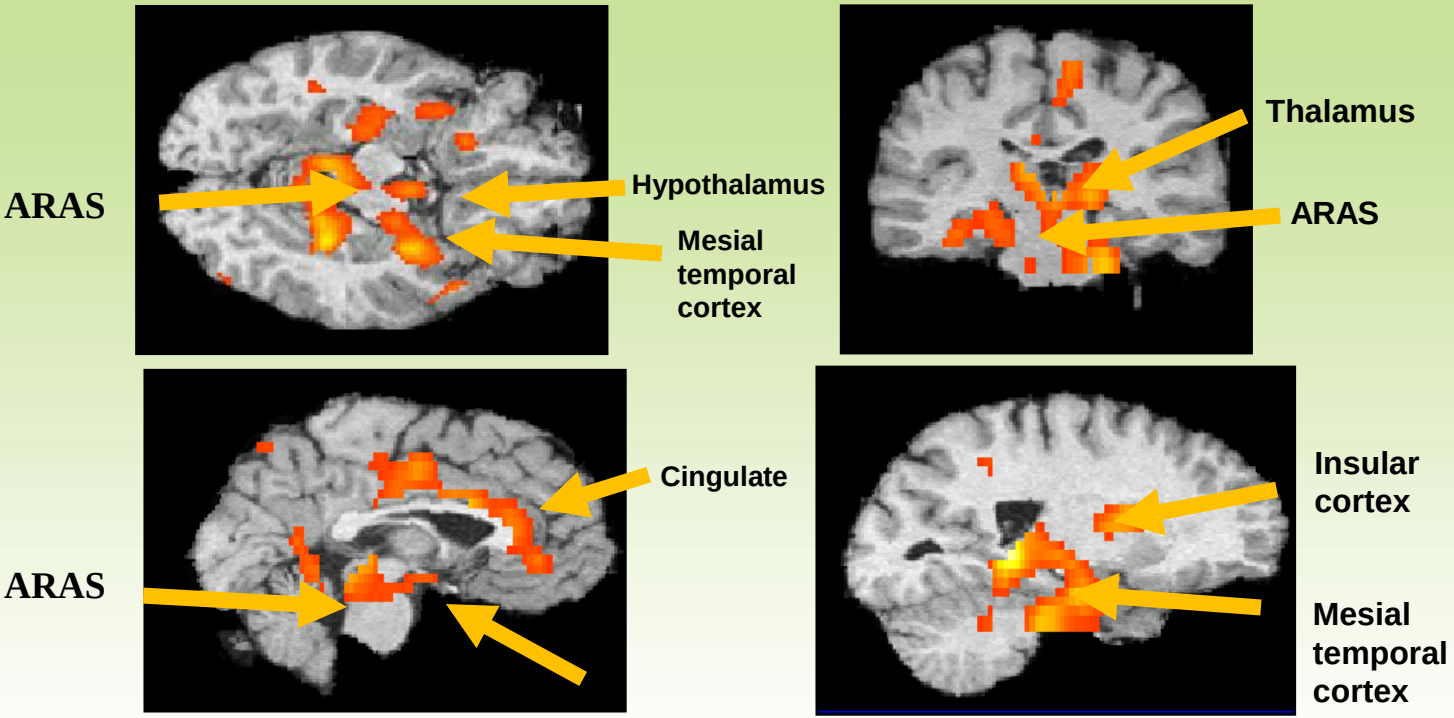
C. Ramelteon

D. Prazosin

Unique Role of Orexin Receptor Antagonists in Insomnia Management: Mechanism and Clinical Implications

Thomas Roth, PhD
Director
Sleep Disorders and Research Center
Henry Ford Hospital
Detroit, MI

Arousal Systems in Insomnia Subjects That Do Not Deactivate from Waking to Sleep

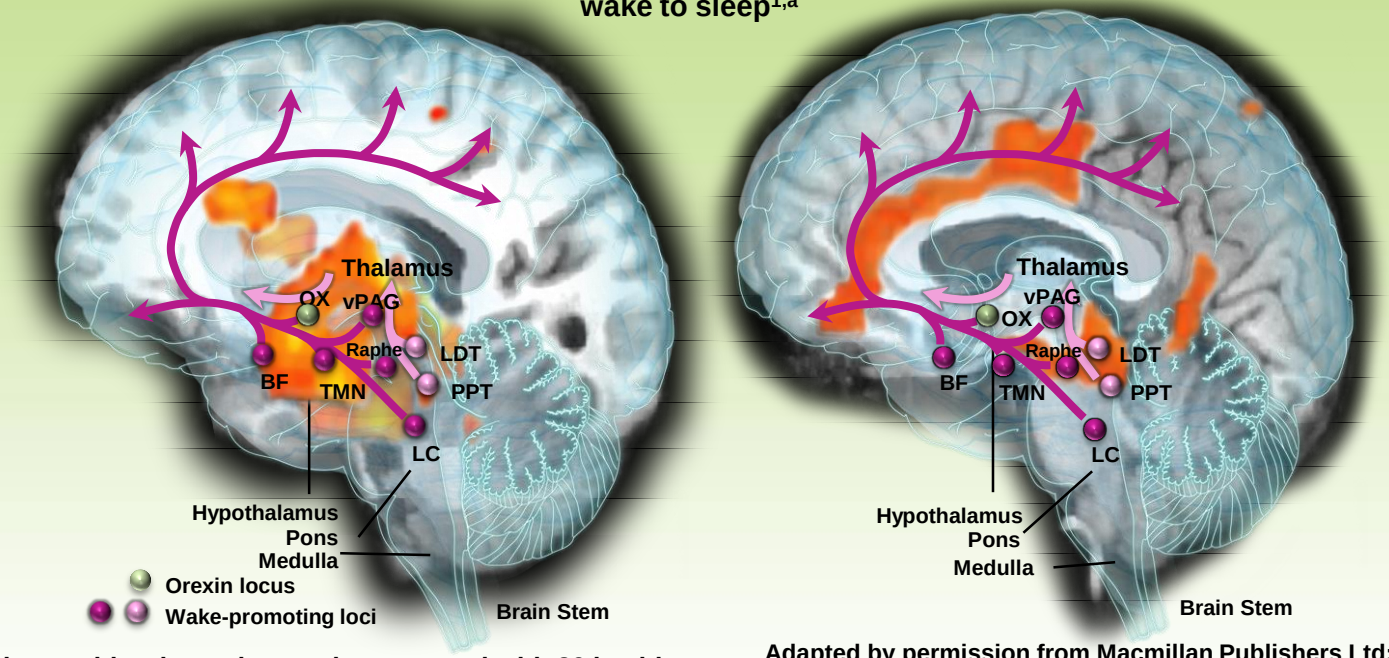


ARAS, ascending reticular activating system

Nofzinger EA, et al. *Am J Psychiatry*. 2004;161:2126-8.

Brain Activity in Wake-Promoting Areas in Patients With Insomnia

Brain structures did not show the expected decreased metabolic activity in wake-promoting areas of the brain during the transition from wake to sleep[1,a]

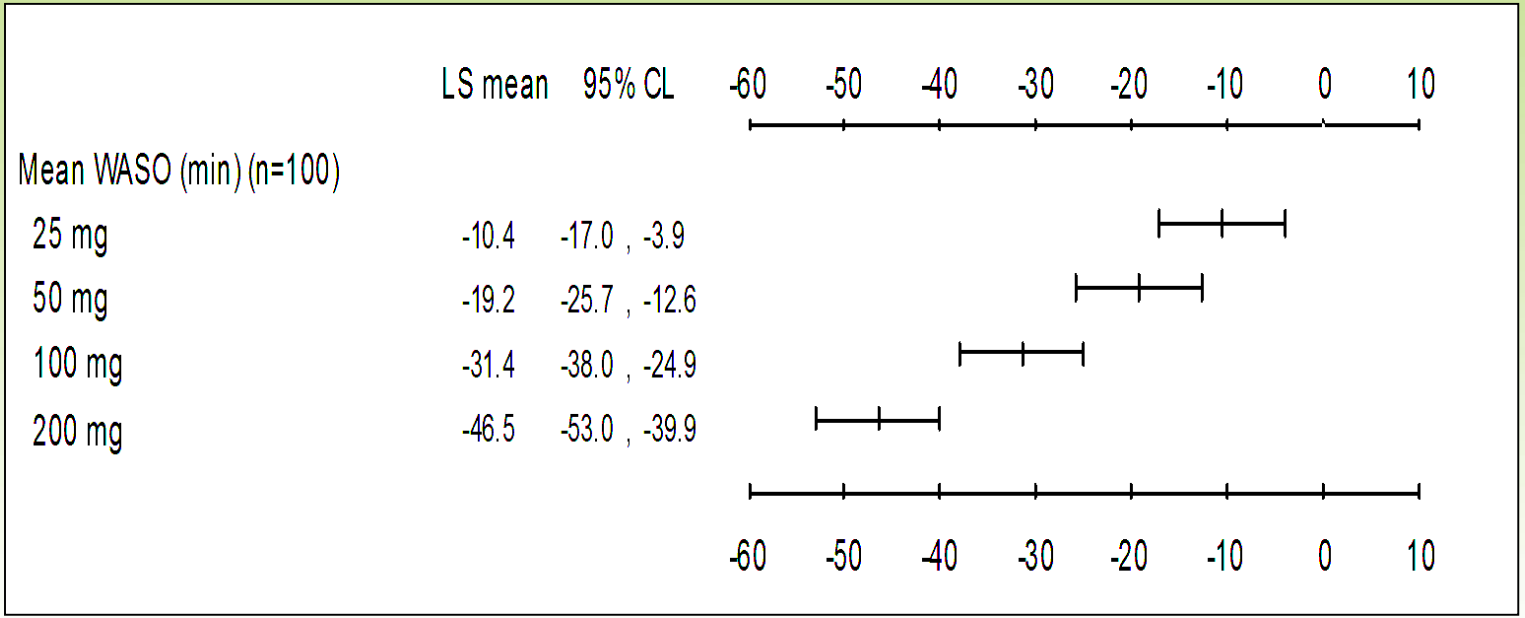


[a]Measured in 7 patients with primary insomnia compared with 20 healthy controls.

1. Nofzinger EA et al. *Am J Psychiatry*. 2004;161:2126–2129.

PSG: Wake After Persistent Sleep Onset (WASO)

(Analysis set: Per protocol; N=100)

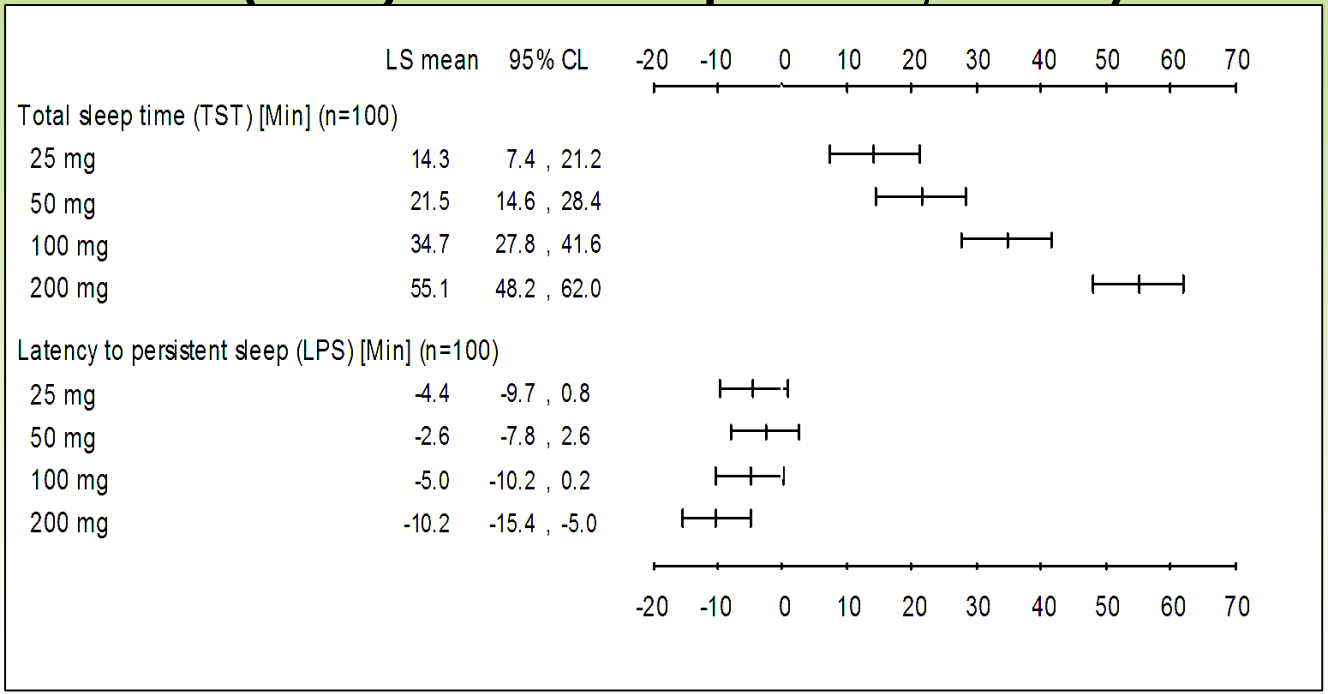


PSG, polysomnography.

Almorexant AC-057A201 Study Results. Available at: https://clinicaltrials.gov/ct2/show/NCT00606593.

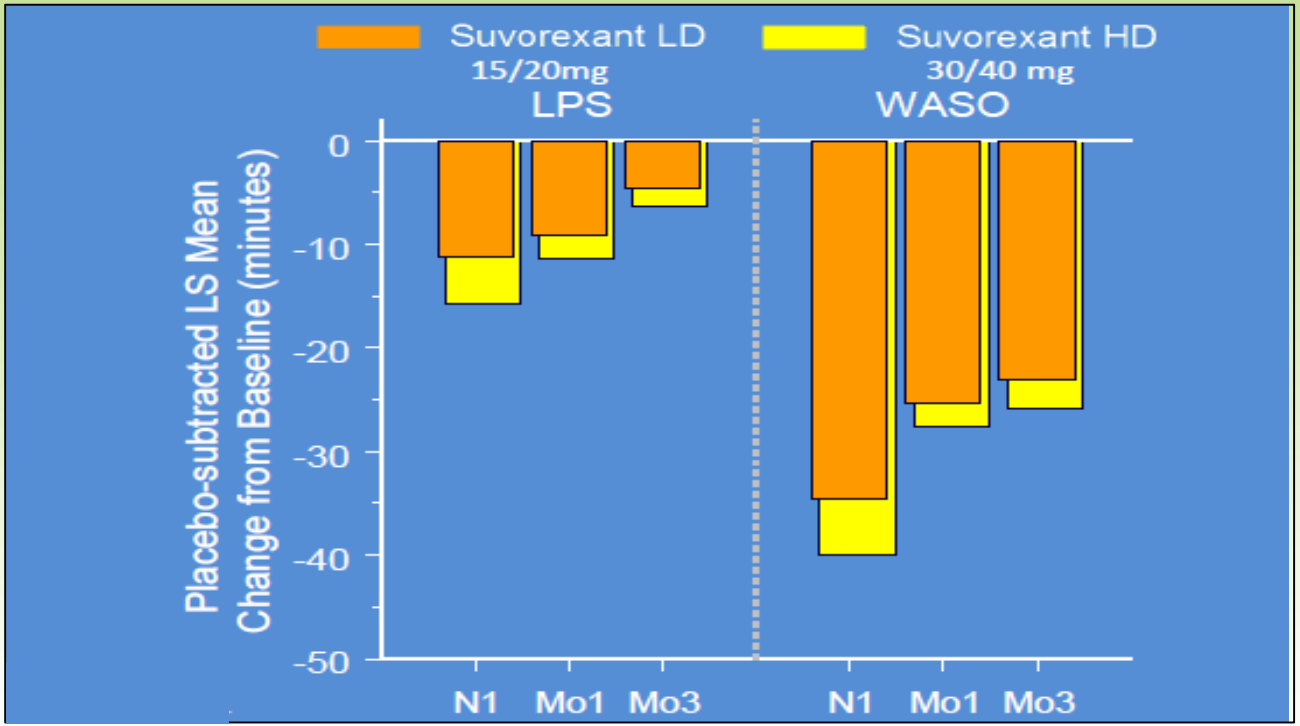
PSG: Total Sleep Time (TST) and Latency To Persistent Sleep (LPS)

(Analysis set: Per protocol; N=100)



Almorexant AC-057A201 Study Results. Available at: https://clinicaltrials.gov/ct2/show/NCT00606593.

Dose-Related Improvement in PSG Measures with Suvorexant…

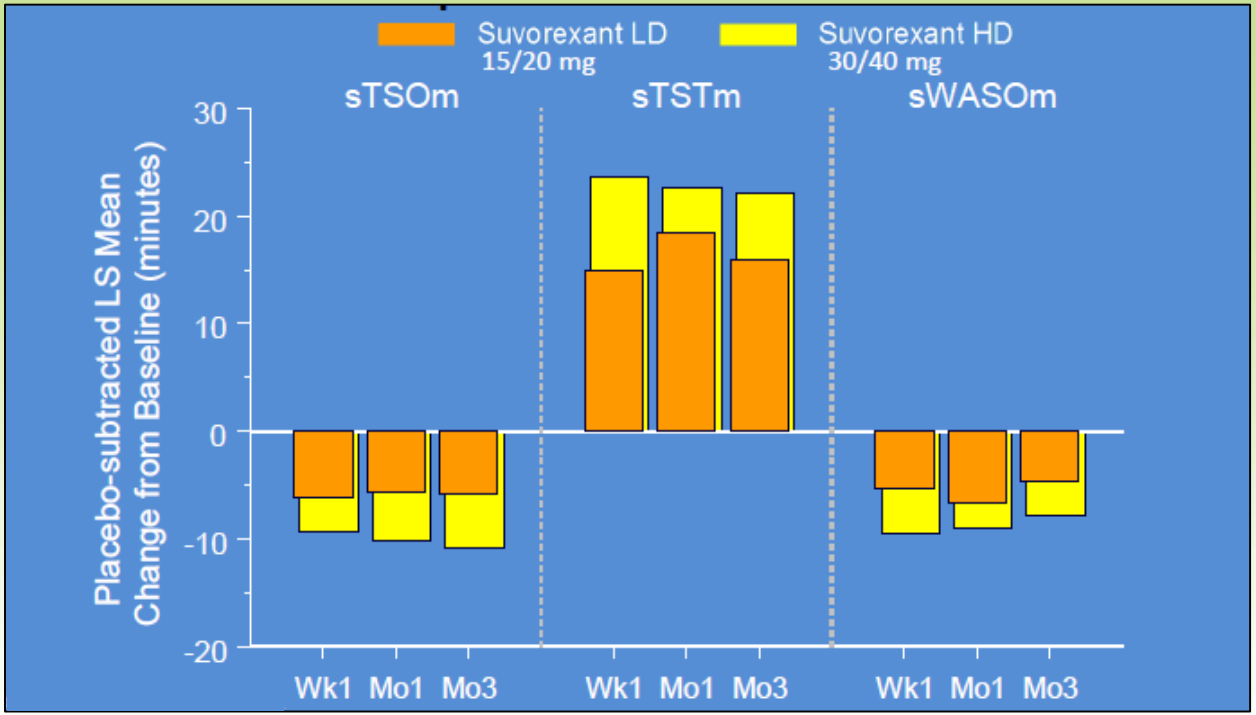


Data from pooled pivotal trials.

LPS, latency to the onset of persistent sleep; WASO, wake after persistent sleep onset; LS, Least-Squares; PSG, polysomnography; HD, high dose (40 mg for non-elderly, 30 mg for elderly); LD, low dose (20 mg for non-elderly, 15 mg for elderly).

Herring WJ, et al. *Biol Psychiatry*. 2016;79:136-48.; Herring WJ, et al. *J Clin Sleep Med*. 2016;12:1215-25.

…Dose-Related Improvements in Subjective Report Measures

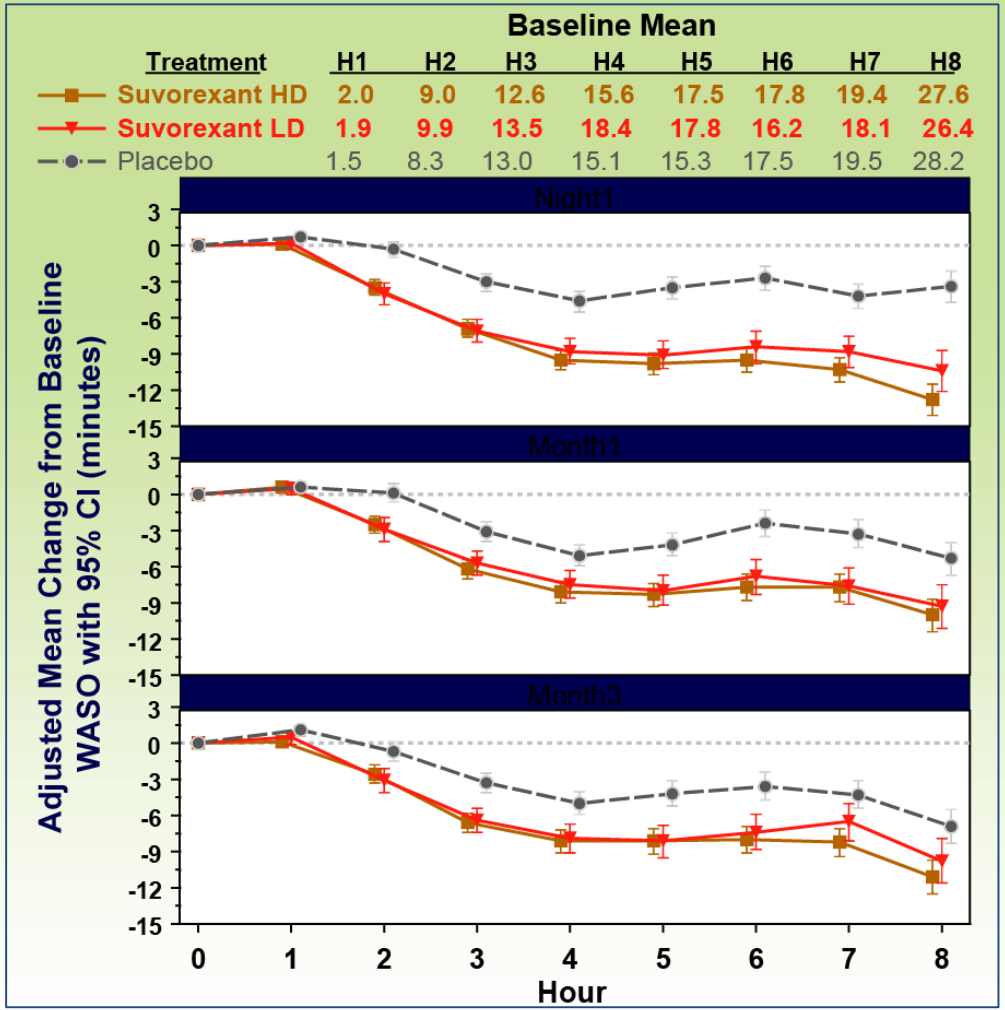


Data from pooled pivotal trials.

sTSOm, subjective Time to Sleep Onset mean; sTSTm, subjective Total Sleep Time mean; sWASOm, subjective Wake After Sleep Onset mean; LS, Least-Squares; HD, high dose (40 mg for non-elderly, 30 mg for elderly); LD, low dose (20 mg for non-elderly, 15 mg for elderly).

Herring WJ, et al. *Biol Psychiatry*. 2016;79:136-48. Herring WJ, et al. *J Clin Sleep Med*. 2016;12:1215-25.

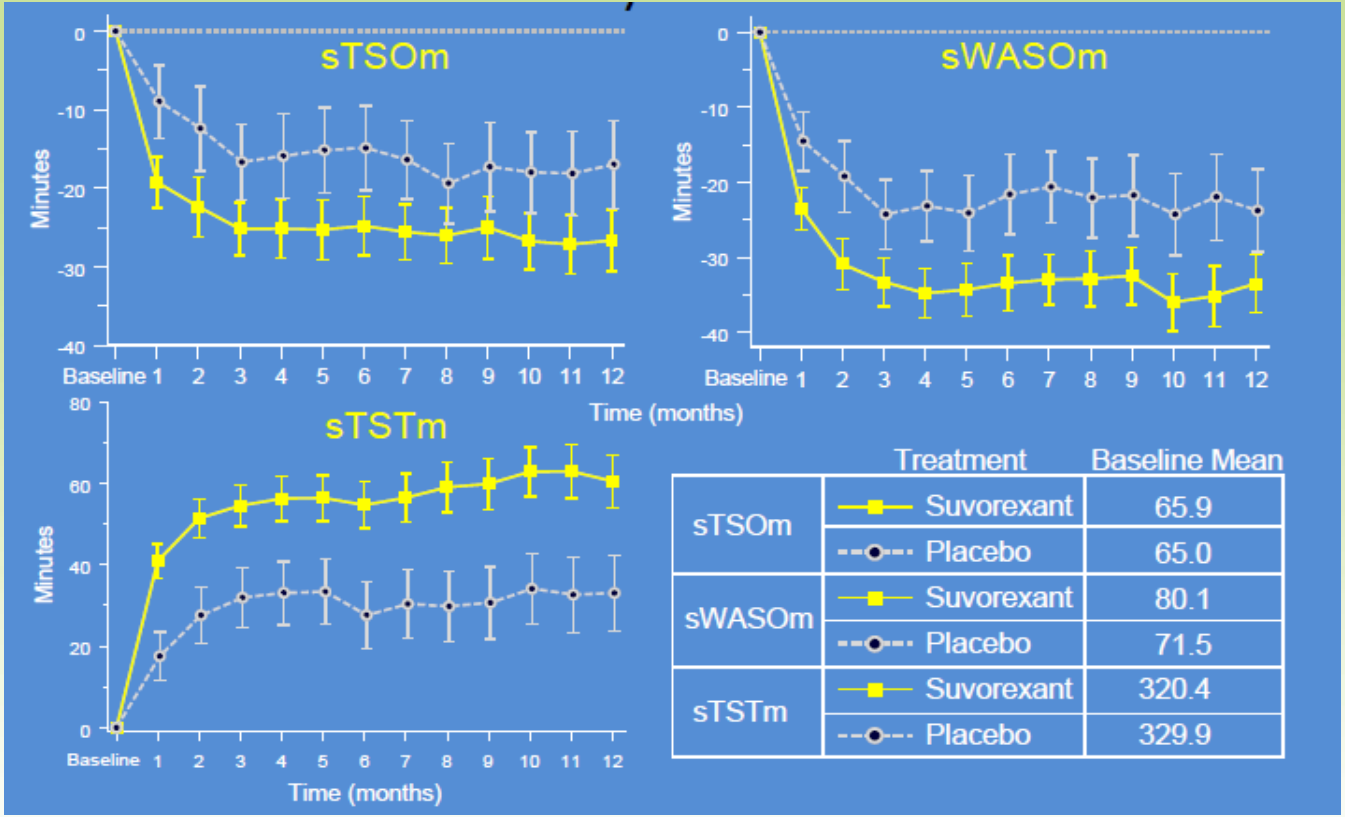
WASO by Hour of Night



WASO, wake after sleep onset.

Herring WJ, et al. *J Clin Sleep Med*. 2016;12:1215-25.

Suvorexant Efficacy Persists for 12 Months

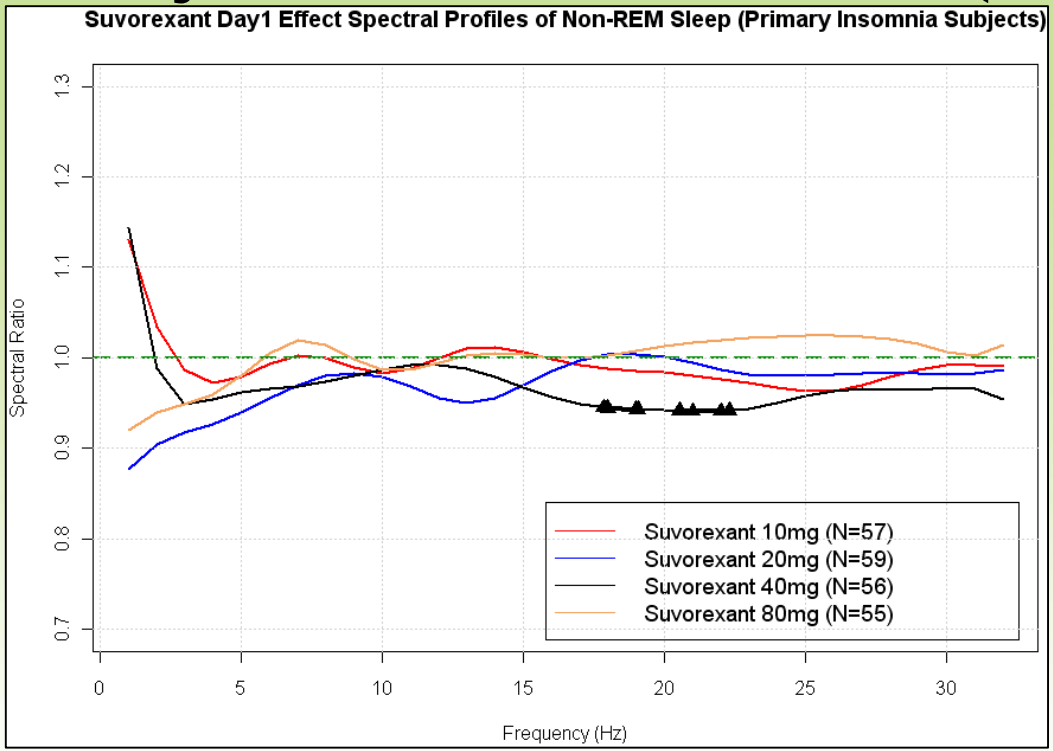


	Treatment	Baseline Mean
sTSOm	Suvorexant	65.9
	Placebo	65.0
sWASOm	Suvorexant	80.1
	Placebo	71.5
sTSTm	Suvorexant	320.4
	Placebo	329.9

Note: Nominal p<0.05 for all endpoints and timepoints. Least-Squares mean changes from baseline and 95% confidence intervals shown in plots. sTSOm, subjective Time to Sleep Onset mean; sWASOm, subjective Wake After Sleep Onset mean; sTSTm, subjective Total Sleep Time mean.; HD, high dose (40 mg for non-elderly, 30 mg for elderly).

Michelson D, et al. *Lancet Neurol*. 2014;13:461-71.

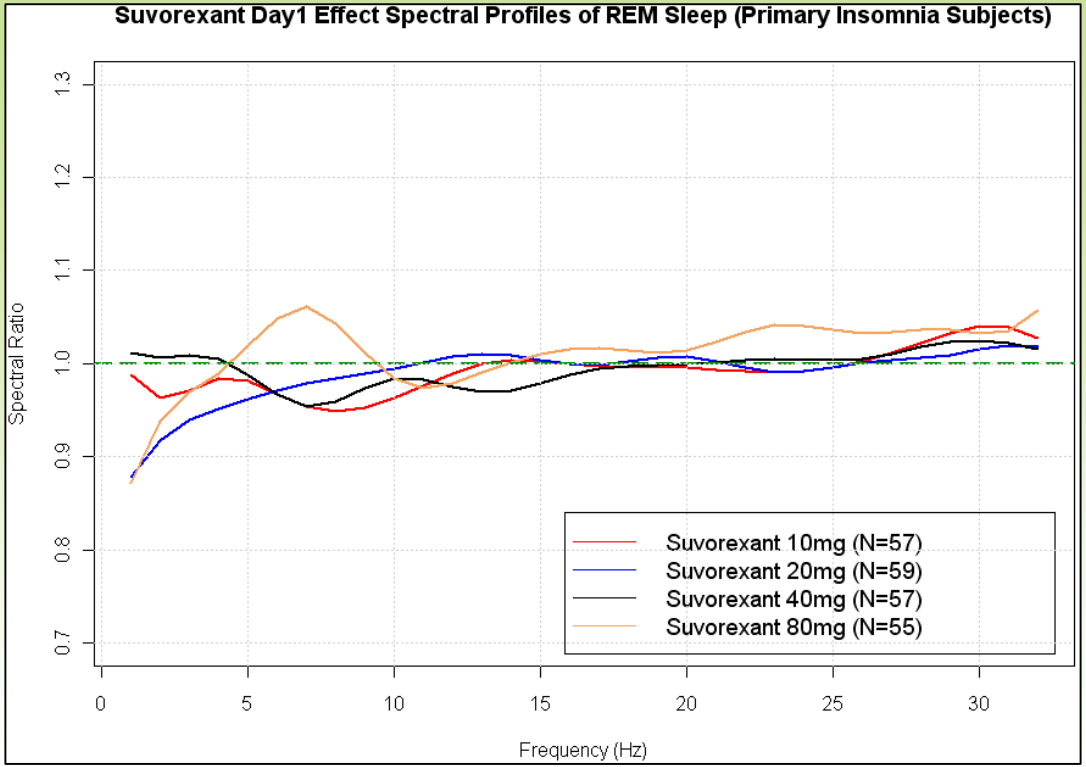
Power Spectral Profile of 4 Doses of Suvorexant in Primary Insomnia Patients (NREM)



Bolded segments with triangle markers are the frequency ranges where the difference between drug and placebo are statistically significant (p<0.05, adjusted for multiplicity)

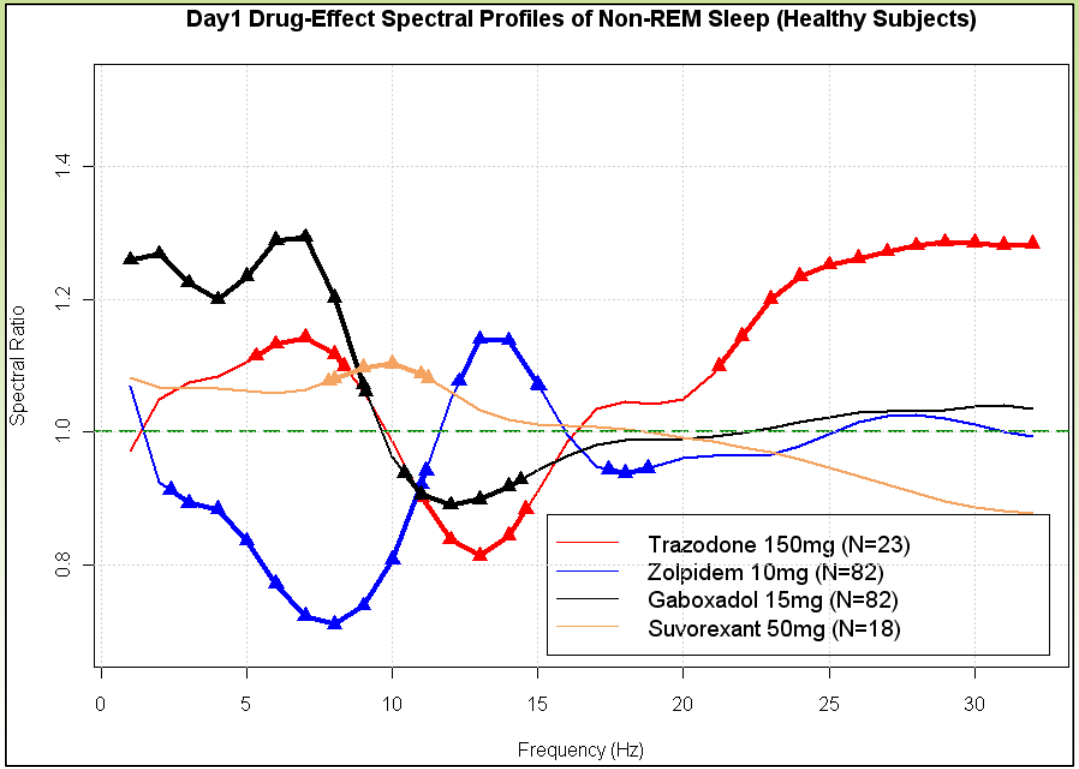
Ma J, et al. *Sleep*. 2014;37:1609-19.

Power Spectral Profile of 4 Doses of Suvorexant in Primary Insomnia Patients (REM)



Ma J, et al. *Sleep*. 2014;37:1609-19.

Power Spectral Profile of Suvorexant Compared with Other Hypnotics in Healthy Subjects (NREM)



Bolded segments with triangle markers are the frequency ranges where the difference between drug and placebo are statistically significant ($p<0.05$, adjusted for multiplicity).

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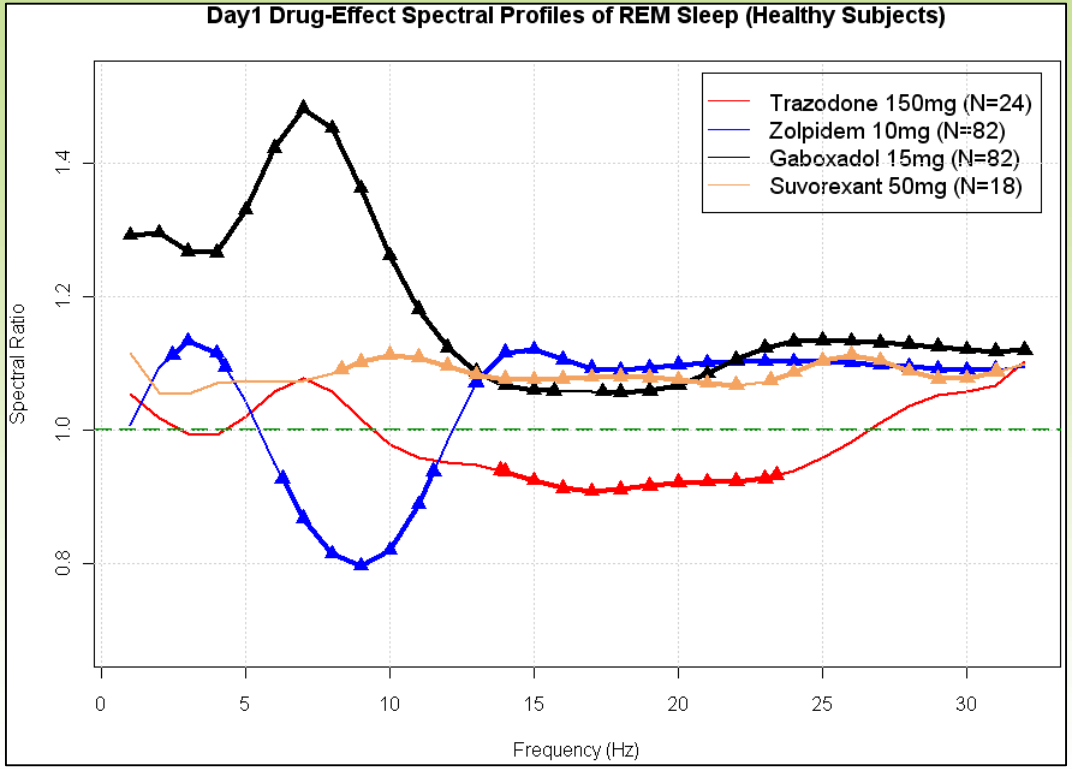
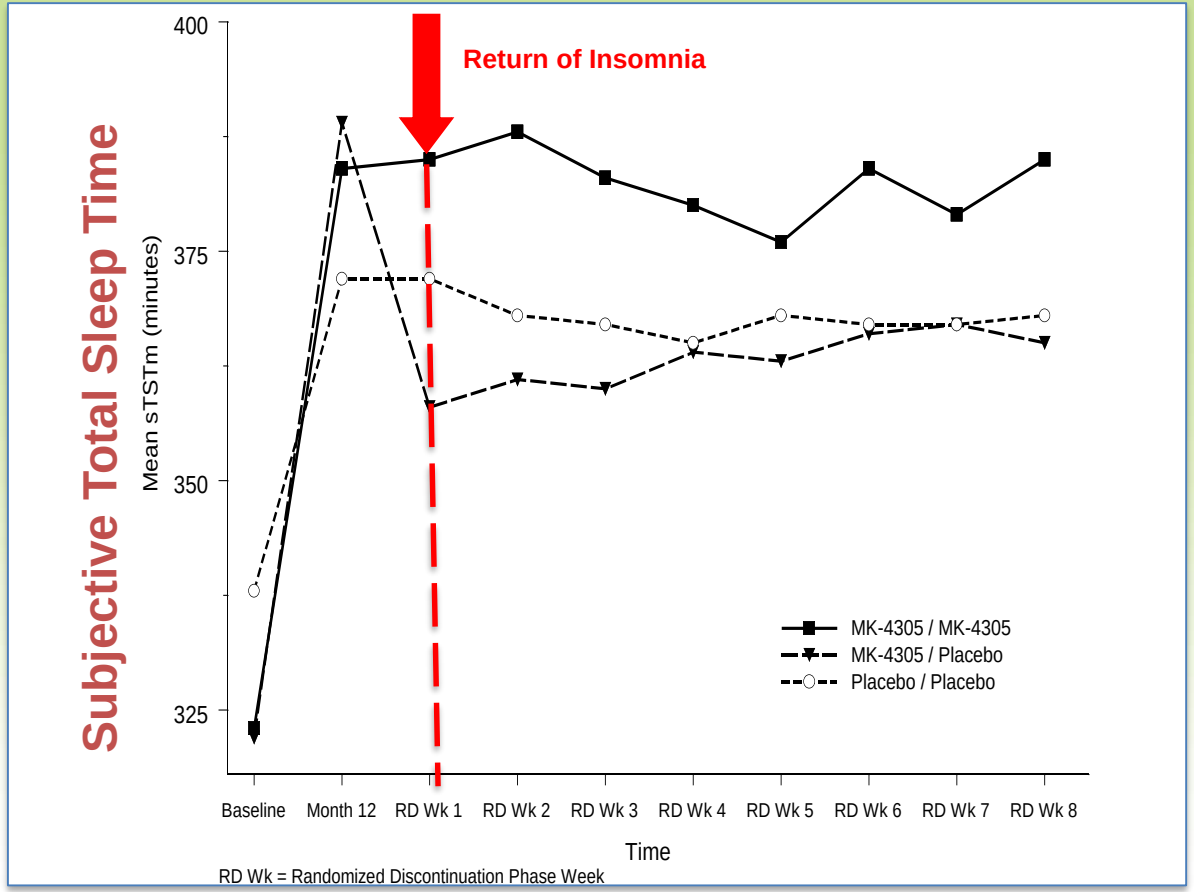
Power Spectral Profile of Suvorexant Compared with Other Hypnotics in Healthy Subjects (REM)



Bolded segments with triangle markers are the frequency ranges where the difference between drug and placebo are statistically significant ($p<0.05$, adjusted for multiplicity).

Ma J, et al. *Sleep*. 2014;37:1609-19.

Insomnia Returns When Suvorexant Stopped



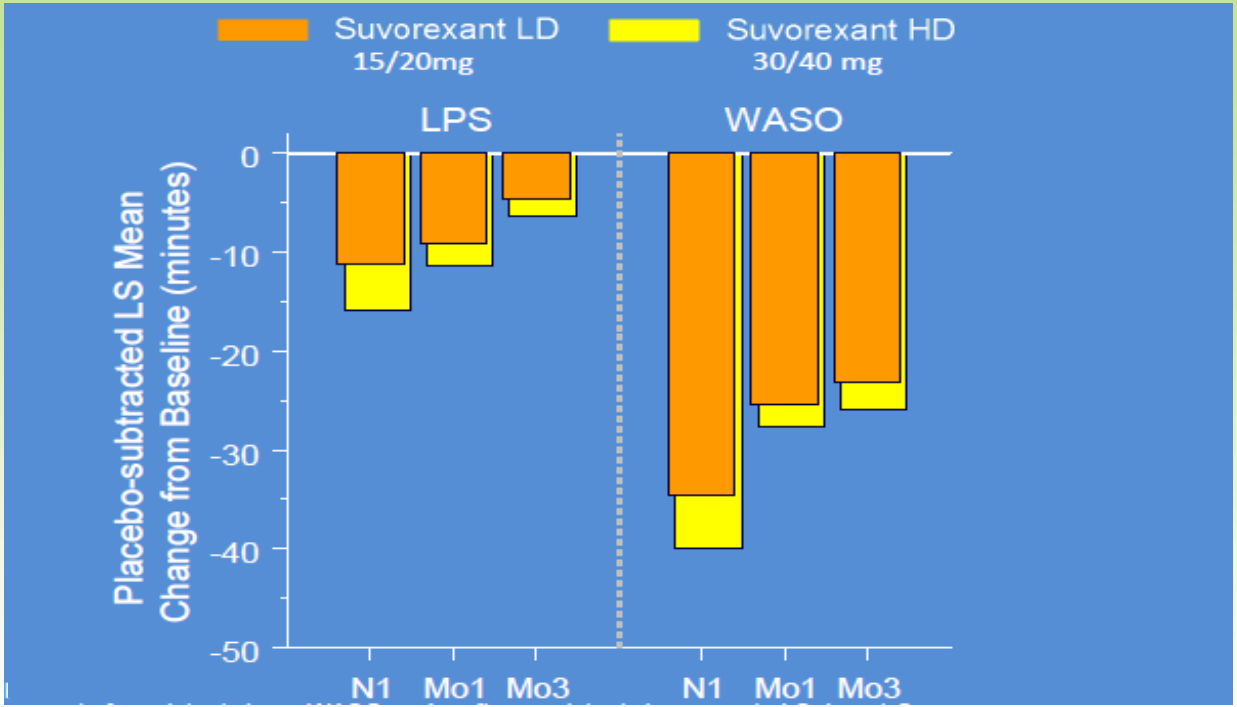
MK-4305=suvorexant

Michelson D, et al. *Lancet Neurol*. 2014;13:461-71.

Definition of Sleep

- Sustained behavioral quiescence
- Stereotypic, species-specific, posture
- Elevated arousal thresholds
- Rapid reversibility
- Characteristic electroencephalographic changes
- Stereotypic, species-specific duration

Dose-Related Improvement in PSG Measures with Suvorexant…



Data from pooled pivotal trials.

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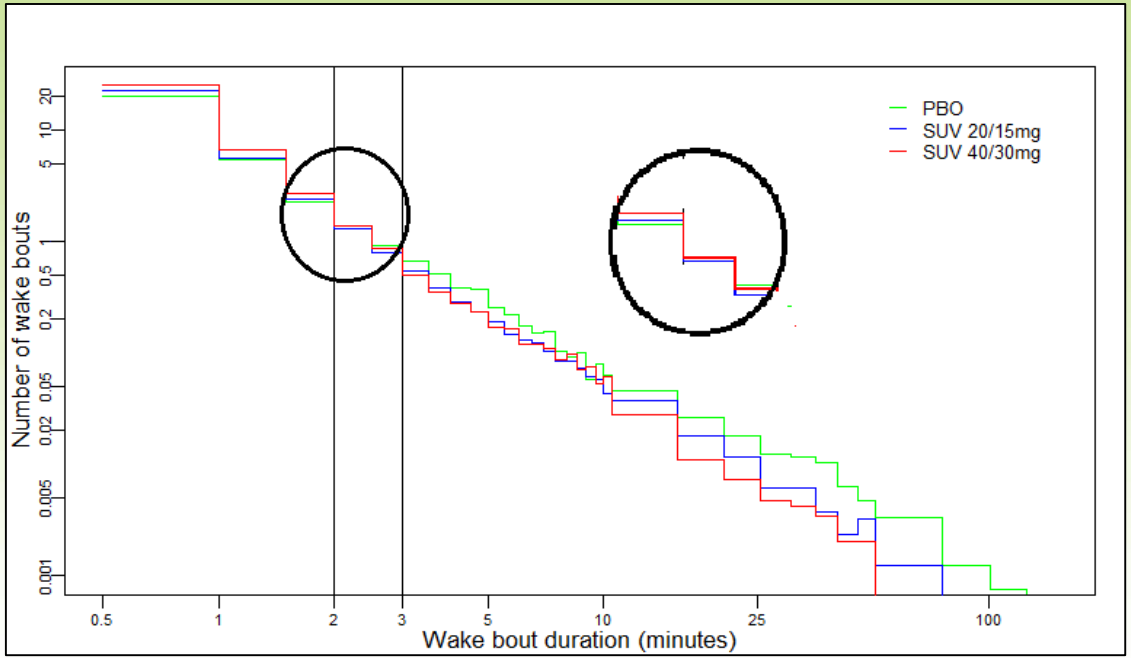
Herring WJ, et al. *Biol Psychiatry*. 2016;79:136-48.; Herring WJ, et al. *J Clin Sleep Med*. 2016;12:1215-25.

Analysis of Sleep and Wake Bouts with Suvorexant

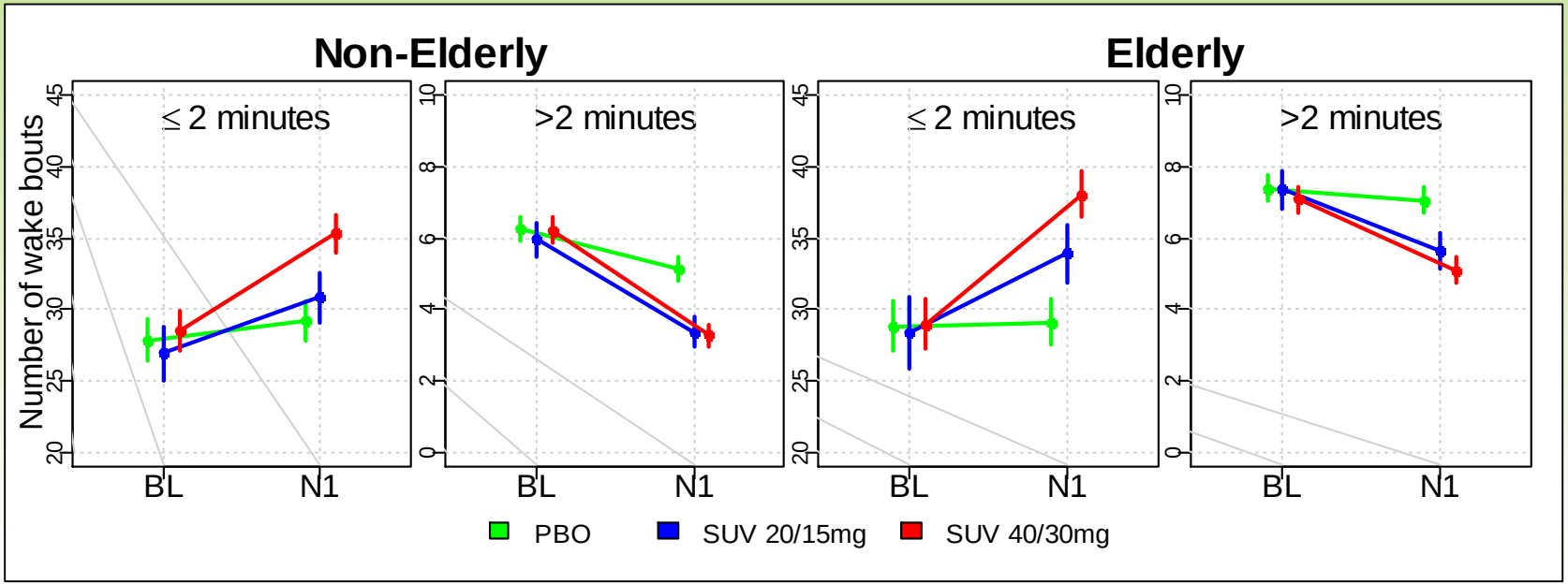
Mean number of wake bouts on Night 1 of treatment by wake bout duration for suvorexant (SUV 20/15 mg, 40/30 mg) and placebo (PBO). X- and Y-axes use logarithmic scales.



Svetnik V, et al. *Sleep*. 2016;39(Suppl 1):A207.

Analysis of Sleep and Wake Bouts with Suvorexant (cont'd)

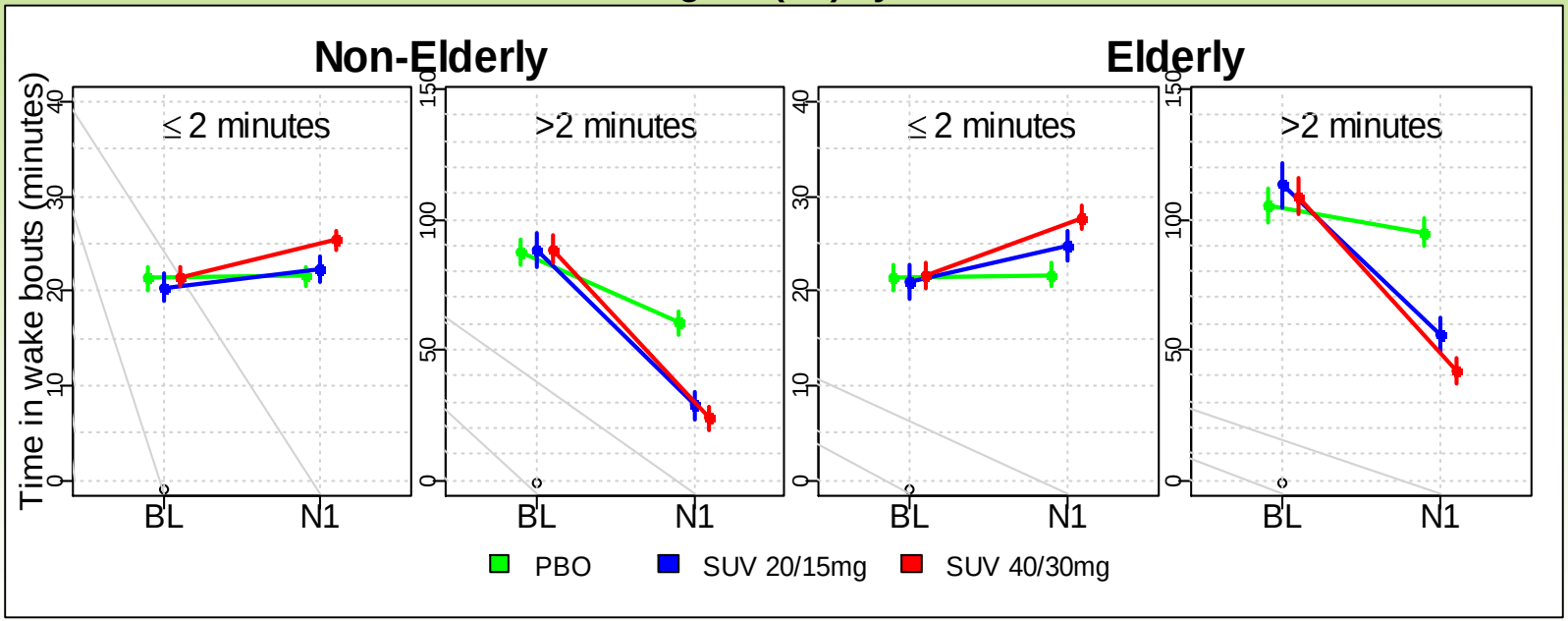
Mean number (±2 SEM) of short (≤2 minutes) and long (>2 minutes) wake bouts at baseline (BL) and Night 1 (N1) by treatment



Svetnik V, et al. *Sleep*. 2016;39(Suppl 1):A207.

Analysis of Sleep and Wake Bouts with Suvorexant (cont'd)

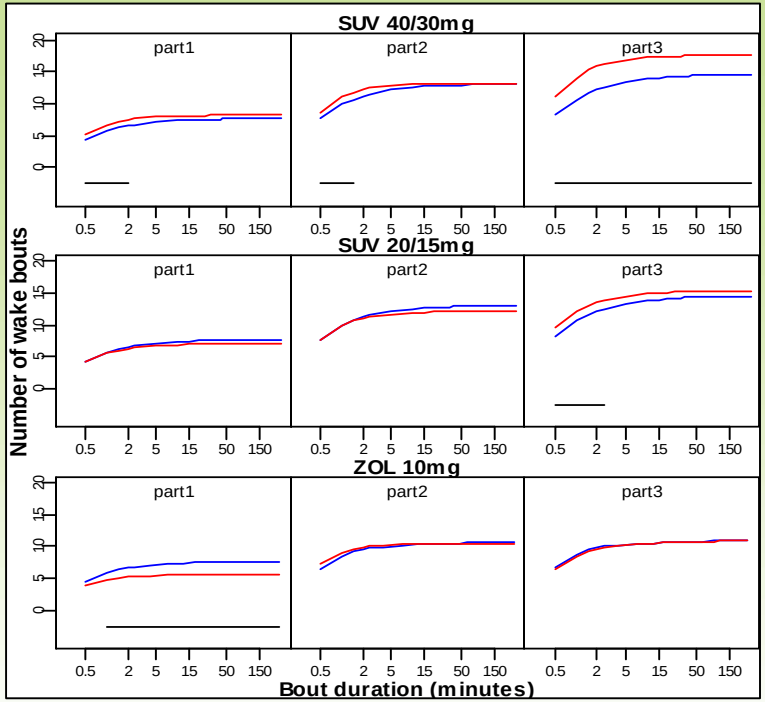
Mean time (±2 SEM) spent in short (≤2 minutes) and long (>2 minutes) wake bouts at baseline (BL) and Night 1 (N1) by treatment

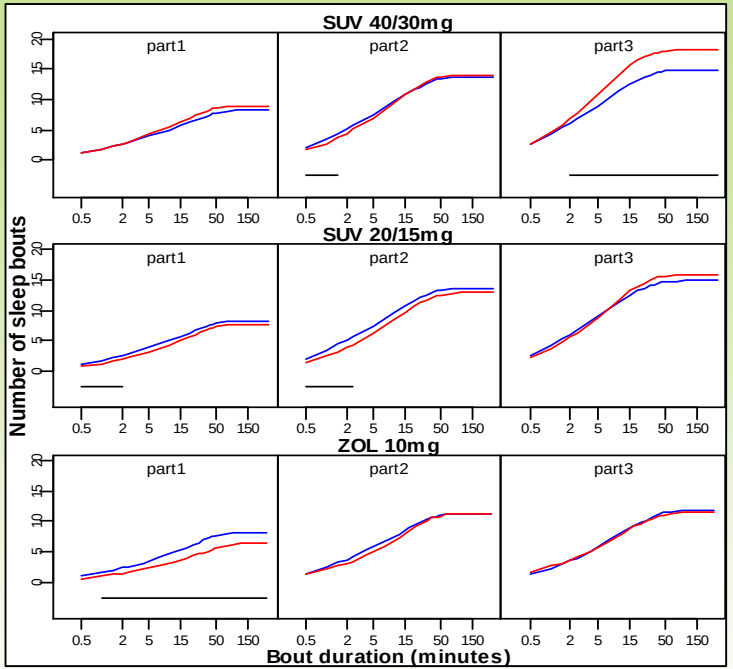


Svetnik V, et al. *Sleep*. 2016;39(Suppl 1):A207.

Analysis of Sleep and Wake Bouts with Suvorexant vs. Zolpidem

Cumulative number of bouts with bout duration ≤ x-axis value for treatment suvorexant (SUV 40/30 mg, 20/15 mg) and zolpidem (ZOL 10 mg) vs. placebo by part of the night.



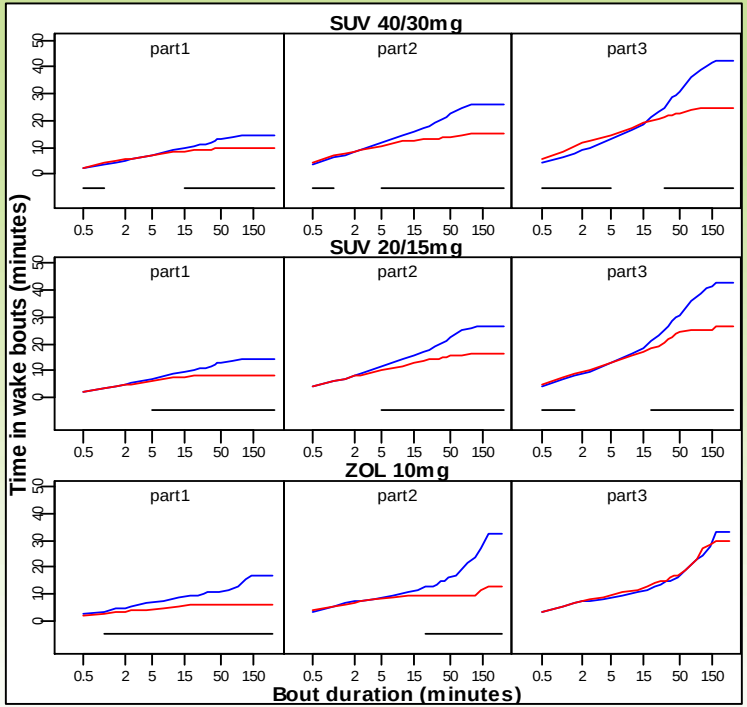


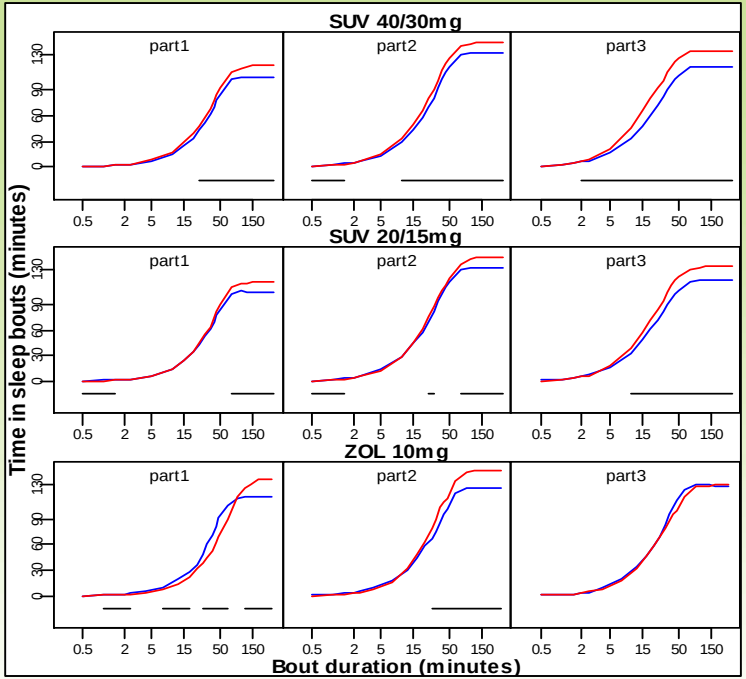
Legend: — **active treatment (SUV (40/30 mg), SUV 20/15 mg, or ZOL 10 mg);** — **placebo (from suvorexant study or from zolpidem study); bout durations where the differences between cumulative time under treatment and under placebo are statistically significant, p-values < 0.05, are indicated by the black bars.**

Svetnik V, et al. *Sleep*. 2016;39(Suppl 1):A207.

Analysis of Sleep and Wake Bouts with Suvorexant vs. Zolpidem (cont'd)

Mean cumulative time in bouts with bout duration ≤ x-axis value for treatment suvorexant (SUV 40/30 mg, 20/15 mg) and zolpidem (ZOL 10 mg) vs. placebo by part of the night.

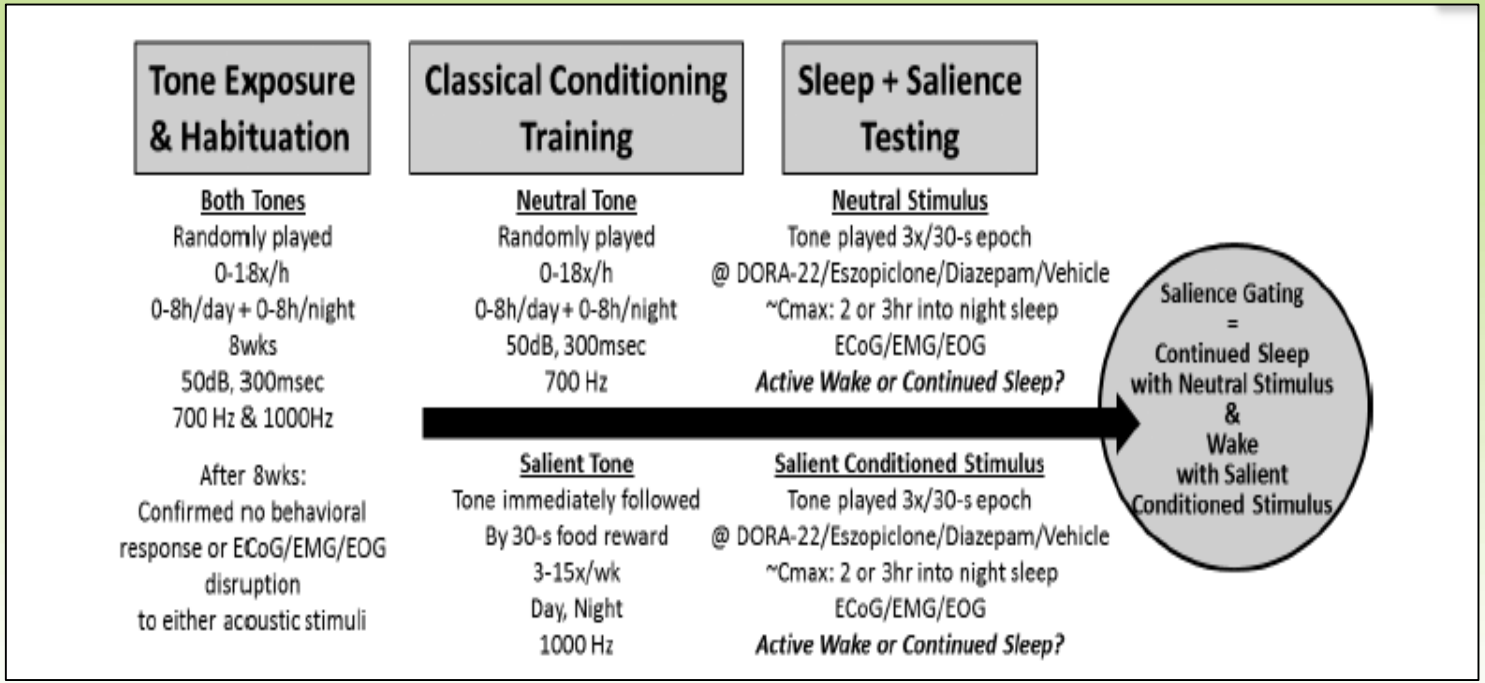




Legend: ── active treatment (SUV (40/30 mg), SUV 20/15 mg, or ZOL 10 mg); ── placebo (from suvorexant study or from zolpidem study); bout durations where the differences between cumulative time under treatment and under placebo are statistically significant, p-values < 0.05, are indicated by the black bars.

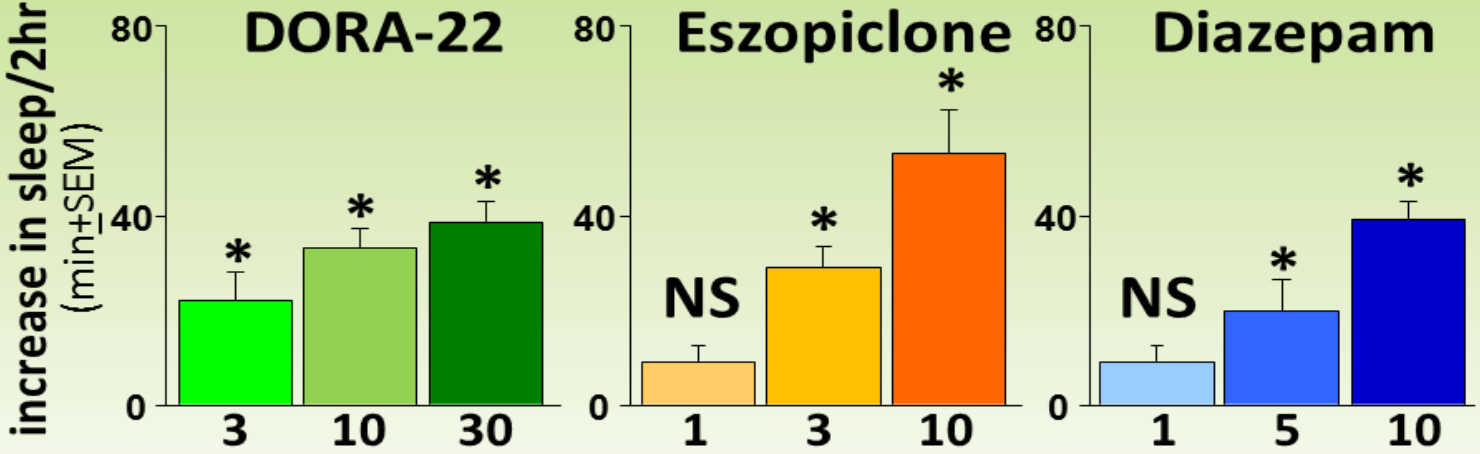
Svetnik V, et al. *Sleep*. 2016;39(Suppl 1):A207.

Orexin Signaling and Salient Arousability



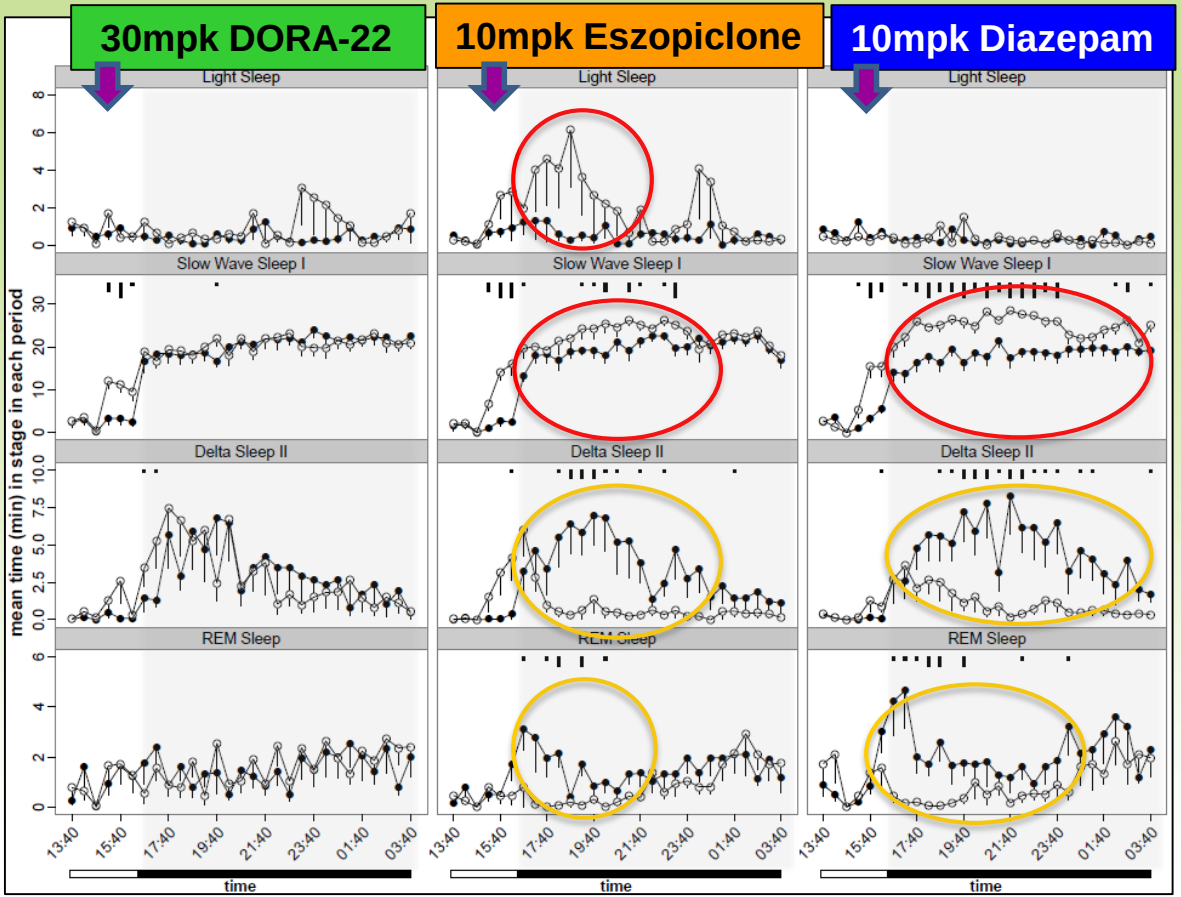
Tannenbaum PL, et al. *Sleep*. 2016;39:603-12.

Monkey + DORA-22, Eszopiclone, Diazepam: All Increase Sleep / Decrease Active Wake



Tannenbaum PL, et al. *Sleep*. 2016;39:603-12.

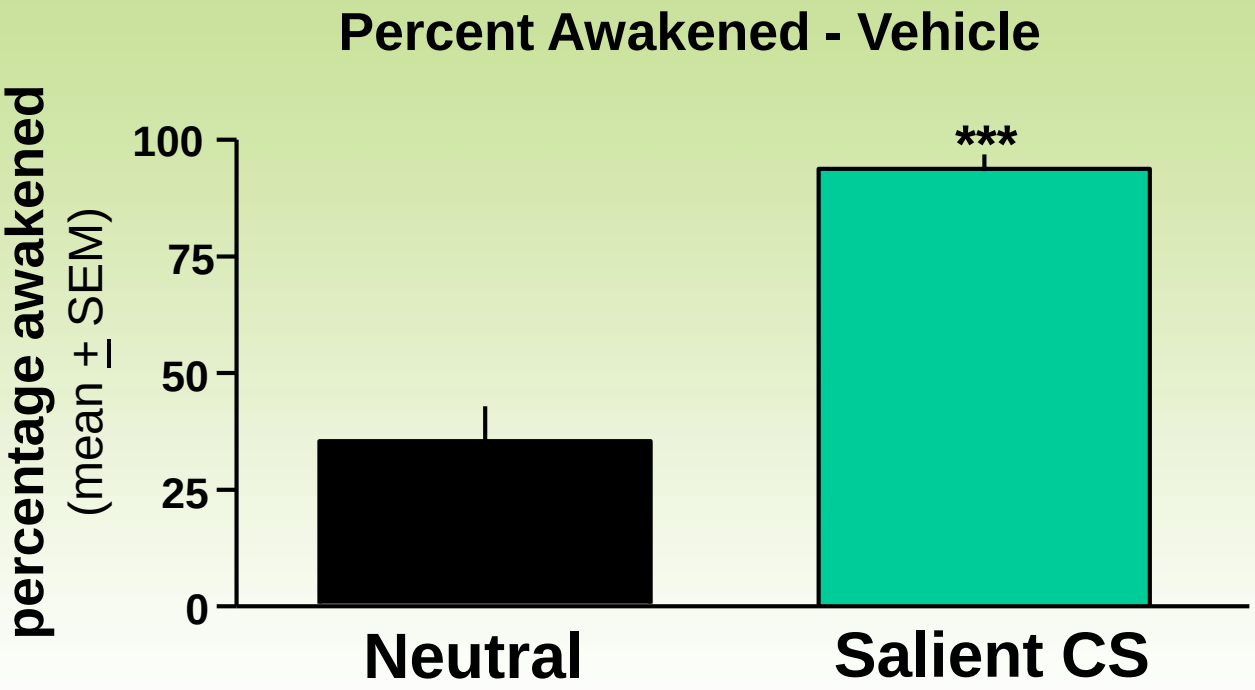
Monkey + GABA-A Modulator Sleep Architecture:
More Light & Slow Wave I, Less Delta II and REM Sleep



Tannenbaum PL, et al. *Sleep*. 2016;39:603-12.

Monkeys + Vehicle (Unmedicated) Sleep:

Wake to Salient Conditioned Stimulus, Sleep Through Neutral Stimulus

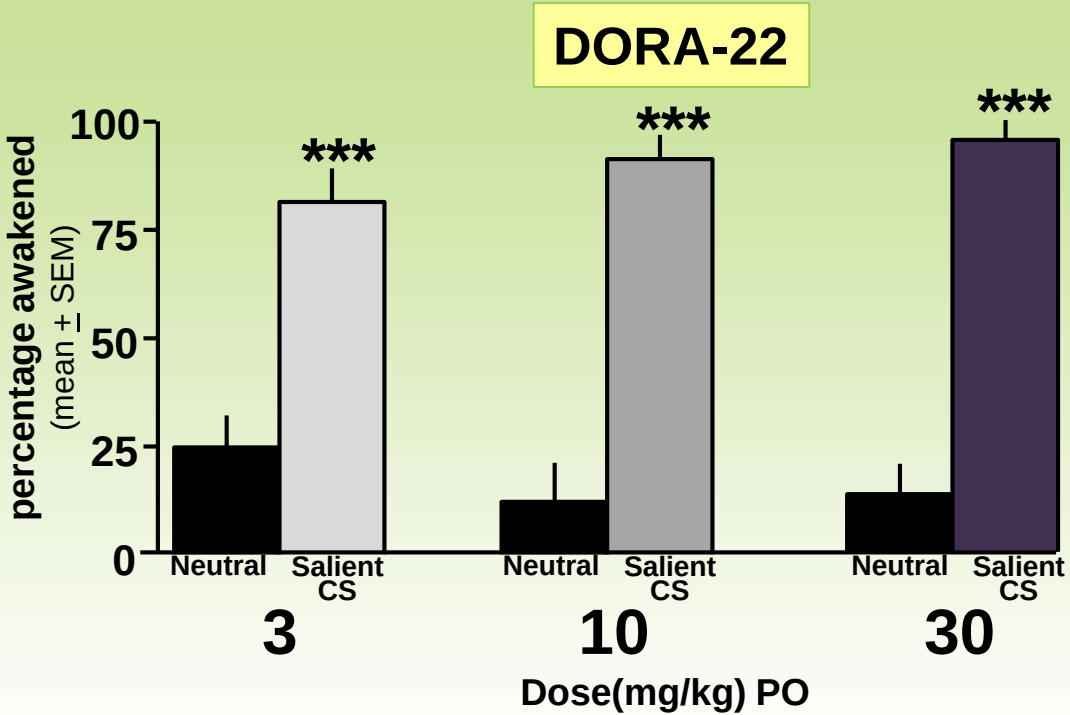


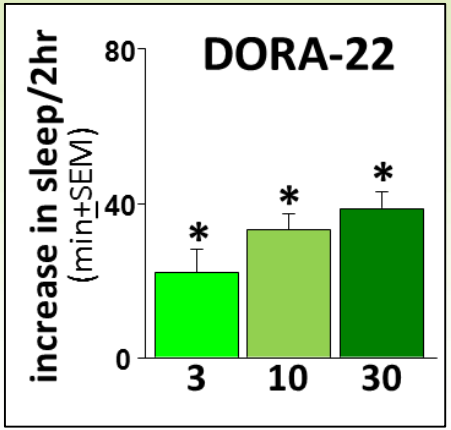
***p<0.001

Tannenbaum PL, et al. *Sleep*. 2016;39:603-12.

Monkeys + DORA-22 Sleep:

Wake to Salient Conditioned Stimulus, Sleep Through Neutral Stimulus

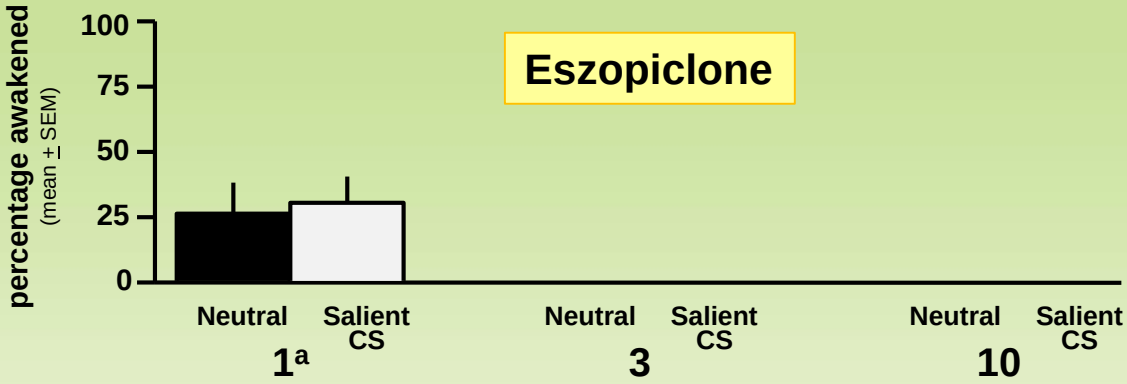


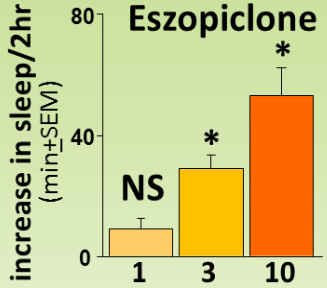


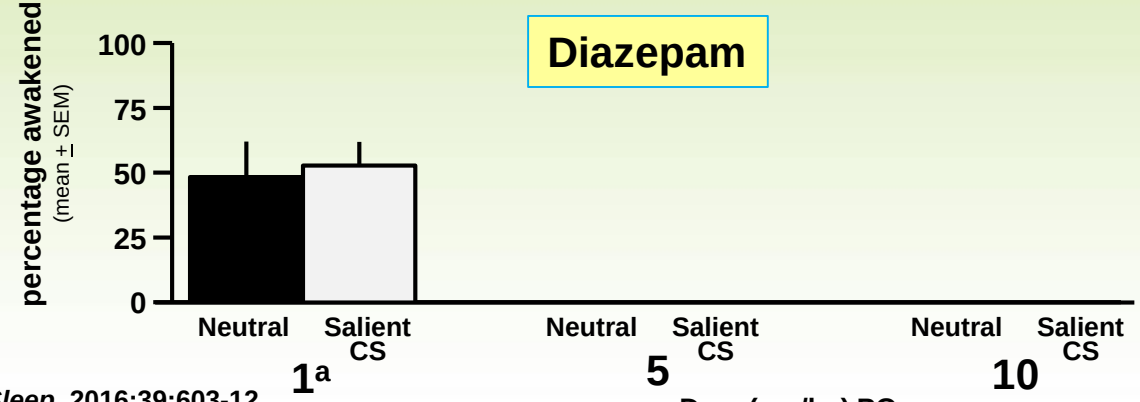
***p<0.001

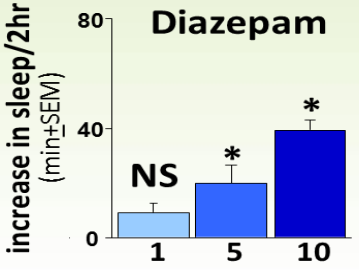
Tannenbaum PL, et al. *Sleep*. 2016;39:603-12.

Monkeys + GABA-A Receptor Modulator Sleep:
Do Not Discriminate Between Neutral and Salient Stimuli







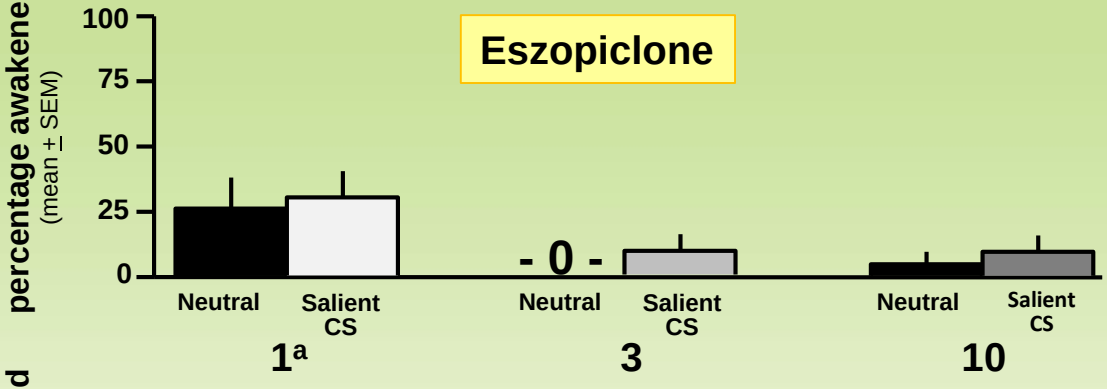


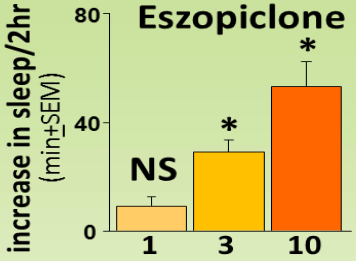
[a]non-sedating dose

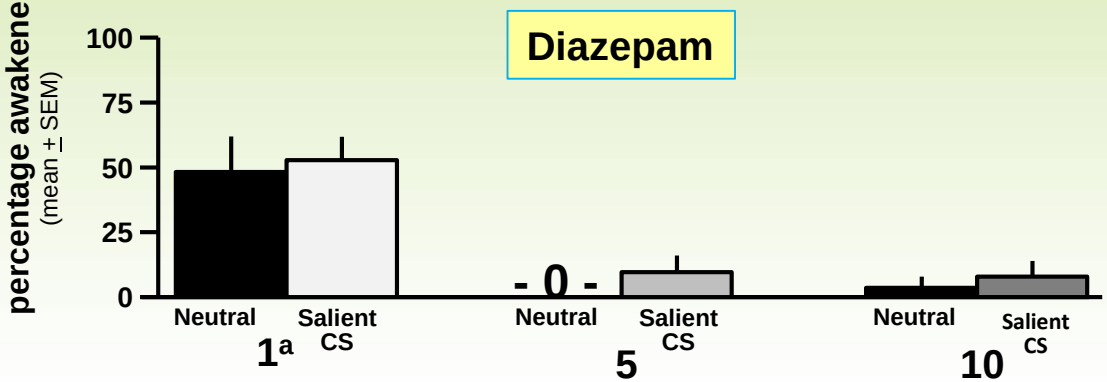
Tannenbaum PL, et al. *Sleep*. 2016;39:603-12.

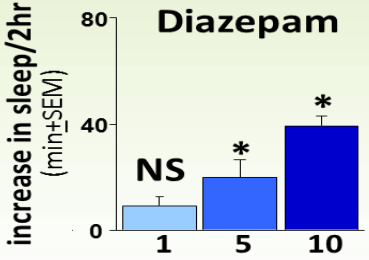
Monkeys + GABA-A Receptor Modulator Sleep:

Do Not Discriminate Between Neutral and Salient Stimuli, Rarely Wake to Salient Conditioned Stimuli









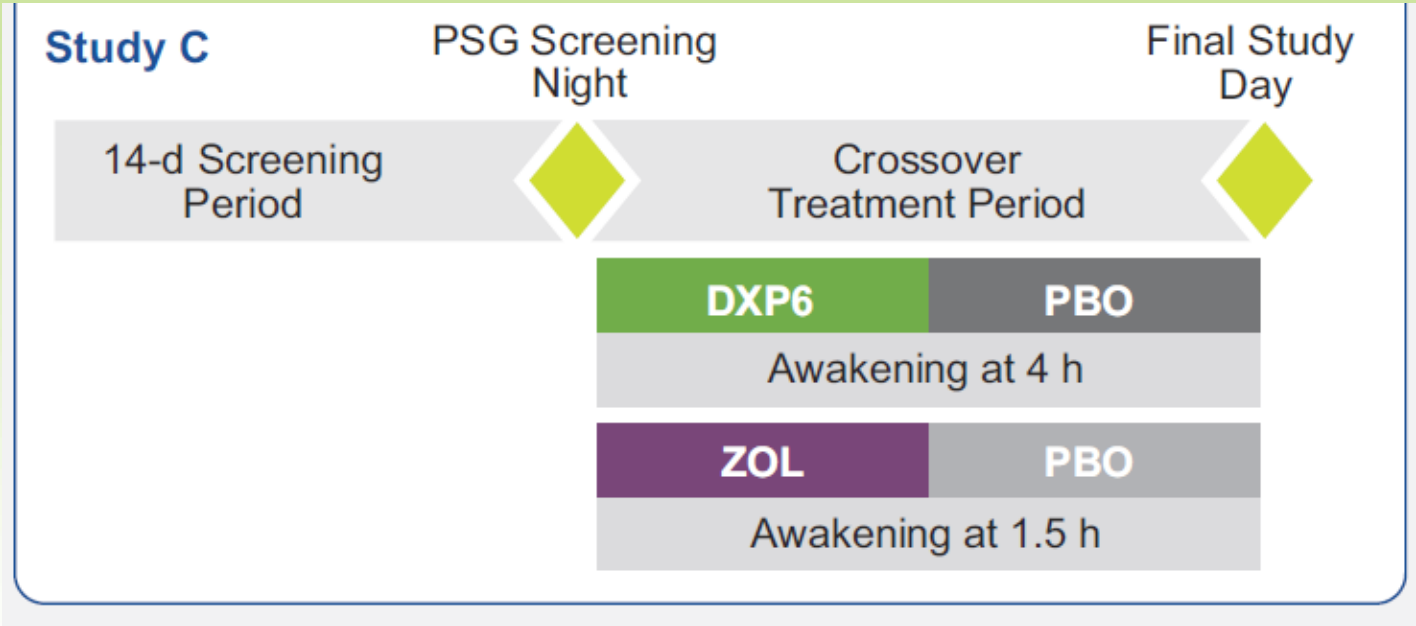
ªnon-sedating dose

Dose(mg/kg) PO

Tannenbaum PL, et al. *Sleep*. 2016;39:603-12.

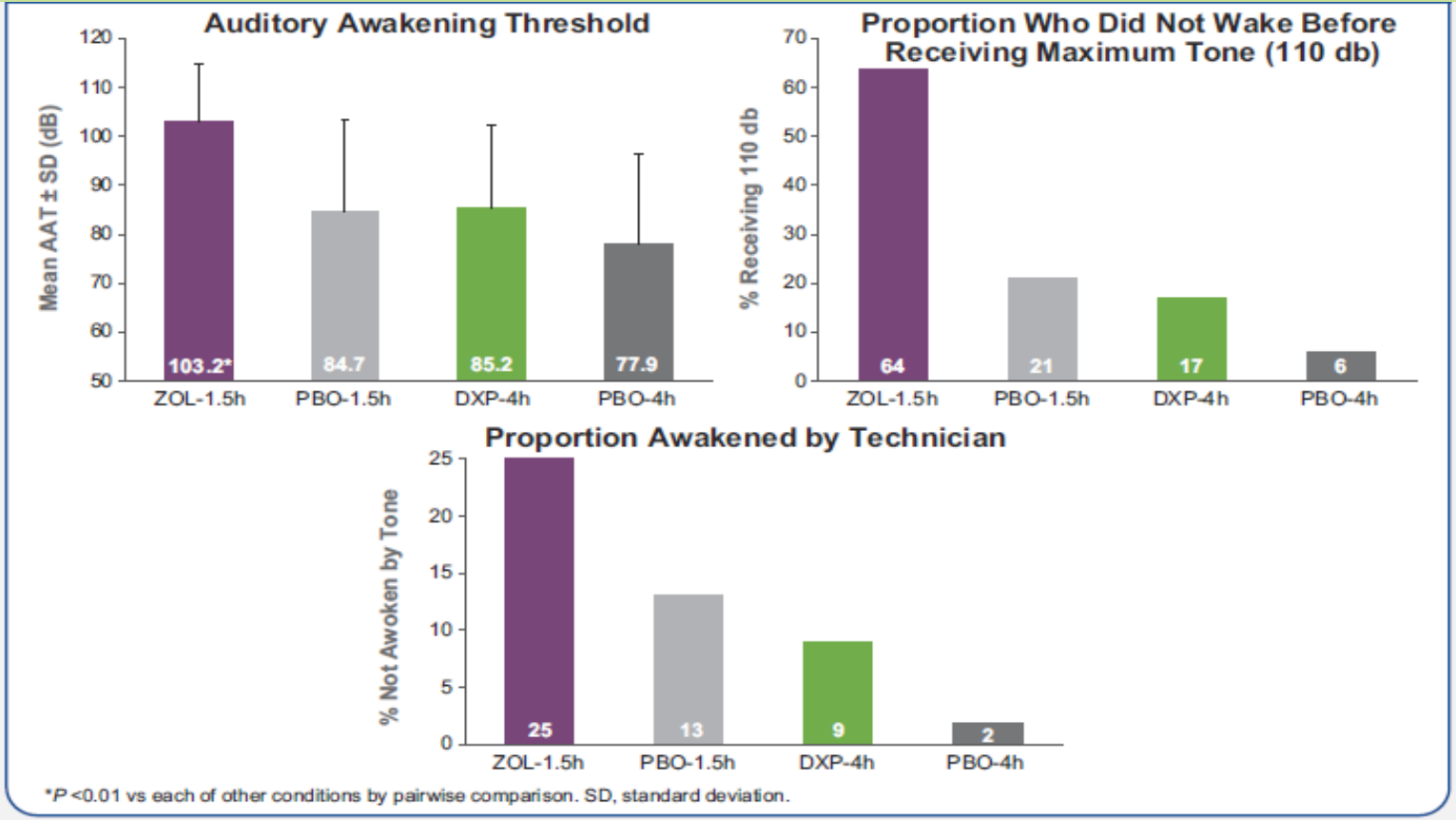
Arousability of Insomnia Patients and Healthy Volunteers: Doxepin (3 and 6 mg) and Zolpidem (10 mg)

Study Design



Durrence H, et al. *Sleep*. 2016;39(Suppl 1):A201.

Arousability Study Results

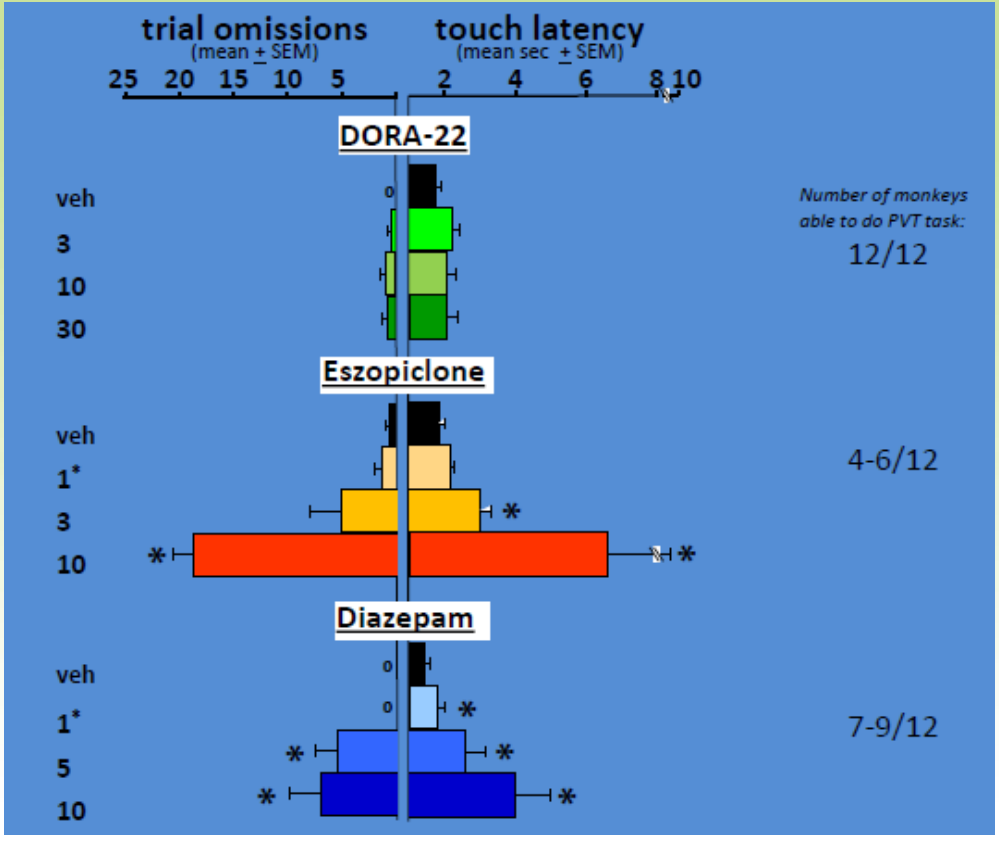


Durrence H, et al. *Sleep*. 2016;39(Suppl 1):A201.

Conditions Associated With Arousal From Sleep

Sleep Apnea
COPD
GERD
Cough
Nocturia
Abnormal Behaviors in Sleep

Monkey Psychomotor Vigilance Testing (PVT): Wake from DORA-22 and Perform As Unmedicated If Wake from GABA-A Modulators Performance Impaired



*p<0.05

Tannenbaum PL, et al. *Sleep*. 2016;39:603-12.

Summary/Key Messages

- Arousal is an important characteristic of sleep
- Arousal from sleep is an important homeostatic response in many sleep and wake disorders
- WASO as a measure of sleep is determined by both arousability and sleep initiation propensity
- Drugs working on wake signaling preserve arousability but improve sleep initiation propensity
- Drugs working on sleep signaling blunt arousability but improve sleep imitation propensity
- Blunting arousability is associated with impaired function post arousal