

# INSOMNIA

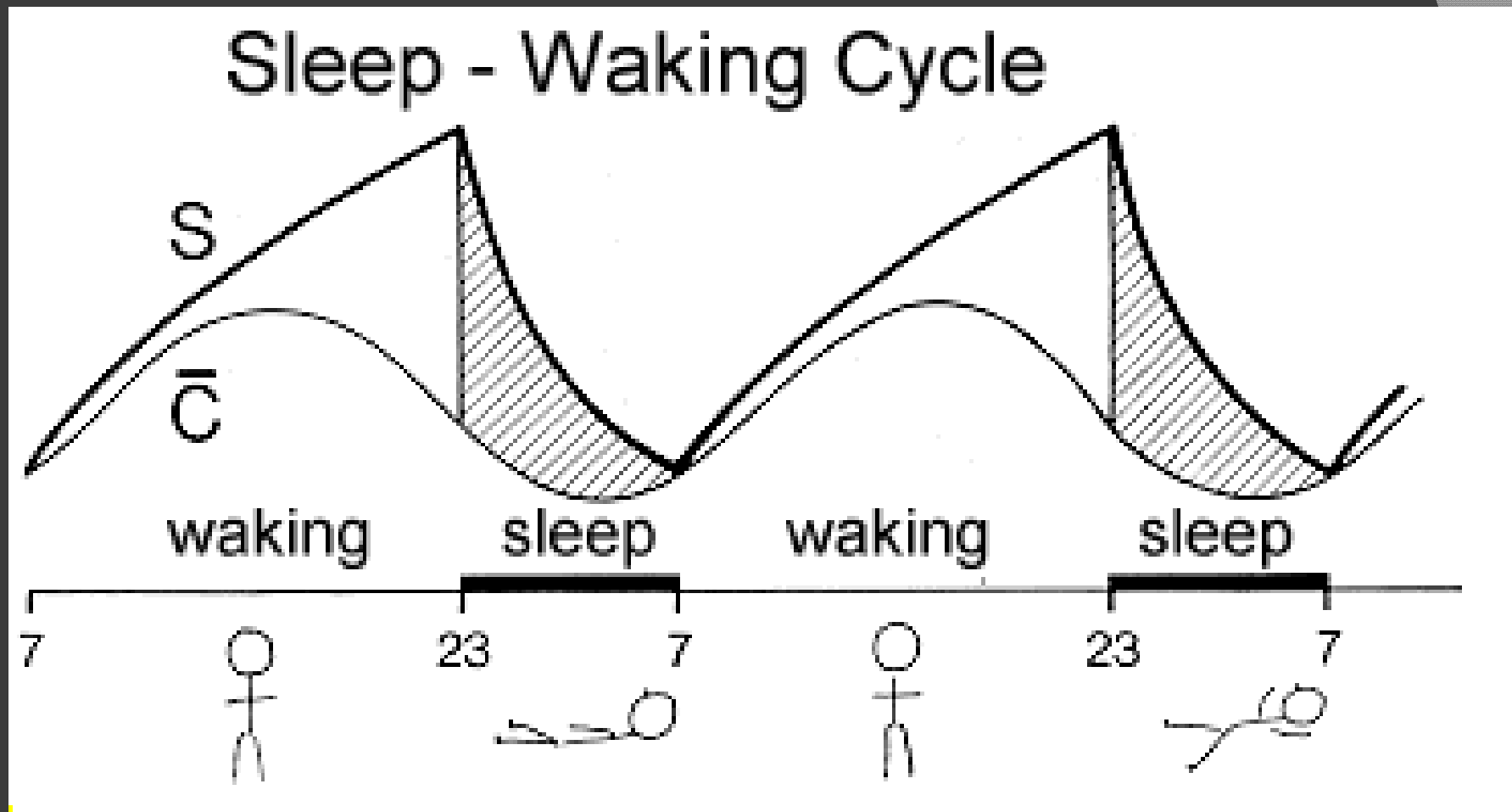
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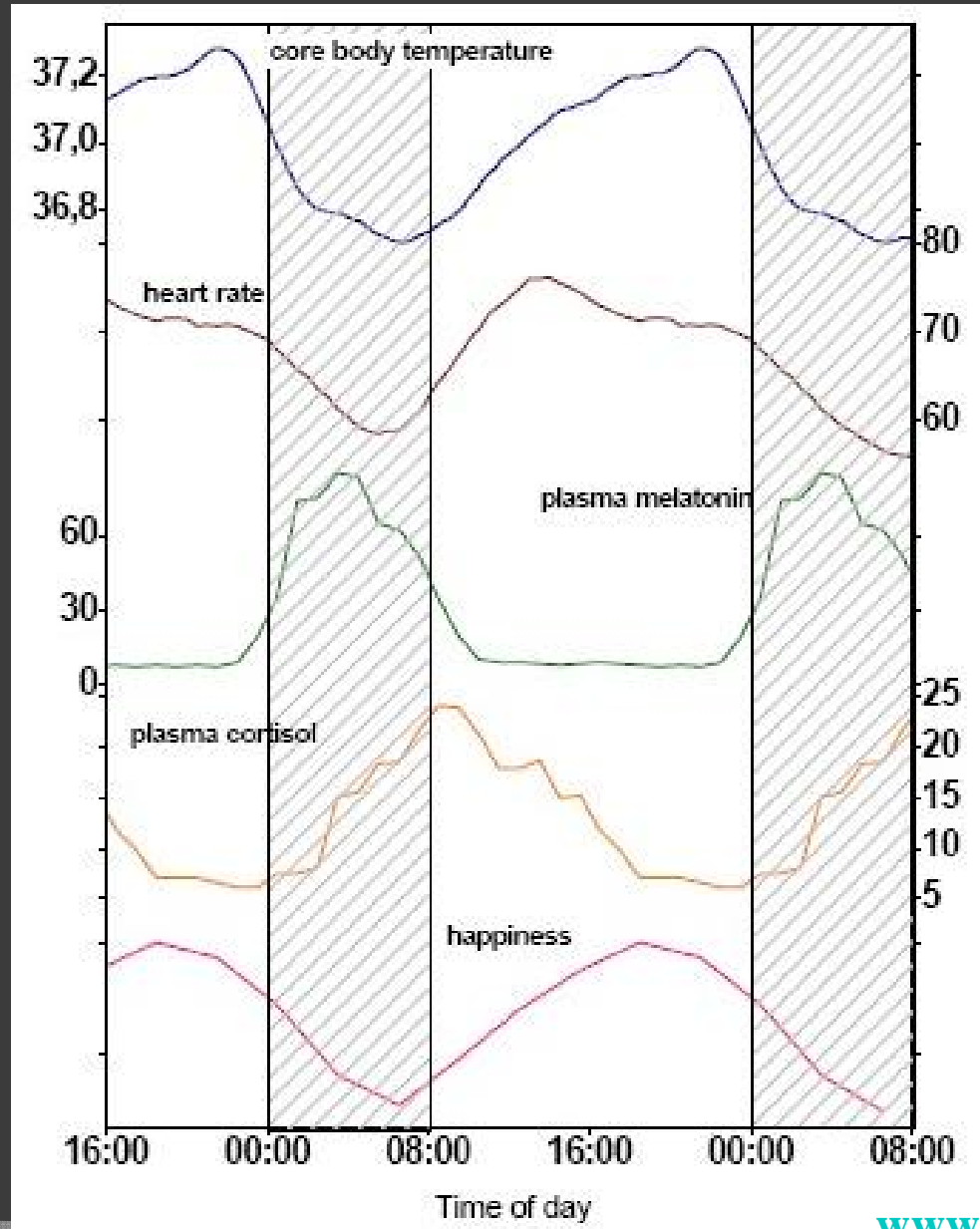


# OBJECTIVE

- ž Pathogenesis
- ž Prevalence
- ž Impact
- ž Pharmacologic treatment
- ž Cognitive-behavioral therapy

# PHYSIOLOGY OF SLEEP





# DEFINITION OF INSOMNIA

- ž *The National Heart, Lung, and Blood Institute (NHLBI)* : Subjective patient complaint of difficulty falling asleep, difficulty staying asleep, poor quality sleep, or inadequate sleep despite adequate opportunity.
- ž **DSM-IV definition**
  - Difficulty initiating or maintaining sleep for at least 1 month
  - Nonrestorative sleep persisting for at least 1 month
  - Accompanied by clinically significant impairment in daytime functioning
- ž **Research criteria**
  - Sleep latency > 30 minutes
  - Sleep efficiency < 85%
  - Sleep disturbance > 3 times per week

# INSOMNIA

## ž Mild

- Almost nightly complaint of non-restorative sleep
- Associated with little or no impairment of social or occupational functioning

## ž Moderate

- Nightly complaints of disturbed sleep
- Mild to moderate impairment of social or occupational function

## ž Severe

- Nightly complaints of disturbed sleep
- Severe daytime dysfunction

# SLEEP PATTERNS IN INSOMNIA

- ž Sleep onset insomnia
  - Difficulty falling asleep
  - Longer time to sleep onset
- ž Sleep maintenance insomnia
  - Difficulty staying asleep
  - Frequent nocturnal awakenings
- ž Sleep offset insomnia
  - Waking too early in the morning
- ž Nonrestorative sleep
  - Fatigue despite adequate sleep duration

# DURATION OF INSOMNIA

- ž Transient insomnia: episodic
  - Acute illness
  - Jet lag
  - Shift change
- ž Short-term insomnia: few days to 3 weeks
  - Major life event
  - Substance abuse
- ž Chronic insomnia : longer than 3 weeks
  - Chronic illness
  - Psychiatric illness



# ACUTE INSOMNIA

- ž Resolves with the management of inciting factors
- ž Adjustment sleep disorder
  - Acute stress such as momentous life events or unfamiliar sleep environments
  - Increased SOL(sleep onset latency), increased awakenings and sleep fragmentation with poor sleep efficiency
  - More common in women and those with anxiety
- ž Jet Lag
  - Symptoms last longer with eastbound travel
  - Remits spontaneously in 2-3 days
  - More common in the elderly

# CHRONIC INSOMNIA

- ž Primary or Intrinsic
- ž Secondary or Extrinsic
- ž Causes
  - Changes in circadian rhythm, behavior, environment
  - Body movements in sleep
  - Medical, neurological, psychiatric disorders
  - Drugs

# PRIMARY/INTRINSIC INSOMNIA

## ž Idiopathic

- Starts early in childhood, rare but relentless course
- Rare disorders affect both genders
- CNS abnormalities, unknown etiology, etc.

## ž Sleep State Misinterpretation (5%)

- Underestimate of the sleep obtained
- Females affected more than males

## ž Psychophysiological insomnia (30%)

- Maladaptive sleep-preventing behaviors develop and progress to become dominant factors
- Females more than males

# SECONDARY/EXTRINSIC INSOMNIA

1. Circadian rhythm sleep disorder: sleep attempted at a time when the circadian clock is promoting wakefulness
  - Advanced sleep phase syndrome
  - Delayed sleep phase syndrome
  - Irregular sleep/wake patterns
  - Non-24 hour sleep/wake syndrome
  - Shift work sleep disorder
  - Short sleeper

2. Behavioral disorders: rooted behaviors that are arousing and not conducive to sleep

- Inadequate sleep
- Limit setting sleep disorder
- Nocturnal eating/drinking syndrome
- Sleep onset association disorder

3. Environmental factors

- Environmental sleep disorder
- Food allergy insomnia
- Toxin-induced sleep disorder

#### 4. Movement disorders

- Periodic limb movement disorder(5%)
- Restless legs syndrome(12%)
- Rapid eye movement sleep behavior disorder

#### 5. Medical Disorders: Respiratory

- Altitude insomnia
- Central alveolar hypoventilation syndrome
- Central apnea syndrome
- Chronic obstructive pulmonary disease
- Obstructive sleep apnea syndrome (4-6%)
- Sleep-related asthma

## 6. Medical: Cardiac

- Nocturnal myocardial ischemia

## 7. Medical: GI

- Peptic ulcer disease
- Gastroesophageal reflux disease (GERD)

## 8. Medical: Musculoskeletal

- Fibromyalgia
- Arthritis

## 9. Medical: Endocrine

- Hyperthyroidism
- Cushing's disease
- Menstrual cycle association
- Pregnancy

## 12. Pharmacological causes

- Alcohol dependent sleep disorder
- Hypnotic dependent sleep disorder
- Stimulus dependent sleep disorder
- Medications
  - B-blockers
  - Theophylline
  - L-dopa



## ž **Medications**

- ž Antidepressants
- ž Bronchodilators
- ž CNS stimulants
- ž Corticosteroids
- ž Decongestants
- ž Diuretics
- ž Thyroid medication
- ž Other – Alcohol, Caffeine, analgesics with caffeine, Nicotine

## 10. Medical: Neurological

- Cerebral degeneration disorder
- Dementia
- Fatal familial insomnia
- Parkinson's disease
- Sleep related epilepsy
- Sleep related headaches

## 11. Medical: Psychiatric

- Alcoholism
- Anxiety disorders
- Mood disorders
- Panic disorders
- Psychosis
- Drug dependency

# EPIDEMIOLOGY OF INSOMNIA

- ž 30-50% of American adults experience insomnia during a 1 year period
- ž Prevalence of chronic/severe insomnia is 10%
- ž 49% of adults surveyed were dissatisfied with their sleep > 5 nights per month
- ž 50% of patients presenting to primary care physicians experience insomnia

# WOMEN AND INSOMNIA

- ž Women are at greater risk for insomnia than men
- ž Influenced by hormonal cycles
  - The menstrual cycle
    - 36% during menstruation
    - 14% during late luteal phase
  - During and after pregnancy
  - During the peri/postmenopausal period

# AGE AND INSOMNIA

- ž Age-related changes in sleep architecture
  - Increased in light/transitional sleep
  - Reduction in slow-wave sleep
  - Decline in overall sleep time
- ž Comorbid illness
  - Age-related illnesses
  - Side effects of medications
  - Primary sleep disorders
- ž Social factors
  - Bereavement
  - Sleep patterns altered by retirement

# PRIMARY VS. COMORBID INSOMNIA

## ž Primary insomnia

- Sleep disturbance that can not be explained by any underlying medical, psychiatric, or environmental problem
- Sleep disturbance that persists after the resolution of the original trigger

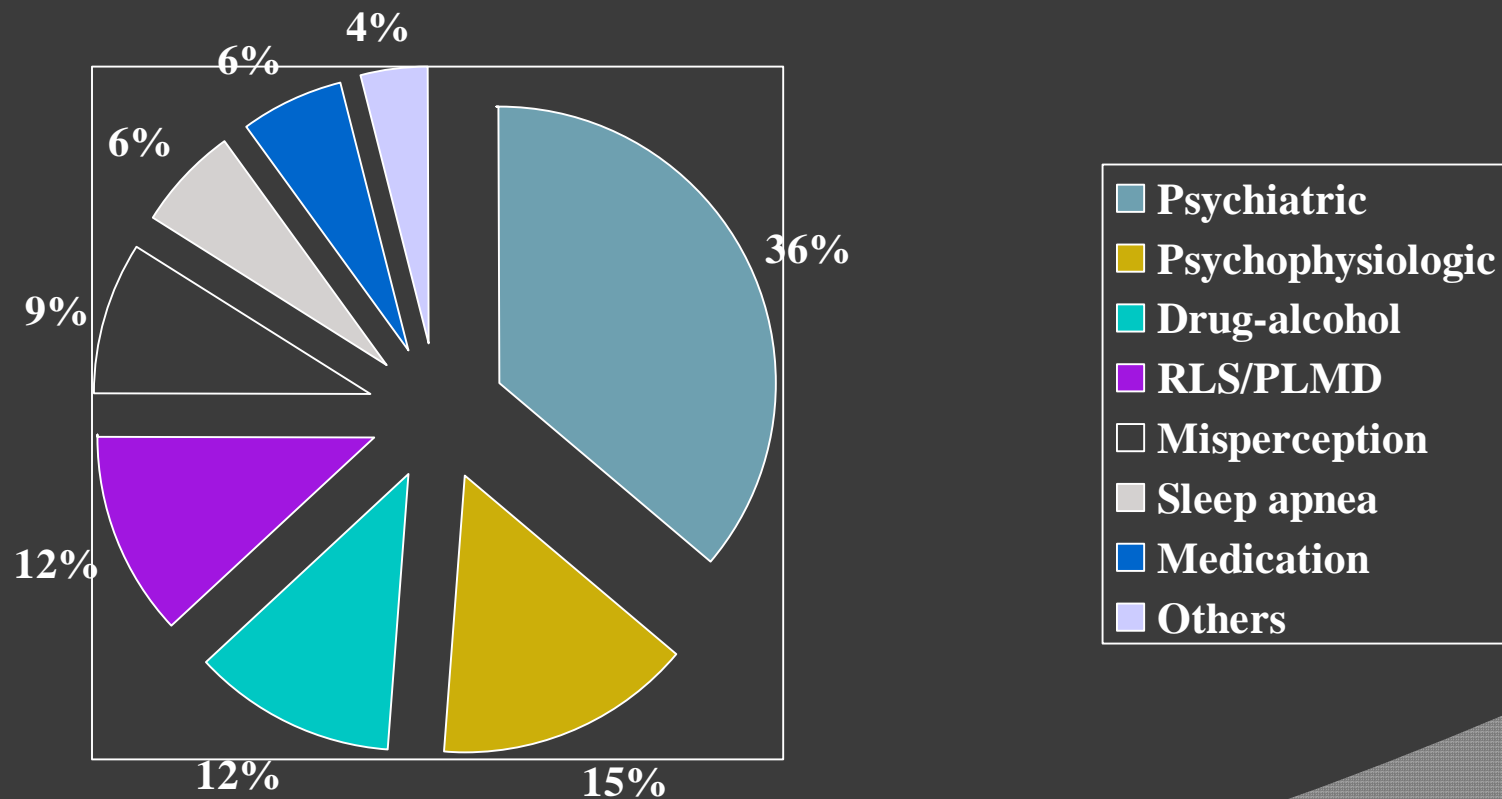
## ž Comorbid insomnia

- Sleep disturbance is comorbid with an underlying problem

# CAUSES OF COMORBID INSOMNIA

Medical Conditions	Psychological Disorders	Sleep Disorders	Pharmacological Agents	Environmental Factors
Asthma	Depression	Obstructive Apnea	Methylphenidate	Temperature
COPD	Anxiety	Central Apnea	Theophylline	Excessive Light
Heart Failure	Panic Attacks	Periodic Limb Movement	Albuterol	Excessive Noise
Parkinsonism	Mania	Restless Leg Syndrome	Pemoline	Bed Discomfort
Diabetes	Bereavement	Advanced Phase	Dextroamphetamine	Pets
Allergies	Post-Traumatic	Delayed Phase	Pseudoephedrine	
Thyroid Disorder	General Stress		Nicotine	
Chronic Pain			Alcohol	
Itching			SSRI (some)	

# DIAGNOSES ASSOCIATED WITH CHRONIC INSOMNIA





# CONTRIBUTING FACTORS TO DEVELOPMENT OF INSOMNIA

## ž Predisposing factors

- Personality
- Sleep-wake cycle
- Circadian rhythm
- Coping mechanisms
- Age

## ž Precipitating factors

- Situational
- Environmental
- Medical
- Psychiatric
- Medications

## ž Perpetuating factors

- Conditioning
- Substance abuse
- Performance anxiety
- Poor sleep hygiene

# COGNITIVE BEHAVIORAL MODEL OF INSOMNIA

## ž Dysfunctional Cognition

- Worry over sleep loss
- Rumination over consequences
- Unrealistic expectations
- Misattributions/ amplifications

## ž Arousal

- Emotional
- Cognitive
- Physiologic

## ž Consequences

- Mood Disturbances
- Fatigue
- Performance impairments
- Social discomfort

## ž Maladaptive Habits

- Excessive time in bed
- Irregular sleep schedule
- Daytime napping
- Sleep-incompatible activities

# CONSEQUENCES OF INSOMNIA

- ž Worsens psychiatric disorders
- ž Prolongs medical illnesses
- ž Reduced quality of life
- ž Higher absenteeism
- ž Increased accident risk
- ž Higher health care costs
- ž Cognitive impairment

# DEPRESSION AND INSOMNIA

- ž Insomnia is both a risk factor for depression and a consequence of depression
- ž Could effective management of insomnia decrease the incidence of depression?
- ž Could effective management of insomnia modify the risk for relapsing depression?

**Table 3. Clinical Risk Factors Associated With Mild and Severe Insomnia at Baseline\***

	Mild Insomnia	Severe Insomnia
Physician-diagnosed conditions		
Major depression	2.6 (1.9-3.5)†	8.2 (5.7-12.0)†
Subthreshold depression	2.2 (1.7-2.7)†	3.4 (2.6-4.6)†
Myocardial infarction	1.9 (1.2-2.9)‡	0.9 (0.4-1.9)
Congestive heart failure	1.6 (1.1-2.2)§	2.5 (1.5-3.9)†
Diabetes mellitus	0.8 (0.7-1.0)	1.0 (0.8-1.4)
Patient-reported comorbidities		
Angina pectoris	1.3 (1.0-1.7)§	1.3 (1.0-1.8)
Obstructive airway disease	1.6 (1.1-2.2)‡	1.5 (1.0-2.3)§
Back problems	1.4 (1.1-1.7)†	1.5 (1.2-2.0)‡
Hip impairment	2.2 (1.3-3.8)‡	2.7 (1.4-5.1)‡
Osteoarthritis	1.4 (1.0-2.0)§	1.6 (1.0-2.5)
Rheumatoid arthritis	1.0 (0.5-2.0)	1.3 (0.6-2.8)
Peptic ulcer	0.9 (0.5-1.5)	1.8 (1.0-3.1)§
Bowel problems	0.9 (0.6-1.3)	0.9 (0.5-1.4)
Prostate problems	1.6 (1.2-2.3)‡	1.4 (0.9-2.3)
Urinary tract infection	1.1 (0.8-1.6)	1.0 (0.7-1.6)

\* Values are odds ratios (and 95% confidence intervals) adjusted for sociodemographic variables, health habits, and study site. The dependent variables are mild and severe insomnia at baseline.

† $P \leq .001$ .

‡ $P \leq .01$ .

§ $P \leq .05$ .

# ECONOMIC IMPACT OF INSOMNIA

## ž Direct Cost

- Drugs: \$1.97 Billion (41% prescription)
- Services: \$11.96 Billion

## ž Indirect Costs

- Decreased productivity
- Higher accident rate
- Increased absenteeism
- Increased comorbidity

## ž Total Annual Cost: \$30-\$107 billion

Walsh JK, Engelhardt CL. *Sleep*. 1999;22(suppl 2):S386-393

Stoller MK. *Clin Ther*. 1994;16:873-879

Chilcott LA, Shapiro CM. *Pharmacoeconomics*. 1996;10(suppl 1):1-14

Minnie Pauz....™

by Dee Adams



I wonder how long it takes for this natural sleep remedy to kick in?

# PHARMACOLOGIC TREATMENT

## ž Historic trials

- Fermented beverages
- Plant preparations
- Laudanum  
(opium/alcohol)
- Chloral hydrate
- Barbiturates

## ž Current trials

- Antihistamines
- Benzodiazepine  
hypnotics
- Nonbenzodiazepine  
hypnotics
- Selective melatonin  
receptor agonist
- Investigational  
compounds



# INSOMNIA – OTC REMEDIES

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**Table 3.—Common Nonprescription Agents Used to Induce Sleep**

Diphenhydramine (Nytol®, Sleep-eze®, Sominex®, others)

Diphenhydramine in combination (Anacin PM®, Doan's PM®, Extra Strength Excedrin PM®, Tylenol PM®, Unisom with pain relief®)

Doxylamine (Unisom Nighttime®)

Tryptophan

Melatonin

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# INSOMNIA – OTC REMEDIES

## ž Problems

- ž No proven efficacy for insomnia with large scale studies
- ž Not effective after a few days
- ž In surveys-31% effective, 33% not effective
- ž Tolerance
- ž Rebound insomnia
- ž Duration of action may not be desirable-drowsiness persists  
e.g
- ž May cause agitation, constipation, dehydration in some

# INSOMNIA – PHARMACOL. Rx

- ž Pharmacological treatment
- ž Medications should have –
- ž Quick onset
- ž Duration-Optimal
- ž Periodic use possible –can be taken when the problem occurs
- ž Safe & Effective
- ž No after effect or hypersomnolence
- ž No rebound insomnia after discontinuation
- ž No tolerance
- ž Should not alter the sleep structure
- ž **Only new meds have objectively demonstrated sleep induction & maintenance properties & evaluation of adverse events**

# HYPNOTICS

ž 5 questions to ask when choosing a hypnotic:

1. Are you looking for sleep initiation or maintenance?
2. What are the daytime residual effects of the drug?
3. Does tolerance develop to this drug?
4. Will rebound withdrawal insomnia occur when discontinued?
5. What is the half-life of the medication?

# INSOMNIA – PHARMACOL. Rx

- ž 2 categories of prescription meds
- ž Approved for Rx of insomnia – 8 meds
- ž Benzodiazepines, BZ receptor agonists
- ž Only 1 – eszopiclone approved for use without time limit
- ž Off label use – approved for other indications but used for insomnia as well e.g. anti – depressants
- ž Trazodone – most commonly used
- ž Doxepin, Amitryptiline, Mirtazapine

# MOST COMMONLY USED DRUGS FOR INSOMNIA

1. Trazodone
2. Zolpidem
3. Amitriptyline
4. Mirtazapine
5. Temazepam
6. Quetiapine
7. Zaleplon
8. Clonazepam
9. Hydroxyzine
10. Alprazolam
11. Lorazepam
12. Olanzapine
13. Flurazepam
14. Doxepin
15. Cyclobenzaprine
16. Diphenhydramine

# CURRENT FDA-APPROVED INSOMNIA TREATMENT MEDS

## ž Benzodiazepine receptor agonists

### – Benzodiazepine hypnotics

- Temazepam (Restoril)
- Flurazepam (Dalmane)

### – Nonbenzodiazepine hypnotics

- Zolpidem (Ambien)
- Zaleplon (Sonata)

## ž Selective melatonin receptor agonist

- Ramelteon (Rozerem)

# INSOMNIA - TREATMENT

## ž Benzodiazepines

- ž work on GABA receptor
- ž BZ complex of GABA receptor has 3 moieties
- ž BZ1, BZ2, BZ3
- ž Sedative, AC, anxiolytic, muscle relaxant actions
- ž BDZ work nonspecifically via BZ complex of GABA receptor
- ž Non specific action
- ž Therefore, other action unrelated to sleep



# BENZODIAZEPINE RECEPTOR AGONISTS

- ž Bind to the benzodiazepine receptor site
- ž Enhances GABA activation of chloride ion channel
- ž Promote sleep by sedating effect
- ž Absorption allows rapid sleep onset
- ž Eliminated half-life and dose determines the duration of action
- ž Immediate and controlled-release formulations

# BENZODIAZEPINES RECEPTOR AGONISTS

- ž **BZ complex of GABA receptor**
- ž BZ1, BZ2, BZ3- sedative, AC, anxiolytic, muscle relaxant actions
  
- ž **Newer medications work on BZ 1 receptor SELECTIVELY**
- ž low affinity for BZ2 & BZ3
- ž **Zaleplon & Zolpidem** - Work mainly on **BZ1** complex,
- ž Little efficacy as anxiolytics, anticonvulsants & myorelaxants
- ž So fewer cognitive & psychomotor side effects
- ž Do not have active clinical metabolites
- ž **Short half life with minimal to no residual sedation**
- ž **Low** receptor binding **affinity**-less acute withdrawal symptoms
- ž **No tolerance** after Zolpidem(179days), Zaleplon(365 days)

# BZRA PRESCRIBING GUIDELINES

- ž Bedtime dosing
- ž Avoid hazardous activities after dose
- ž Allow sufficient time in bed
- ž Dose adjustments
  - Elderly and debilitated patients
  - Hepatic impairment
- ž Nightly vs. as needed dosing
- ž Middle of the night dosing?
- ž Taper dose on discontinuation?

# BZRA ADVERSE EFFECTS

- ž Residual effects
- ž Dizziness
- ž Headache
- ž Somnolence
- ž Blurred vision
- ž Nausea/diarrhea
- ž Fatigue
- ž Ataxia
- ž Anterograde amnesia
- ž Sonambulism/complex sleep behavior

# BZRA DISCONTINUATION EFFECTS

- ž Rebound insomnia: sleep worsened relative to baseline for 1-2 days
- ž Recrudescence: return of original insomnia symptoms
- ž Withdrawal: new cluster of symptoms not present prior to treatment

# BENZODIAZEPINES

	<b>Dose</b>	<b>Half-life</b>	<b>Comments</b>
Flurazepam(Dalmane)	15,30 mg	Long	Daytime drowsiness common; rarely used
Clonazepam(Klonopin)	0.5-2 mg	Long	Used for PLM, REM behavior disorder; can cause morning drowsiness
Temazepam (Restoril)	15,30 mg	Intermediate	Intermediate onset
Estazolam (ProSom)	1-2 mg	Intermediate	Rapid onset, Can cause agranulocytosis
Triazolam (Halcion)	0.125,0.25 mg	Short	Rapid onset, Rebound insomnia may occur
Zolpidem (Ambien)	5,10 mg	Short	A nonbenzodiazepam
Zopiclone (Sonata)	5,10 mg	Short , 1-1.5 hours	A nonbenzodiazepam

# INSOMNIA – TREATMENT

**TABLE 17.1** Currently Available Agents for the Treatment of Insomnia: Benzodiazepines

Agent	Adult Dosages	Duration of Action	Primary Metabolism/ Excretion	Important Adverse Effects	Important Drug Interactions	Not Recommended	Comments
<b>Estazolam</b>	1–2 mg at bedtime; 0.5 mg for (1) elderly or (2) debilitated patients	Intermediate- acting	Hepatic/ renal	Dizziness Drowsiness Headache	Alcohol Azole antifungals Barbiturates Muscle relaxants Opioid analgesics Sodium oxybate	Benzodiazepine hypersensitivity Chronic pulmonary insufficiency Elderly or debilitated patients Pregnancy or lactation Sleep apnea	Can cause withdrawal symptoms after abrupt discontinuation. Caution if history of substance abuse or severe depression.
<b>Flurazepam</b>	15–30 mg at bedtime; 15 mg for (1) elderly and (2) debilitated patients	Long-acting	Hepatic/ renal	Dizziness Drowsiness Headache	Alcohol Azole antifungals Barbiturates Muscle relaxants Opioid analgesics Sodium oxybate	Benzodiazepine hypersensitivity Chronic pulmonary insufficiency Pregnancy or lactation Severe depression Severe liver dysfunction Sleep apnea	Hangover sedation on the morning after nighttime administration. Potential for dependency.

# INSOMNIA – TREATMENT

<b>Quazepam</b>	7.5–15 mg at bedtime; 7.5 mg for elderly patients	Long-acting	Hepatic/ renal	Dizziness Drowsiness Fatigue Headache	Alcohol Azole antifungals Barbiturates Muscle relaxants Opioid analgesics	Benzodiazepine hypersensitivity Chronic pulmonary insufficiency Elderly or debilitated patients Pregnancy Sleep apnea	Hangover sedation on the morning after nighttime administration. Reduction in dosage in hepatic disease.
<b>Temazepam</b>	15 mg at bedtime; 7.5 mg for (1) elderly or (2) debilitated patients Maximum recommended dose: 30 mg	Intermediate- acting	Hepatic/ renal	Dizziness Drowsiness Fatigue Headache	Alcohol Azole antifungals Barbiturates Muscle relaxants Opioid analgesics Sodium oxybate	Benzodiazepine - hypersensitivity Chronic pulmonary insufficiency Pregnancy or lactation	Can cause withdrawal symptoms after abrupt discontinuation.
<b>Triazolam</b>	0.25 mg at bedtime; 0.125 mg for (1) elderly, (2) debilitated patients, or (3) liver dysfunction Maximum recommended dose: 0.5 mg	Short-acting	Hepatic/ renal	Confusion Drowsiness Fatigue Headache	Alcohol Azole antifungals Barbiturates Muscle relaxants Opioid analgesics Sodium oxybate	Benzodiazepine hypersensitivity Chronic pulmonary insufficiency Pregnancy Severe depression Severe liver dysfunction	Can cause rebound insomnia or withdrawal symptoms after drug discontinuation. Potential for dependency.



# INSOMNIA – TREATMENT

**TABLE 17.2** Currently Available Agents for the Treatment of Insomnia: Nonbenzodiazepines

Agent	Adult Dosages	Primary Metabolism/ Excretion	Important Adverse Effects	Drug Interactions	Not Recommended	Comments
<b>Eszopiclone</b>	Initial dose: 2 mg before bedtime; 1 mg before bedtime for (1) elderly or (2) use with strong CYP3A4 inhibitor Maximum recommended dose: 3 mg (2 mg for elderly)	Hepatic/renal	Headache Unpleasant taste Xerostomia	Azole antifungals Clarithromycin Ciprofloxacin Diclofenac Doxycycline Erythromycin Ethanol Isoniazid Ketoconazole Nefazodone Olanzapine Quinidine Verapamil	Hypersensitivity to eszopiclone Pregnancy or lactation (use caution) Depression Severe hepatic impairment	Should be administered immediately prior to bedtime or after bedtime if the patient has difficulty falling asleep. Tablet should not be crushed or broken. Avoid taking after a heavy meal.
<b>Zaleplon</b>	Initial dose: 10 mg at bedtime; 5 mg for (1) elderly, (2) debilitated, (3) low body weight, or (4) mild to moderate hepatic impairment Maximum recommended dose: 20 mg	Hepatic/renal, gastrointestinal	Dizziness Headaches Somnolence	Cimetidine Ethanol Rifampin	Hypersensitivity to zaleplon Pregnancy or lactation Severe hepatic impairment	Has little effect on sleep stages. Reduces sleep latency.

# INSOMNIA – TREATMENT

<b>Zolpidem</b>	10 mg at bedtime; 5 mg for (1) elderly, (2) debilitated or (3) hepatic impairment Maximum recommended dose: 10 mg Dosage adjustment needed during dialysis	Hepatic/renal	Dizziness Drowsiness Headache Nausea	Antidepressants Ethanol Ketoconazole Rifampin Ritonavir	Hypersensitivity to zolpidem	Reduce sleep latency. Decreases number of awakenings. Increases total sleep time. Delays onset of REM. Increases stages 3 and 4 sleep time.
<b>Trazodone</b>	Initial dose: 50 mg at bedtime	Hepatic/renal	Arrhythmias Blurred vision Delirium Dizziness Drowsiness Hypotension Priapism	Antihypertensives Chlorpromazine Droperidol Monoamine Oxidase inhibitors Trifluoperazine Warfarin	Hypersensitivity to trazodone Pregnancy or lactation Cardiac disease or arrhythmias	Not FDA approved for therapy of insomnia.



# INSOMNIA - TREATMENT

## ž **Zaleplon**

- ž Rapid GI absorption
- ž T-max ½ -1 hour
- ž Half-life 1-2 hours
- ž Duration 1-3 hours
- ž Metabolism – hepatic to inactive metabolites-by CYP3A4
- ž Excretion - renal
- ž Residual drowsiness – minimal to none
- ž Rebound insomnia - none
- ž Preserves sleep stages
- ž Available as 5mg and 10 mg capsules

- ž **Zolpidem** (available as 5mg & 10 mg tablets) – CR 12.5 mg
- ž Specifically binds to omega-1 site of GABA-A receptor complex
- ž Rapid GI absorption
- ž T max – 1 ½ hours
- ž Half-life 1.4-3.8 hours – longer duration of action with CR
- ž Decreased SOL, Incr. sleep efficacy in 5 week trial (placebo controlled)
- ž **Preserves sleep pattern** (BDZs shorten III,IV & REM)
- ž **No residual next day effects**
- ž **No objective evidence of rebound insomnia**
- ž **Hepatic metabolism** to inactive metabolites, renal excretion
- ž No known absolute contraindications
- ž **Caution** in elderly & those with hepatic impairment
- ž Longer acting version in trials (Zolpidem XR)

ž **Zolpidem dosage**

ž Start with 5-10 mg HS

ž Can go up to 20 mg HS

ž **Caution** – in **elderly patients** and patients with **hepatic disease** - start with 5 mg HS

ž **Renal disease or dialysis** – no effect

ž For faster effect, take on empty stomach

ž Should not be taken along with alcohol

ž Should not be used with other CNS depressant

## Adverse Effects with Zolpidem

- ž **Headache**
- ž **Dizziness, Drowsiness**
- ž Nausea, Vomiting, diarrhea
- ž Sleep walking – especially if childhood history of the same
- ž **Falls in elderly-** specially dosage above 20mg.
- ž No teratogenecity in animal studies
- ž 0.004%-0.0019% excretion in milk
- ž No fatalities reported with dosages up to 400mg.
- ž LD50 for mouse 2700mg/kg
- ž Flumazenil an effective antidote
- ž Precautions

# INSOMNIA – DRUG INTERACTIONS

- ž **Zolpidem & Haldol –**  
no significant effect on pharmacology of Zolpidem
- ž **Zolpidem & Imipramine-**  
20% reduction in peak plasma concentration of imipramine,  
additive effect on decreased alertness
- ž **Zolpidem & Chlorpromazine-**  
no pharmacological effect except additive effect for  
decreased alertness & psychomotor performance
- ž **Zolpidem & Alcohol –**  
additive effect for decreasing psychomotor performance
- ž **Zolpidem in depression**  
Caution-Intentional overdose more common in this group



# SELECTIVE MELATONIN RECEPTOR AGONIST

- ž Ramelteon (Rozerem)
- ž MT1: attenuation of circadian alerting signal
- ž MT2: circadian phase reinforcement or shifting
- ž Acts on the suprachiasmatic nucleus
- ž Influences the circadian rhythm effects on the sleep-wake cycle
- ž No abuse liability, not a drug enforcement administration controlled substance

# SELECTIVE MELATONIN RECEPTOR AGONIST

## ž Ramelteon

- ž Prescription medication
- ž 8 mg HS
- ž High affinity MT1 & MT2 receptor agonist
- ž No binding to other sites (e.g. GABA)
- ž T<sub>max</sub> ~20 minutes, T<sub>1/2</sub> 1.2 hours
- ž Efficacy in a transient insomnia paradigm
- ž Decreased sleep latency, increased total sleep time

# SELECTIVE MELATONIN RECEPTOR AGONIST

- ž FDA approved for sleep onset insomnia
- ž No limitation on duration of use
- ž Non-sedating
- ž Single dose: 8 mg
- ž Take about 30 minutes prior to bedtime
- ž Half-life: 1-2.6 hrs

# SELECTIVE MELATONIN RECEPTOR AGONIST

- ž Adverse events
  - Somnolence
  - Dizziness
  - Fatigue
- ž Avoid with hepatic impairment

# INSOMNIA- ANTIDEPRESSANTS

- ž Used for treatment of depression
- ž But also at times used for insomnia
- ž Trazodone (desyrel)
- ž Amytryptiline (elavil)
- ž Doxepin (sinequan)
- ž Fluvoxamine (luvox)
- ž Mirtazapine (remeron)
- ž Nefazodone (serzone)
- ž Hypnotics in lower doses than anti-depressant
- ž Can exacerbate PLMS
- ž Most SSRIs may exacerbate insomnia in 1<sup>st</sup> 2-4 weeks of use

# INSOMNIA Rx

- ž **Anti-histamines**
- ž Promote sleep
- ž Effect less than BDZs
- ž Lose effectiveness over time

# FIRST GENERATION ANTIHISTAMINE

- ž Postsynaptic histaminic and muscarinic blockade
- ž Diphenhydramine
- ž Regulated by the FDA
- ž Half-life: 8 hrs
- ž Rapid tolerance to sedating effects
- ž Pill strengths (mg): 25, 37.5, 50

# FIRST GENERATION ANTIHISTAMINE

## Potential adverse effects(AE s – Anticholinergic effects)

- Residual effects
- Delirium
- Dry mouth
- Constipation
- Blurred vision
- Urinary retention
- Narrow angle glaucoma exacerbation



# DIETARY SUPPLEMENTS

- ž Not FDA regulated
- ž Valerian
- ž Kava-Kava
- ž Melatonin
- ž Passion flower
- ž Skullcap
- ž Lavender
- ž Hops

# INSOMNIA– MELATONIN

- ž Hormone secreted by the pineal gland - decreases with age
- ž Secretion related to amount of light
- ž Higher level in winter & lower level with short summer nights
- ž Melatonin rises naturally right before falling sleep
- ž Taking melatonin (0.5 mg) at night causes phase advance
- ž Can cause vasoconstriction-? Risk in patients with cardiocascular disease
- ž Animal studies started in 1990s to test safety and efficacy
- ž Applied to FDA to test for safety of melatonin in humans
- ž FDA(drug regulating arm) denied asking for more animal trials
- ž Yet the food regulating arm of FDA approved the sale of melatonin as a food additive
- ž Soon claims of efficacy- health, happiness, longevity, sex life



# COGNITIVE-BEHAVIORAL TREATMENT FOR INSOMNIA

## ž Indications

### – Primary Insomnia

- Psychophysiological Insomnia
- Inadequate Sleep Hygiene

### – Comorbid Insomnia

- With a medical condition
- With a mental disorder

## ž Important to combine both cognitive and behavioral components

# BEHAVIORAL TREATMENTS

## ž Sleep hygiene education

- Specific behaviors will directly interfere with the ability to sleep
- The behaviors can be changed with education
- No sufficient as a ‘stand alone’ treatment

## ž Sleep restriction therapy

- Increased propensity to sleep by increasing homeostatic sleep drive with partial sleep deprivation
- Systematic reduction of time in bed to the amount of total sleep time from sleep log data
- Increase time in bed by 15 minutes only when sleep efficiency exceeds 90% for 5 nights

# BEHAVIORAL TREATMENTS

## ž Stimulus control therapy

- Assumes that there is a learned associated between wakefulness and the bedroom
- To break the cycle, the patient must not spend time wide awake in the bedroom
- Go to bed only when sleepy
- Do not use the bedroom for sleep-incompatible activities
- Leave the bedroom if awake for more than 20 minutes
- Return to bed only when sleepy
- Do not nap during the day
- Arise at the same time every morning

# BEHAVIORAL TREATMENTS

## ž Relaxation training

- Progressive muscle relaxation
- Guided Imagery
- Biofeedback
- Self-hypnosis

# COGNITIVE THERAPY

- ž Cognitive restructuring
- ž Rational-Emotive therapy
- ž Specific techniques for rumination
  - Thought-stopping
  - Meditation techniques



# REFERENCE

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