Insomnia – conceptualization and management in 2011

Martin Reite MD
Clinical Professor of Psychiatry
University Hospital Sleep and Insomnia Clinic
University of Colorado Denver

University Hospital Sleep and Insomnia Clinic

- Diagnostic and treatment clinic for all sleep disorders – insomnias, hypersomnias, and parasomnias
- Not a sleep lab, but may refer to sleep lab
- Located in Pulmonary Clinic, 7th floor Anschutz
- Meets Wednesdays
- Staff includes:
  - Jean Tsai MD
  - Sheila Tsai MD
  - Jann Shire RN MSN
  - Martin Reite MD

Three Questions to Screen for Sleep Disorders

- Are you content with your sleep? (picks up the insomnias)
- Are you excessively sleepy during the day? (Picks up the EDS disorders like narcolepsy, primary hypersomnia and and obstructive apnea)
- Does your bedpartner (or parent) complain about your sleep? (picks up the parasomnias)

These questions will take about 20 seconds, and pick up 90% of serious sleep problems

If you get the “wrong” answer to any question consider taking a sleep history

Insomnia – the most common sleep complaint

30% of people in the general population experience symptoms consistent with insomnia

Symptoms may include:
Cant get to sleep, cant stay asleep, wake to early, sleep not refreshing, all of the above

Consequences of chronic insomnia

- Diminished quality of life, impaired memory and concentration, ↓ ability to accomplish daily tasks, ↓ ability to enjoy interpersonal relationships
- ↑ risk of developing anxiety and depression*
- ↑ health care costs
- Impaired memory consolidation
- ↓ hippocampal volumes** (?memory?)

*Neckelmann et al Sleep 30:873, 2007

**Riemannn et al Sleep 30:955, 2007

Consquences of sleep loss in normal subjects

- ↓ psychomotor performance
- ↓ antibody performance following immunization*
- ↓ leptin and↑ grehlin production**
- ↑ C-reactive protein***
- ↑ risk for insulin resistance and type 2 diabetes
- Chronic insomniacs may be at increased risk for all the above

*Lange et al Psychosom Med 65:831, 2003

**Spiegel et al Ann Int Med 141:846, 2005*

***Meier-Ewert et al J Am Coll Cardiol 43:678, 2004

Differential Diagnosis of a chronic insomnia complaint - a 6 step process

:

Step 1. Medical conditions and dementia
Step 2. Psychiatric disorders
Step 3. Substance misuse
Step 4. Circadian rhythm disorders
Step 5. Movement disorders including Restless leg syndrome (RLS) and Periodic Leg Movements in Sleep (PLMS)
Step 6. The primary insomnia, conditioned insomnia and SSMP group

- Primary insomnia
- Conditioned insomnis
- Sleep State Misperception Syndrome (SSMS)

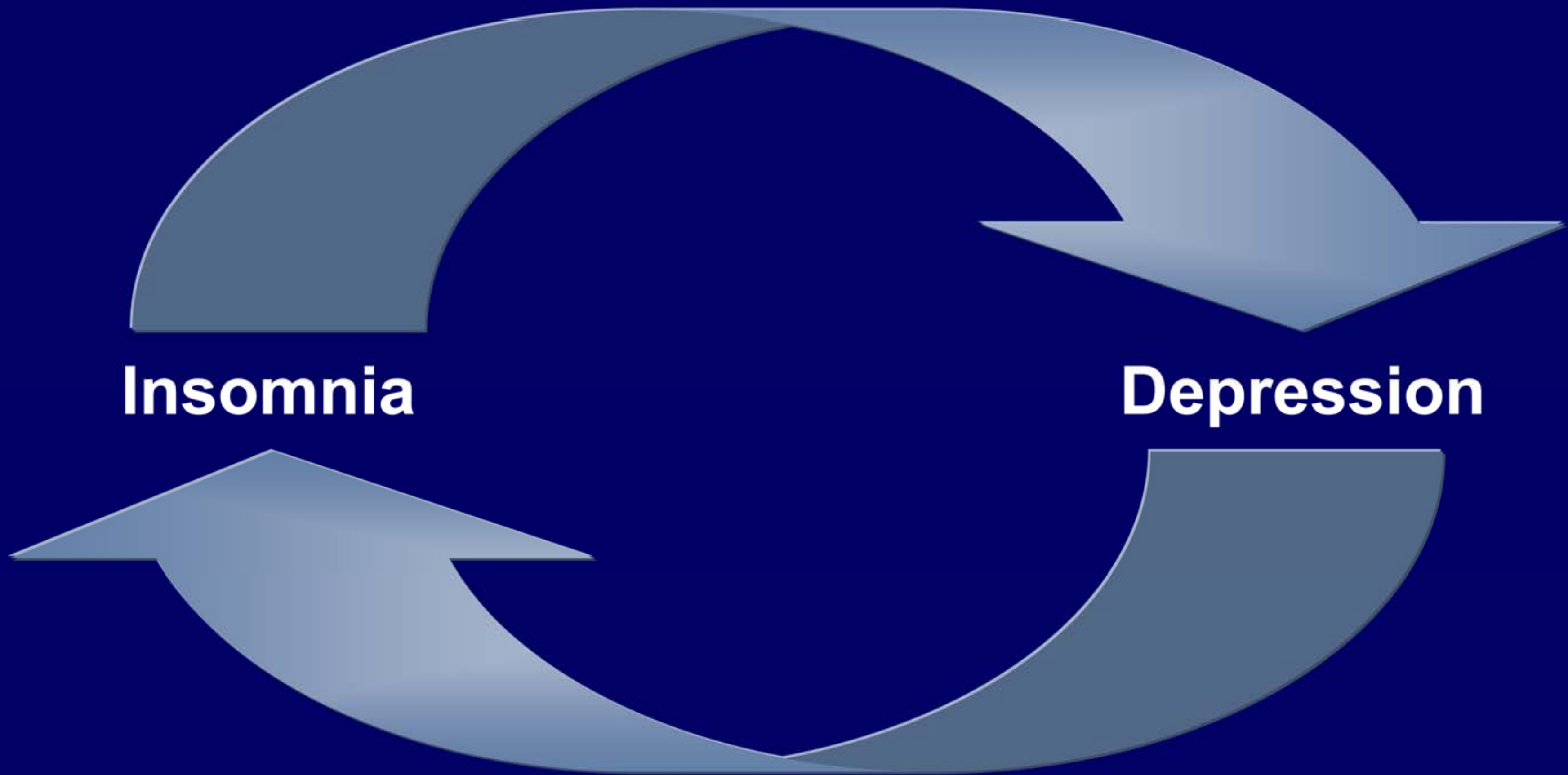
Medical conditions associated with insomnia

- Respiratory – asthma, COPD, bronchitis
- Gastrointestinal – GERD
- Neurologic – dementia, Parkinson's
- Musculoskeletal – fibromyalgia, rheumatoid arthritis
- Endocrinological – hyperthyriodism, menopause
- RLS, PLMS

Psychiatric conditions associated with insomnia

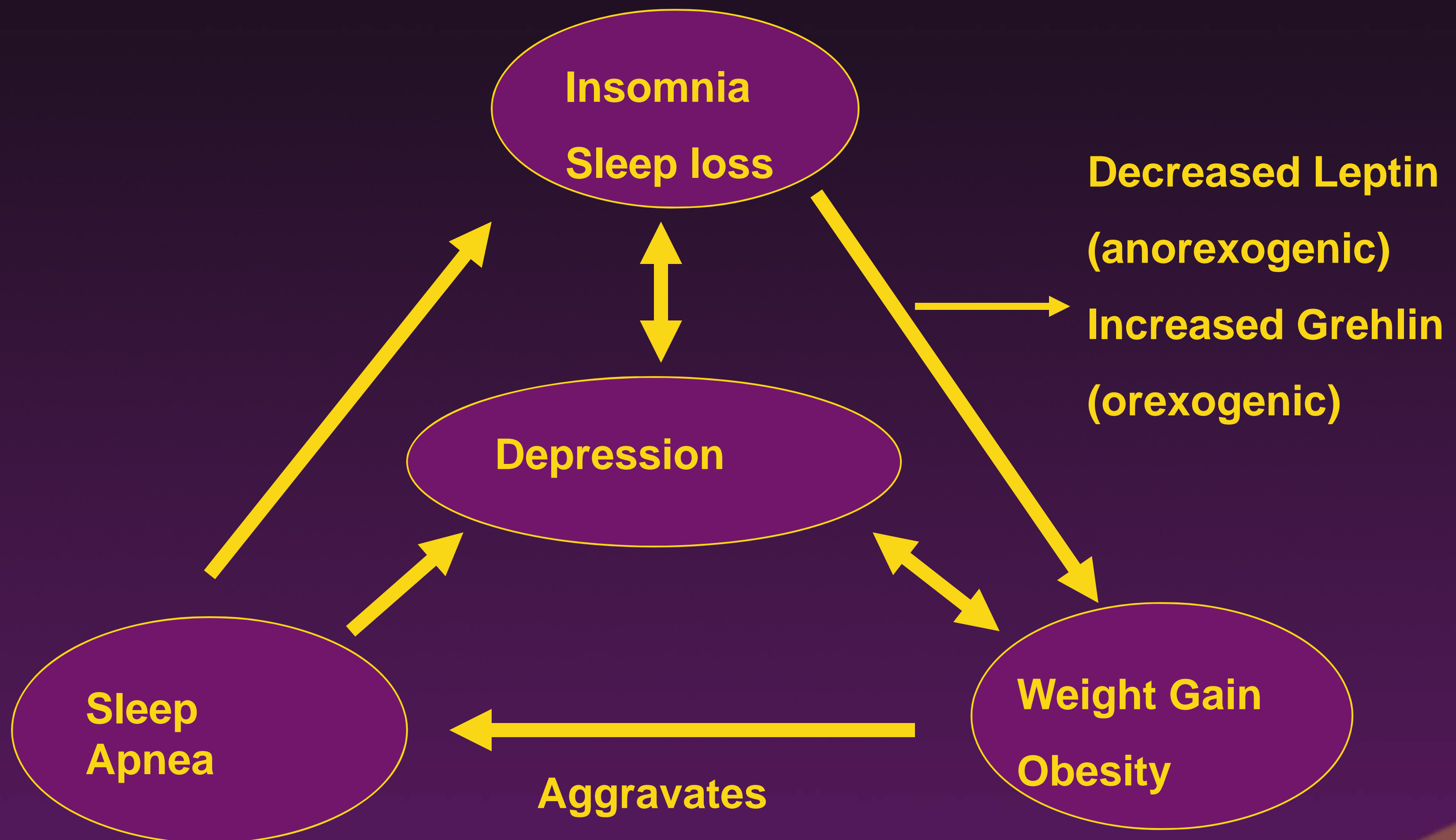
- Mood disorders – depression, bipolar disorder
- Anxiety disorders – GAD, panic
- Substance abuse
- Psychosis
- ADHD

Interrelationship Between Depression and Insomnia



THE VICIOUS CIRCLE

(The obese depressed insomniac with sleep apnea)



Overview of the Effects of Antidepressants on Sleep

	EEG sleep effects			
Drug	**Continuity**	**SWS**	**REM**	**Sedation**
TCAs				
Amitriptyline (Elavil®)	↑↑↑	↑	↓↓↓	++++
Doxepin (Sinequan®)	↑↑↑	↑↑	↓↓	++++
Imipramine (Tofranil®)	↔↑	↑	↓↓	++
Nortriptyline (Pamelor®)	↑	↑	↓↓	++
Desipramine (Norpramin®)	↔	↑	↓↓	+
Clomipramine (Anafranil®)	↑↔	↑	↓↓↓↓	±
MAOIs				
Phenelzine (Nardil®)	↓	↔	↓↓↓↓	↔
Tranylcypromine (Parnate®)	↓↓	↔	↓↓↓↓	↔

From:Reite, Nagel & Ruddy, A Concise Guide to the Evaluation and Treatment of Sleep Disorders, 3rd Ed. APA Press, in press.

Drug	EEG sleep effects			Sedation
	Continuity	SWS	REM	
SSRIs				
Fluoxetine (Prozac®)	↓	↔↓	↔↓	±
Paroxetine*(Paxil®)	↓	↔↓	↓↓	±
Sertraline (Zoloft®)	↔	↔	↓↓	↔
Citalopram (Celexa®)	↓	↔	↓	**ND**
Fluvoxamine (Luvox®)	↓	↔	↓	**ND**
Others				
Bupropion (Wellbutrin®)	↓↔	↔	↑	↔
Venlafaxine (Effexor®)	↓	↓	↓↓↓	++
Trazodone (Desyrel®)	↑↑↑	↔↑	↓	++++
Mirtazapine (Remeron®)	↑↑↑	↑↑	↔	+++
Nefazodone (Serzone®)	↑	↔	↑	+

If not the result of a comorbid condition -

Does the insomnia complaint represent a Process S (homeostatic sleep drive) or Process C (circadian) problem?

Failure to recognize a circadian component leads to treatment failures and frustration

Process S: Homeostatic Sleep Drive

Non-REM sleep (especially Stage 3-4) – the process by which the brain reverses the neurometabolic effects of waking brain activity.

- Increases with increased time and intensity of preceding wakefulness
- Neurons in the VLPO serve to initiate and maintain sleep
- Purine nucleotide adenosine might serves as a "final common factor"
- Associated with synaptic "pruning and tuning" previous days learning

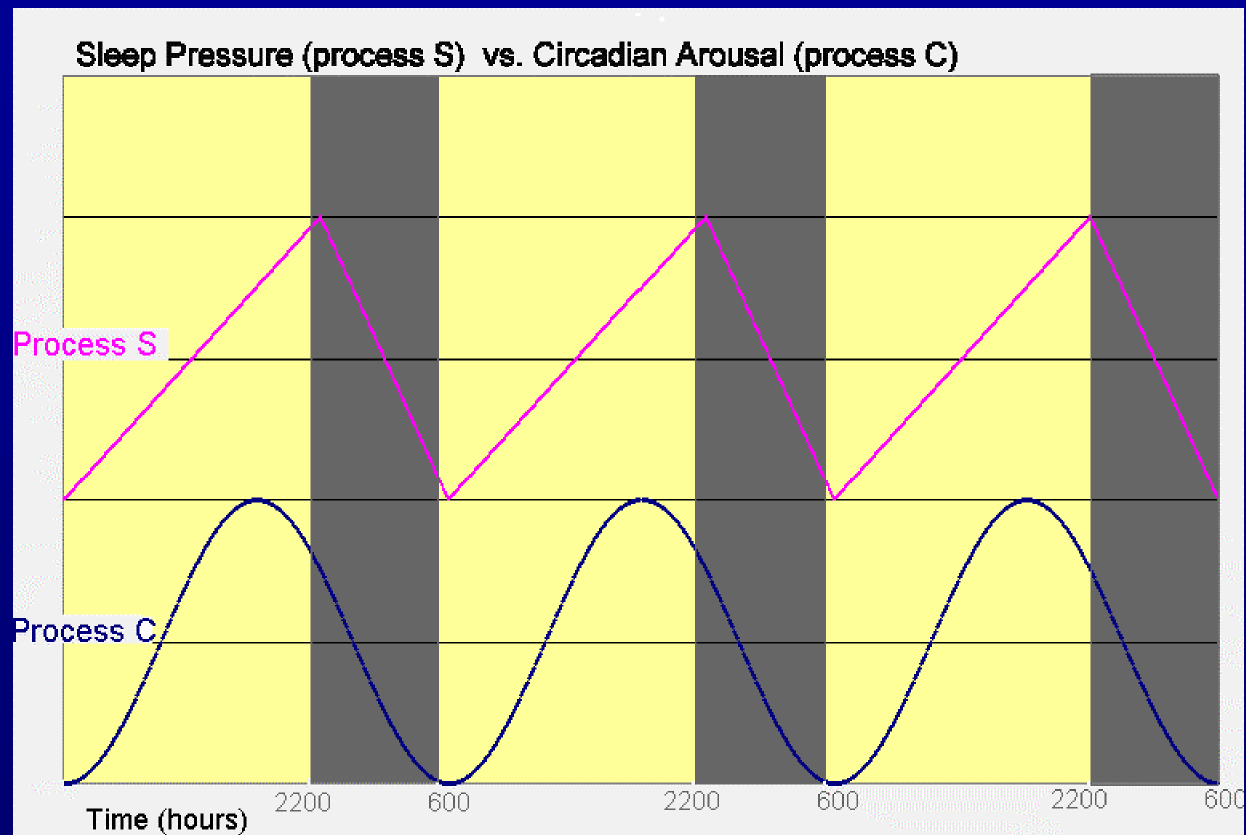
Process C: Circadian Wakefulness Drive

The circadian tendency to maintain alertness-

- maximally expressed in the late afternoon and early evening, and minimally expressed in the morning hours (e.g., 3:00-4:00 am) – closely related to body temperature rhythm.
- Controlled by light from retina to SCN via retino-hypothalamic tract
- mediated by melatonin and orexin/hypocretin

REM cycle – q90min/24hours a day – but role of REM sleep uncertain

Process S & Process C



Common circadian rhythm disorders

Delayed sleep phase syndrome

- most common – usually familial/genetic causes
- Onset adolescence & early adulthood

Advanced sleep phase syndrome

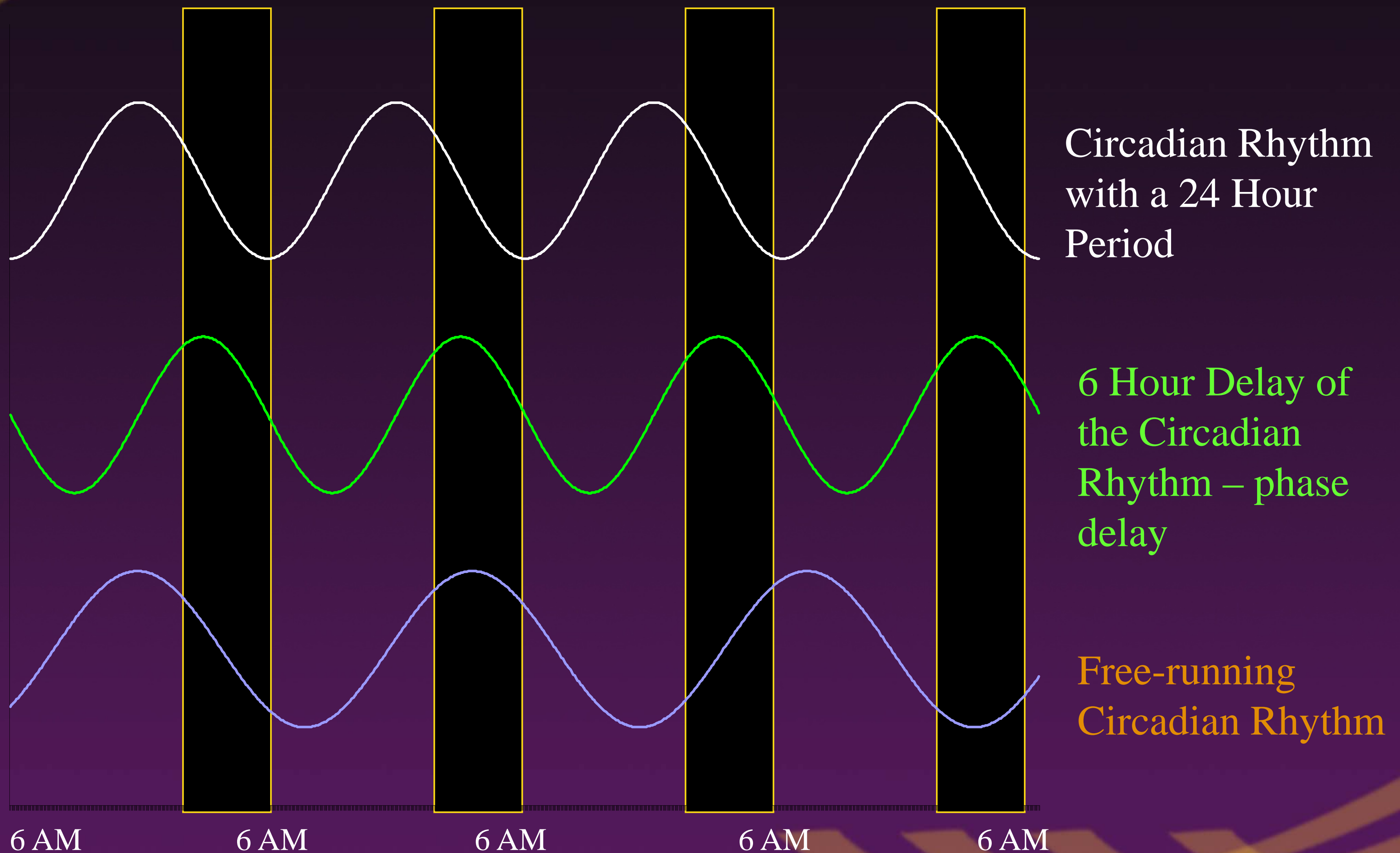
- Onset late adulthood
- Both familial and age related causes

Non-24 hour sleep wake rhythm

- Seen in 50% of blind persons
- Also seen in developmental disorders

All masquerade as "insomnia"

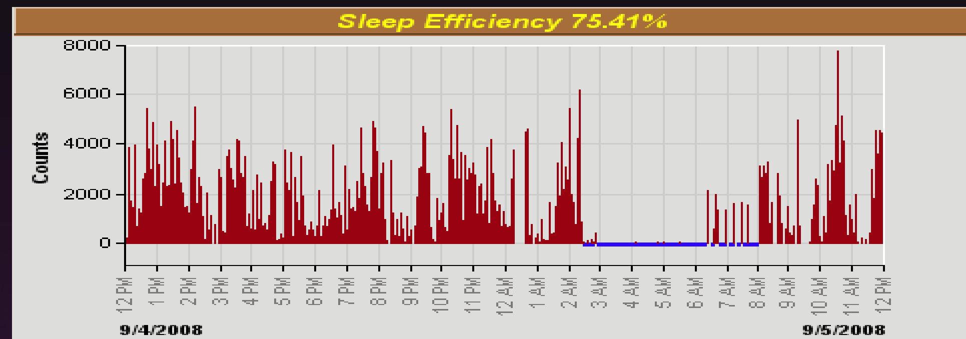
Alterations in the Circadian Rhythm

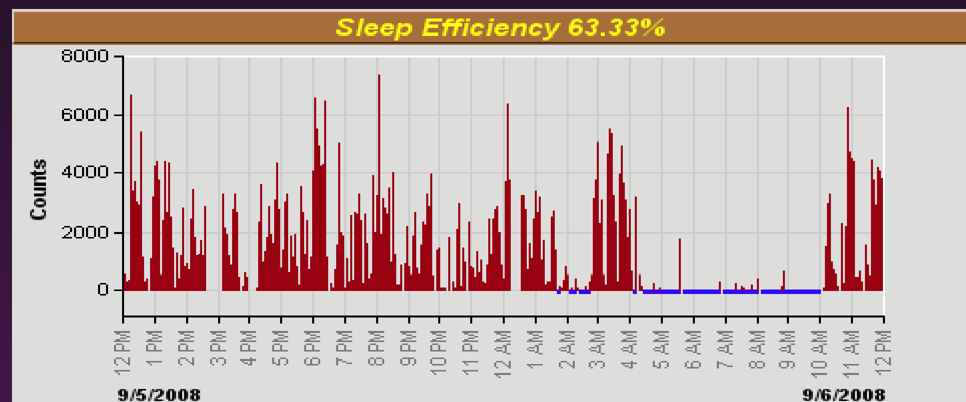


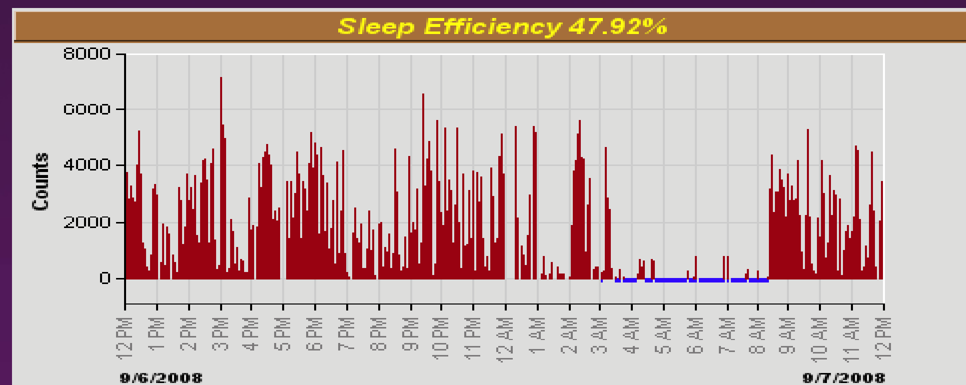
Diagnosis of circadian rhythm disorders

- History
- Actigraphy
- Polysomnography usually not helpful
- DLMO ay be available

Actigraphy in DSPD







Treatment of circadian rhythm disorders

- Light treatment at appropriate time based upon phase response curve
- Appropriately timed melatonin
- Strict sleep schedule – no more than 1 hour variation
- Limited use of hypnotics

If not circadian – is it a Process S disorder?

- Disturbance of Process S homeostatic sleep regulation may be due to altered brain function in both medical (e.g. fibromyalgia) and psychiatric (eg depression) disorders
- Process S also impaired in primary insomnia, conditioned insomnia, and sleep state misperception syndrome (paradoxical insomnia).

The Primary Insomnia, Conditioned Insomnia, Sleep State Misperception (Paradoxical Insomnia) Group – often termed "psychophysiological insomnia"

Primary Insomnia a DSM-4 diagnosis

- Difficulty initiating, maintaining, or non restorative sleep >1mo
- Causes significant daytime functional impairment
- Other med,, circadian causes ruled out
- Likely related to physiological hyperarousal

Conditioned arousal or "Learned" insomnia

- Starts with stressful situation impairing sleep
- Fear of going to bed because wont be able to sleep leads to hyperarousal
- May sleep normally in other places e.g. sleep lab

Sleep state misperception syndrome

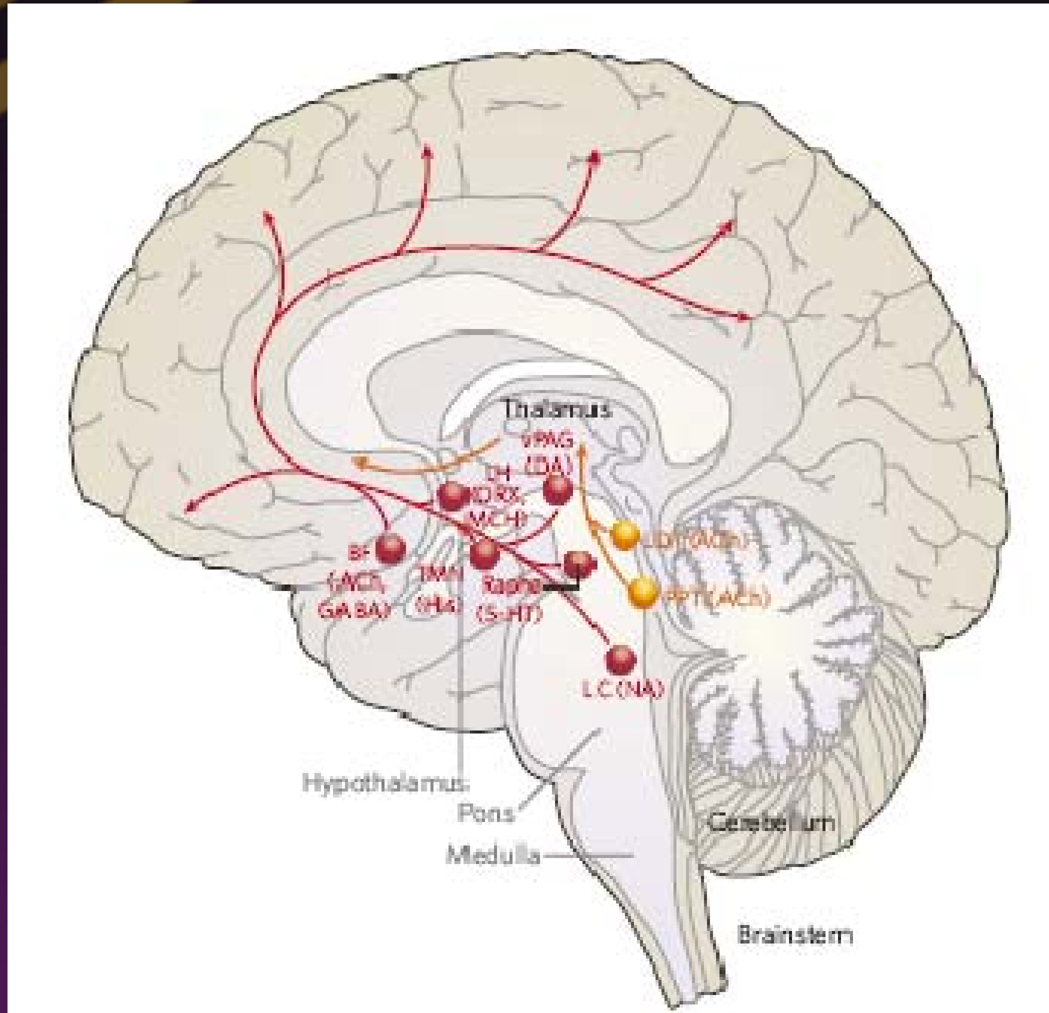
- Unaware of being asleep – increased fast activity in sleep EEG
- May have "normal" PSG in lab (yet complain of not having slept)
- Daytime impairment similar to primary insomnia
- Termed "paradoxical insomnia"

Treatments for this group will usually entail both behavioral (e.g. CBT) and pharmacological components

Pharmacological treatment may be targeted to increasing activity in GABAergic inhibitory systems, decreasing activity in ARAS arousal systems, or both.

Brief review of arousal and inhibitory sleep control systems may be useful.

Arousal control systems



Saper et al. Nature 437:27, 2005

BF basal forebrain

LC locus coeruleus

LDT laterodorsal tegmental

LHA lateral hypothalamus

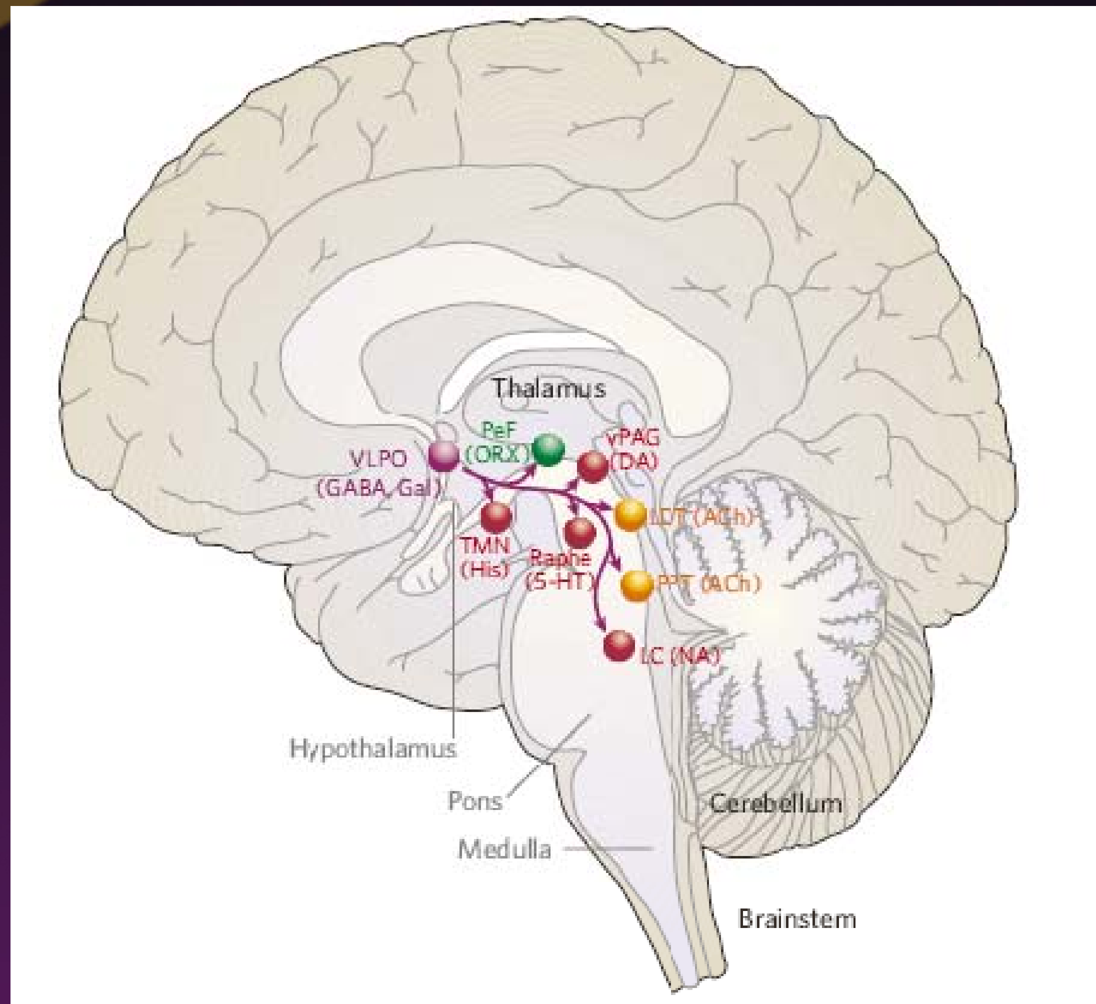
PPT pediculopontine

TMN tuberomammillary

Increased ARAS activity increases arousal - e.g. sympathomimetics

Decreased ARAS activity decreases arousal - e.g. H1 & 5HT2a antagonists

Sleep control systems



VLPO ventrolateral preoptic nucleus

ORX orexin neurons

GABAergic hypnotic agents promote VLPO activity – BZs, zolpidem, zaleplon, eszopiclone

Saper et al. Nature 437:27, 2005

Histamine and wake/sleep regulation

Three receptor subtypes:
H1 & H2 widespread in brain as well as peripheral – postsynaptic and promote excitatory neurotransmission & wakefulness – antagonists promote sleep (mirtazapam, doxepin, (low dose) diphenhydramine)

H3 presynaptic in brain – activation decreases histamine release and promotes sleep – antagonists promote wakefulness

Histaminergic neurons in tubero-mammilary nucleus (TMN) of post hypothalamus

Hypocretin neurons project to and regulate TMN histamine production via hcrt-2 receptor subtype

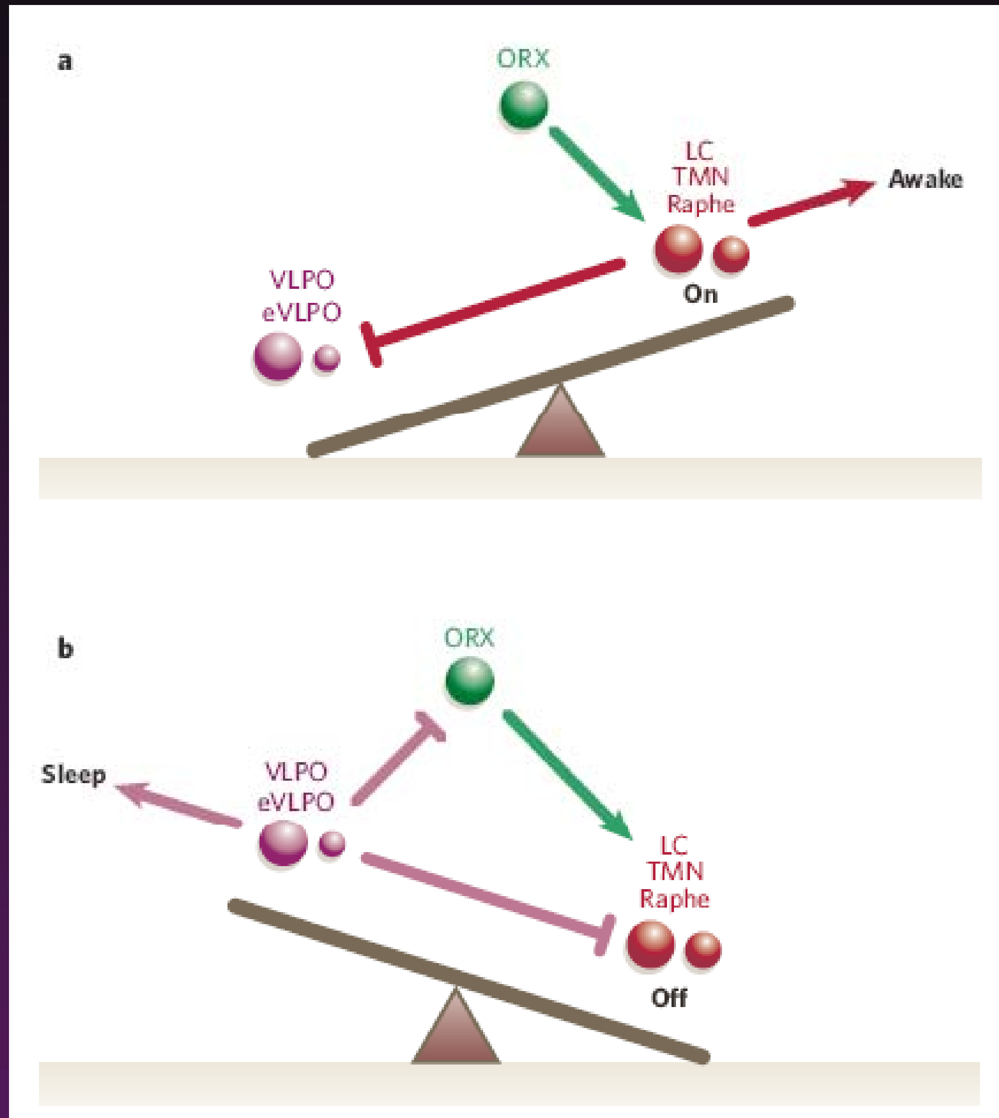
CSF histamine decreased in narcolepsy & primary hypersomnia

Kanbayashi et al Sleep 32:181, 2008 Nishino et al Sleep 32:175. 2008

Orexin modulated flip-flop switch

Awake state

Sleep state



Saper et al. Nature 437:27, 2005

General treatment considerations

- Treat any comorbid medical or psychiatric condition
- Independent treatment of insomnia component may also be necessary

Medications used for insomnia bind to different CNS receptors

Drug	Class	CNS receptor target(s)
Diphenhydramine[1], doxylamine[1]*, chlorpheniramine[1]*	Antihistamines[1]	H_1
Amitriptyline[1]*, doxepin[1]*	Tricyclic antidepressants[1]	5HT, NE, H_1; also DA, Ach
Trazodone[1]*	Antidepressant chemically unrelated to tricyclics, tetracyclics, and MAOIs[1]	$5HT_2$; also α-adrenergic and modest H_1 blockade; weakly blocks presynaptic α_2-adrenergic receptors and strongly inhibits postsynaptic α_1 receptors
Olanzapine[1]*	Atypical antipsychotic (structurally similar to the benzodiazepines)[1]	$5HT_{2A}$ antagonism, as well as activity at other 5HT receptors; antimuscarinic, antihistaminic and α_1-adrenergic antagonist properties
Quetiapine[1]*	Atypical antipsychotic[1]	$5HT_{2A}$ antagonism; potent, reversible D_2 receptor antagonist; H_1 and α_1-adrenergic antagonist
Ramelteon[1]	Melatonin receptor agonist[1]	MT_1, MT_2
Triazolam[2], temazepam[2] estazolam[2], quazepam[2] flurazepam[2]	Benzodiazepines[2]	$GABA_{\alpha}$ (nonselective)
Zaleplon[2], eszopiclone[2], zolpidem[2], zolpidem extended-release[2]	Nonbenzodiazepine benzodiazepine receptor agonists (BzRAs)[2]	$GABA_{\alpha 1}$ (preferential)

Please see important safety information on slides 1& 2.

*Not FDA-approved for insomnia.

1. Buysse DJ, et al. In: Kryger MH, et al, eds. *Principles and Practices of Sleep Medicine*. 4th ed. 2005:452-467.
2. Mendelson WB. In: Kryger MH, et al, eds. *Principles and Practices of Sleep Medicine. 4th ed.* 2005:444-451.

Other sleep agents

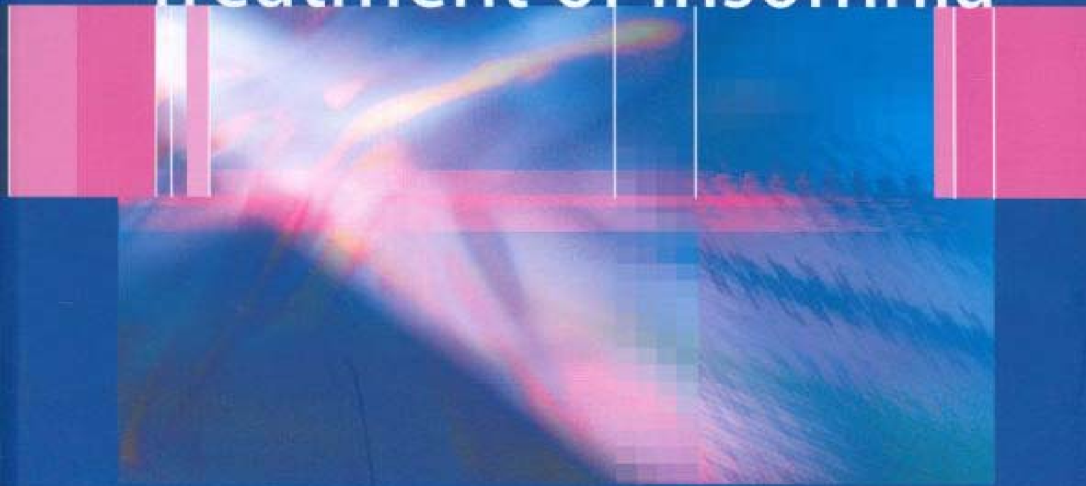
- Tiagabine (Gabitril) inhibits GABA reuptake, approved for seizure control only – improved sleep in chronic pain (Todorov et al, 2005), increases SWS in elderly
- Gaboxadol increases SWS at 15mg – unique extrasynaptic GABAa agonist
- Sodium oxybate (Xyrem) – approved for narcolepsy – increases Stage 3-4 sleep – considerable potential risk –– may be useful in fibromyalgia*
- Silenor (doxepin 3-6mg) being released by Somaxon and P&G

- *Sharf et al J Rheumatol 35(4):1070, 2003

Copyrighted Material

Michael L. Perlis
Carla Jungquist
Michael T. Smith
Donn Posner

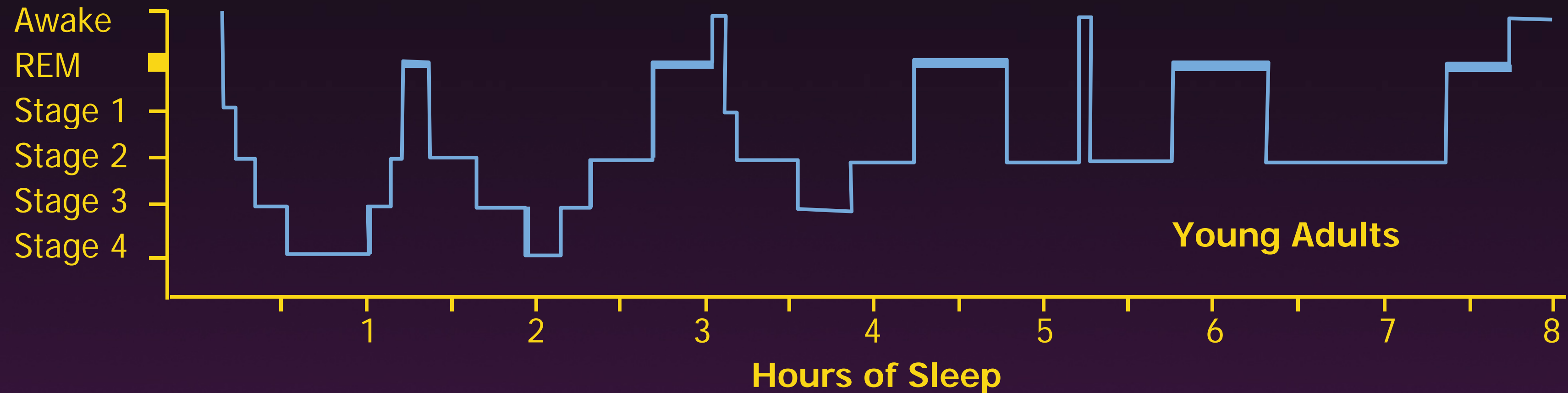
Cognitive Behavioral Treatment of Insomnia

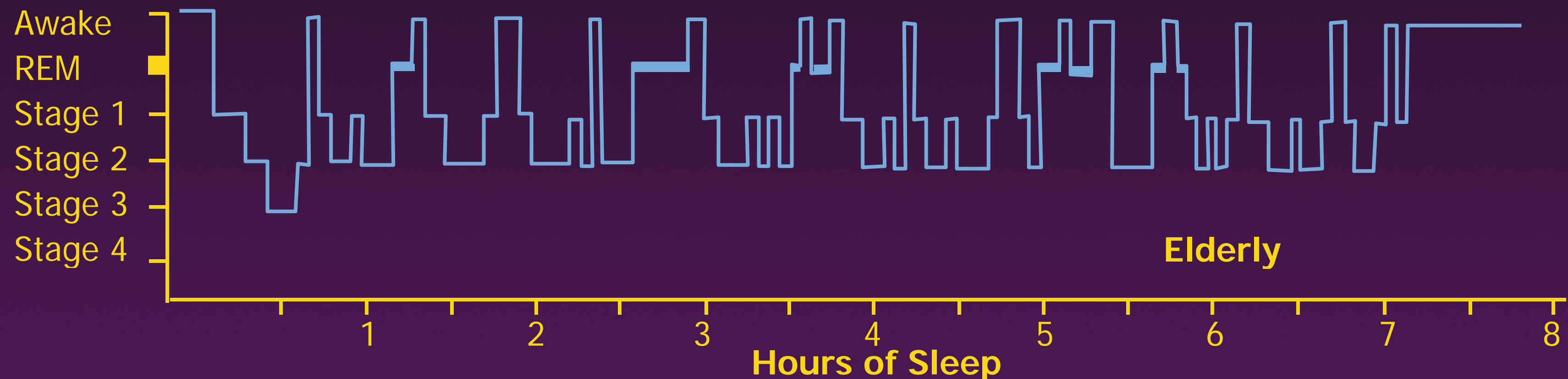


A Session-by-Session Guide

Copyrighted Material

Comparison of Sleep Cycles in Young Adults and the Elderly





The elderly tend to have less stage 3 and 4 sleep and develop advanced phase sleep syndrome (go to bed early, wake up early), while the young tend to have delayed phase shift syndrome (go to bed late, wake up late).

Neubauer DN. *Am Fam Physician*. 1999;59:2551-2558.

Millman RP, Working Group on Sleepiness in Adolescents/Young Adolescents. Pediatrics. 2005;115:1774-1786.

Sleep and aging

- Process S – 50% loss of VLPO neurons with age
- Process C – decreased melatonin production with age
- Aging impairs ER quality control unfolded protein response (UPR) to sleep deprivation & fragmentation – leading to impaired folding*
- Does sleep loss, deprivation, and fragmentation in the elderly contribute to many of the symptoms attributed to "normal" aging – e.g. cognitive difficulties, inflammation, weight/diabetes?
- Where do we stand with respect to long term hypnotic use to improve sleep in otherwise healthy older adults?
- If we have safe and effective hypnotic agents why should they be withheld?
- *Naidoo et al, J. Neurosci 28:6539, 2008

Overall Summary

- Sleep complaints should be taken seriously
- Accurate differential diagnosis important
- Sleep studies usually for EDS disorders
- Sleep studies usually not needed for insomnia
- Safe and effective treatments available for insomnia
- Long term treatment may be necessary for insomnia as in depression
- Don't neglect behavioral (eg CBT) treatments