

Treatment of Insomnia


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Presentation Objectives:

- ◆ Briefly review function of sleep and neurotransmitters associated with promotion of sleep
- ◆ Review current and newly approved therapies for the treatment of insomnia – including mechanisms of action and pharmacology
- ◆ Discuss agents in clinical development for the potential treatment of insomnia and their mechanisms of action

Function of Sleep

“If sleep does not serve an absolutely vital function, then It is the *biggest* mistake the evolutionary process ever made.”



A. Rechtschaffen

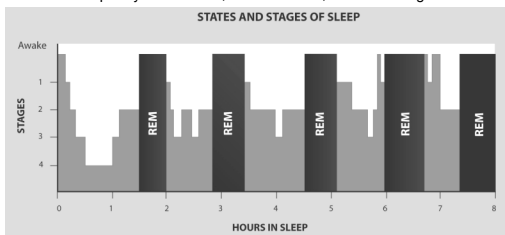
Function of Sleep

- 👁️ **Restoration and recovery**
 - Sleep serves to reverse and/or restore biochemical and / or physiological processes degraded during prior wakefulness
- 👁️ **Energy conservation**
 - 10% reduction of metabolic rate below basal level
- 👁️ **Memory consolidation**
- 👁️ **Thermoregulation**
- 👁️ **Homeostasis**

The Sleep Cycle

Alternating states and stages of sleep that occur over an 8-hour time period:

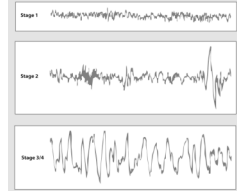
- **NREM:** Non-Rapid Eye Movement; Stages 1-4; 75% of the night
- **REM:** Rapid Eye Movement; Dreams occur; 25% of the night



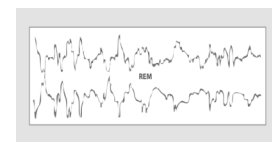
During the Sleep Cycle

- ◆ Brain waves represent different stages of sleep.

NREM Stages of Sleep

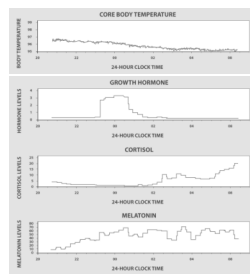


REM Sleep



During the Sleep Cycle (cont.)

- ◆ Body temperature lowers
- ◆ Hormone levels rise and fall



Sleep needs vary over the life cycle.

Newborns/Infants	0 - 2 months: 2 - 12 months:	10.5-18 hours 14-15 hours
Toddlers/Children	12 mo - 18 mo: 18 mo - 3 years: 3 - 5 years: 5 - 12 years:	13-15 hours 12-14 hours 11-13 hours 10-11 hours
Adolescents	On Average:	9.25 hours
Adults/Older Persons	On Average:	7-9 hours

Sleep patterns and characteristics change over the life cycle.

Newborns/Infants	More active in sleep; 50% REM; several periods of sleep; need naps
Toddlers	Sleep begins to resemble adult patterns
Children	Experience more deep sleep
Adolescents	Shift to later sleep-wake cycle; experience daytime sleepiness
Adults	Need regular sleep schedule to obtain sufficient, quality sleep
Older Adults	More likely to have medical problems; sleep disrupters & disorders; sleep less efficiently

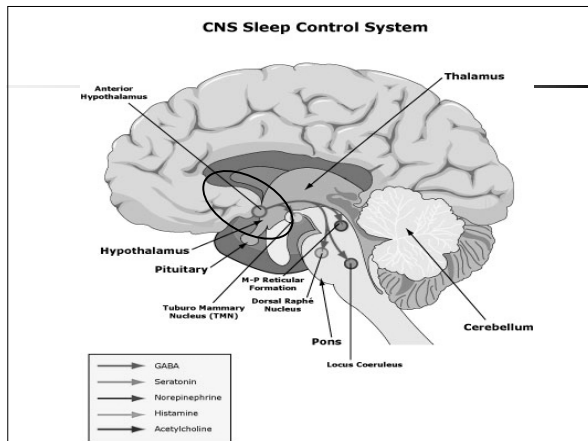
Sleep Promoting CNS Neurotransmitters

◆ GABA (inhibitory amino acid)

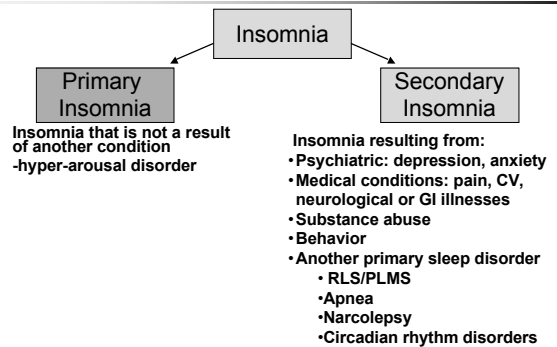
- Ventral Lateral Pre-Optic Nucleus (VLPO) within anterior hypothalamus -- "command & control center" for sleep
 - Inhibitory connections to thalamus, descending projections inhibit cell bodies and dendrites of serotonin, norepinephrine, histamine, acetylcholine-producing inter-neurons
 - Role: Initiation and maintenance of sleep spindles and SWS

◆ Melatonin (hormone of darkness)

- Secreted from pineal gland during darkness/ indirectly feedbacks to SCN
- High levels secreted prior to sleep
- Levels low during wakefulness

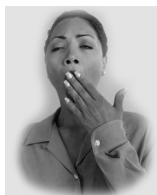


Conditions of Insomnia:



Insomnia Prevalence

- ◆ Over 30% of American adults experience occasional insomnia; 10% on a chronic basis
- ◆ Those most at risk:
 - Women
 - Older adults
 - Pts w/ psychiatric disorders
 - Pts w/ medical disorders (pain syndromes, asthma, CV)
 - 2nd / 3rd shift workers



Causes and Types of Insomnia

Cause	Type	Duration
Change: acute illness; jet lag, emotional stress Stress: loss of loved one or job	Acute	Transient: few nights a week Short Term: 1 – 2 weeks
Severity of physical, medical, psychiatric or environmental conditions	Chronic	> 1 month (at least 3 nights a week)
Not associated with underlying or known cause.	Primary	> 1 month
Chronic stress, hyperarousal, or behavioral conditioning may contribute.	Chronic	

Reduced Total Sleep Time Impacts Health & Next-day Functioning

- Increased number (4.5-fold) of serious accidents or injuries²
 - 200,000 MVA each year caused by drowsiness (US DOT)
- Impaired alertness & memory
- Impaired psychomotor performance
- Increased healthcare utilization³ and absenteeism

¹Mahowald et al. *Sleep Medicine*. 2000; 1: 179. ²Balter et al. *J Clin Psychiatry*. 1992; 53 Suppl: 34
³Simon et al. *Am J Psychiatry*. 1997; 154: 1417

Treatment of Insomnia

- ◆ Behavioral Interventions – CBT (Cognitive Behavioral Therapy)
- ◆ Pharmacological
 - OTCs (Over-The-Counter)
 - Diphenhydramine
 - Doxylamine
 - L-Tryptophan
 - Melatonin
 - Alcohol
 - Plant based herbals – Valerian, Chamomile, Hops, Lemon Balm, Lavender, Ylang Ylang, Melissa, Passion Flower, Kava Kava
 - Barbiturates
 - Chloral Hydrate
 - Antidepressants
 - GABA-A Receptor Allosteric Modulators
 - Benzodiazepines
 - Non-Benzodiazepines
 - Melatonin Receptor Agonists

Antidepressants

- ◆ Tricyclic Antidepressants (TCAs)
- ◆ SSRIs/SNRIs
- ◆ Trazodone

TCAs (Not FDA approved for hypnotic use)

- ◆ Tertiary amines (amitriptyline, doxepin, imipramine..) greater sedation than secondary amines (desipramine, nortriptyline, protriptyline)
- ◆ TCAs decrease REM sleep & prolong REM latency
- ◆ May increase TST but may worsen periodic limb movements (PLMs)/ specific agents may prolong SWS
- ◆ MOA: Block 5-HT and NE reuptake/ anticholinergic and antihistaminic activity
- ◆ Weak alpha-1 blockade results in orthostatic hypotension
- ◆ TCAs have poor sleep onset activity
- ◆ Acute withdrawal can cause REM rebound

SSRIs/SNRIs (Not FDA approved for hypnotic use)

- ◆ Antidepressant drugs can both improve and disturb sleep, as well as have effects on waking function.
- ◆ Evaluation of the effects of these drugs on sleep and wakefulness is complicated by the fact that many individuals with depression typically have:
 - disturbed sleep
 - daytime fatigue
 - sleepiness
 - somatic complaints
 - decreased cognitive and psychomotor functioning
- ◆ PSG (polysomnogram) and subjective patient reports of sleep do not always correlate

Schweitzer P. *Principles and Practice of Sleep Medicine*, 3rd Edition, 441.

Effects of Newer Antidepressants on Sleep and Waking Behavior

- ◆ Most SSRIs ↑ wakefulness, ↓ TST (no data on sertraline and no change in TST or W with citalopram)
- ◆ Insomnia incidence in SSRI treated patients ranges from 5-16%
- ◆ Daytime sedation incidence in SSRI treated patients ranges from 2-26%
- ◆ Venlafaxine (5HT/NE reuptake inhibitor): similar to SSRIs, insomnia 8%, sedation 3-31%
- ◆ Bupropion (DE/NE reuptake inhibitor): insomnia 5-19%

Trazodone (Not FDA approved for hypnotic use)

- ◆ Produces sedating effects via antagonistic effects at H1 & 5-HT₂ receptors
- ◆ Low doses (50-100mg) often used as adjunct to SSRI treatment
- ◆ Men must be counseled about priapism (persistent and painful erections)
- ◆ Severe postural hypotension can occur due to antagonism of alpha-1 receptors
- ◆ Long T_{1/2} may lead to daytime sedation
- ◆ Recent concerns about *administration with strong inhibitors of CYP3A4 (i.e.. itra-, ketoconazole)*

Select Benzodiazepines*

Drug	Usual adult oral dose (mg)	T _p (hrs)	T _{1/2} (hrs)	Protein binding (%)	Urinary excretion, unchanged (%)
Estazolam (Prosom®)	1-2	2	8-28	93	< 5
Flurazepam (Dalmane®)	15-30	0.5-1 (7.6-13.6) ¹	2-3 (47-100) ¹	97	< 1
Quazepam (Doral®)	7.5-15	2 (1-2)	41 (47-100) ¹	> 95	Trace
Temazepam (Restoril®)	15-30	1.2-1.6	3.5-18.4 (9-15)	96	0.2
Triazolam (Halcion®)	0.125-0.5	1-2	1.5-5.5	78-89	2

¹N-desalkylflurazepam, active metabolite

*Not all BZDs have been approved by the FDA for insomnia

Facts and Comparisons, eFacts

Benzodiazepines

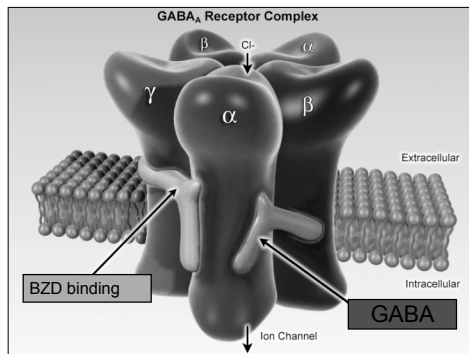
- ◆ BZDs suppress SWS and REM sleep as well as prolong REM latency
- ◆ Stage 2 sleep is prolonged with an increase in spindle density, sleep latency is shortened, TST is increased
- ◆ Flurazepam has long elimination half-life of up to 100 hours
- ◆ Shortest acting is triazolam with half-life of 1-5.5 hours
- ◆ Acute withdrawal is associated with decreased TST as well as REM & SWS rebound

MOA of BZDs and Non-BZDs: The Role of GABA_A Receptors

- ◆ The GABA_A receptor is a pentameric complex
- ◆ Currently, there have been 7 subunit families comprising at least 18 subunits in the CNS:
 - α_{1-6} , β_{1-3} , γ_{1-3} , δ , ϵ , θ , ρ_{1-3}
- ◆ The major subtype combination (60% of all GABA-A receptors) consist of $\alpha_1\beta_2\gamma_2$

Mohler H et al. J Pharmacology and Experimental Therapeutics, 300: 1:2-8.

MOA and GABA_A Receptor Complex



Non-Benzodiazepines (GABA-A Receptor Allosteric Modulators)

Drug & class	Half Life (hr)	Dose (mg)	Indications	Side Effects	Contraindications and Drug Interactions
Eszopiclone (Lunesta) cyclopyrrolone	5-7	1-3	Tx of insomnia	Unpleasant taste, dry mouth, drowsiness, dizziness	Drugs that inhibit CYP3A4, etoh, olanzapine
Zolpidem (Ambien, Ambien CR) imidazopyridine	3	5-10; 6.25-12.5 (CR)	Short term Tx of insomnia (Tx of insomnia – CR)	Drowsiness, dizziness, occasionally amnesia	Possibly drugs that inhibit CYP3A4, etoh
Zaleplon (Sonata) pyrazolopyrimidine	1	5-20	Short term Tx of insomnia (SL)	Drowsiness	Possibly drugs that inhibit CYP3A4, etoh, imipramine, thioridazine

Adapted from Silber M, NEJM 353:8: 806.

Non-benzodiazepines, cont.

- ◆ Zolpidem (Ambien®) / Zaleplon (Sonata®)
 - Approved for short term use (7-10 days)
 - Reassess in 2-3 weeks
 - Decrease sleep latency and increase TST (zolpidem)
- ◆ PK
 - T_{1/2} = 2.5 hrs for 10 mg Zolpidem; inactive metabolites
 - CYP3A4 main route of metabolism; minor renal elimination
 - T_{1/2} = 1 hr for 10 mg Zaleplon; elderly dose = 5 mg
- ◆ Efficacy
 - Zolpidem: longest nightly use 5 weeks/ 8-12 weeks intermittent use
 - Zaleplon: 30 days nightly use
 - Can be taken late at night without next-day effects

Non-benzodiazepines (cont)

- ◆ Safety: Minimal changes in sleep architecture
 - Minimal next-day effects
 - No improvement in middle insomnia (sleep maintenance).
- ◆ Adverse Events
 - Zolpidem: common ADR's: drowsiness, headache, dizziness
 - Amnesia more common at doses > 10mg
 - No significant rebound insomnia (5 week study)
 - Reports of abuse in those with hx of substance abuse
 - Rare reports of hallucinations at recommended doses

Non-benzodiazepines (cont)

- ◆ **Ambien CR™** (zolpidem tartrate extended release tablets)
- Approved Sept 6, 2005 – indicated for the treatment of insomnia (sleep onset/maintenance)
- ◆ Zolpidem CR consists of a coated two-layer tablet:
 - One layer releases drug immediately
 - Another layer that allows slower release of additional drug
- ◆ Available in 6.25 mg and 12.5 mg strengths
- ◆ The clinical trials were both 3 weeks in duration (assessment of SL and maintenance were performed after 2 weeks of treatment)

Ambien CR press release – Sept 6, 2005
Ambien CR package insert

Non-benzodiazepines (cont)

- ◆ **Eszopiclone (Lunesta™): non-benzodiazepine cyclopyrrolone**
- ◆ **Indications: Sleep onset and sleep maintenance insomnia –Approved for long term use**
- ◆ **Eszopiclone = (S)-Zopiclone, contains pharmacologic activity of racemate**
 - Available since 1987
 - Racemic (R,S)-zopiclone (Imovane, Zimovan, Zimovane)
 - Currently marketed in over 85 countries at doses of 5-10 mg

Non-benzodiazepines (cont)

- ◆ **Eszopiclone: PK**
 - T_{1/2} = 5-7 hrs for 3 mg eszopiclone; active metabolite, but to lesser degree than parent compound
 - CYP3A4 main route of metabolism, 2E1 minor path
 - T_{max} = 1 hr for 3 mg; elderly dose = 1-2 mg
- ◆ **Efficacy**
 - Longest study was 2-6 month double blind randomized studies of eszopiclone 3 mg vs. placebo with a 6 mo open label extension
 - Decrease in sleep latency, increase in TST
 - Minimal changes to sleep architecture
- ◆ **Adverse Events & Safety**
 - Unpleasant taste, dry mouth, dizziness and drowsiness
 - No significant PSG rebound after 44 nights of therapy nor after 180 nights with 3 mg dose
 - Abuse study performed with s-isomer

Ramelteon (Rozerem™)

- ◆ Ramelteon was approved by the FDA in July 2005 for the treatment of insomnia characterized by difficulty with sleep onset
- ◆ Ramelteon specifically targets the MT1 and MT2 receptors in the brain, believed to be critical in the regulation of the body's sleep-wake cycle
- ◆ **PK**
 - T_{1/2} = 2-5 hours, dose is 8 mg 30 minutes before going to bed
 - Metabolized by CYP1A2, CYP2C and CYP3A4 minor paths
 - Should not be used in severe hepatic impairment or with fluvoxamine, and used with caution in patients with moderate hepatic impairment
 - Do not take with a high fat meal

Ramelteon package insert.

Indiplon (Not FDA approved for hypnotic use)

- ◆ MOA: GABA-A Receptor Allosteric Modulator
- ◆ In development for insomnia (Neurocrine)
- ◆ IR and modified release (MR) indiplon are under investigation for both adults and elderly
- ◆ Indiplon is a pyrazolopyrimidine (same class as zaleplon)
- ◆ In a 35-day DB, parallel trial: 194 patients diagnosed w/ primary insomnia randomized to either 10 mg or 20 mg IR indiplon or placebo
- ◆ Primary end point: latency to persistent sleep (LPS) confirmed via PSG
- ◆ Results: 10-mg dose significantly reduced LPS by 28 minutes, compared with a mean latency of 37 minutes for placebo ($P < .002$). The 20-mg dose reduced LPS by 27 minutes ($P < .05$)
- ◆ Adverse events reported higher than placebo: somnolence and headache

APSS 2005 Abstract # 0683; APA 2005 Abstract #551

Gaboxadol (Not FDA approved for hypnotic use)

- ◆ MOA: GABA-A Receptor Allosteric Modulator - affinity for the $\alpha_4\delta$ GABA_A extrasynaptic receptors (located in cortex, thalamus, and limbic system)
- ◆ In development for insomnia (Merck & Lundbeck)
- ◆ Several phase III studies are currently underway.
 - 8 week to 12 month chronic insomnia duration studies

Low Dose Doxepin – SO-101 (Not FDA approved for hypnotic use)

- ◆ MOA: Inhibits serotonin and norepinephrine reuptake, anticholinergic and antihistaminergic (Tertiary amine TCA)
- ◆ In development for insomnia (Somaxon)
- ◆ Several phase III studies are currently underway.
 - 8 week to 12 month chronic insomnia studies

Other Compounds/Mechanisms (Not FDA approved for hypnotic use)

- ◆ Other GABA-A Receptor Allosteric Modulators
 - Higher selectivity for different alpha subtypes
- ◆ GABA Transport Inhibitor (GAT-1 antagonist/GABA reuptake inhibitor)
 - Tiagabine (Gabatril®) (Cephalon) – in phase II development
- ◆ Partial GABA agonists
- ◆ Other M1-M2 agonists
- ◆ Hypocretin/orexin receptor antagonists
- ◆ Selective Serotonin subtype receptor antagonists (5HT_{2A})
- ◆ Substance P antagonists
- ◆ Neurosteroids

Other Compounds/Mechanisms, cont.

(Not FDA approved for hypnotic use)

- H₃ receptor agonists
 - H₃ receptor agonists have a sedative effect
 - H₃ autoreceptors modulate activity of histaminergic neurons
- Selective H₁ receptor antagonists
 - Could induce sedative effect without side effects associated with OTC antihistamines

Conclusions

- ◆ **The function and mechanisms of sleep are complex**
- ◆ **Insomnia may be a symptom of another illness, may co-exist with another illness or exist alone**
- ◆ **Insomnia impacts psychiatric and medical illness and next-day functioning**
- ◆ **Sleep hygiene should always be cornerstone of treatment**

Conclusions

- ◆ **Barbiturates & BZDs change sleep architecture; withdrawal can ppt rebound effects**
- ◆ **Non-BZDS are safer, minimal next-day effects, but most are approved for short term use and best for sleep onset insomnia**
- ◆ **The wide array of compounds in current development appear promising for the treatment of chronic insomnia**

Information on sleep and sleep disorders

- ◆ American sleep disorders association
(<http://www.asda.org>)
- ◆ The national sleep foundation
(<http://sleepfoundation.org>)
- ◆ Sleep home pages
(www.sleephomepages.org/)
- ◆ American academy of sleep medicine (AASM)
(<http://www.aasmnet.org>)
- ◆ Associated professional sleep societies (APSS)
(<http://www.apss.org>)