Development of Sleep

Roffwarg HP, Muzio JN and Dement WC. Science 1966.
Figure 2. Reported Hours Slept: Older Versus Younger Adults

Data from National Sleep Foundation. Older adults do not report sleeping fewer hours than younger adults.
Common Sleep Disorders in the Elderly

• Insomnia
2. Circadian Rhythm Issues
3. Restless Leg Syndrome
4. Obstructive Sleep Apnea
5. REM Sleep Behavior Disorder
Definition of Insomnia

Not a diagnosis, but a clinical problem presenting as one or more of the following:

- Difficulty falling asleep
- Difficulty maintaining sleep
- Patient’s perception of poor sleep quality

Resulting in

- Daytime sleepiness or fatigue
- Impaired function

Naylor MW, Aldrich Ms, In: Kryger MH, et al, eds. Principles and Practice of Sleep Medicine, 1994:413-417
Prevalence of Insomnia* in the General Adult Population

*Insomnia = sleep disturbance every night for two weeks or more, or similarly stringent criteria.

Insomnia in Patients With Chronic Medical Conditions

*Sleep disturbance “some” or “a good bit” of the time for four weeks.
†Sleep disturbance “most” or “all” of the time for four weeks.
MI = myocardial infarction; CHF = congestive heart failure; BPH = benign prostatic hyperplasia. 
Chronic insomnia is associated with poorer physical and emotional health
Sleep Disturbance Precedes the Onset of Depression

• Insomnia or difficulty sleeping under stress increased risk for depression later in life
  - Johns Hopkins Precursors Study; Chang, 1997

• Insomnia predicted depression in elderly populations
  - Dryman and Eaton, 1991; Livingston, 1993

• Precedes dysphoria, dissatisfaction, crying and irritability
Sleep Disturbance Precedes the Onset of Psychiatric Illness in General Adult Population

- Odds of developing depression during a year of insomnia - 39.8
- If insomnia resolved during the year - 1.6

Causes of Insomnia

Pharmacologic

- Alcohol
- Anticancer agents
- Antihypertensives
- Autonomic agents
- Caffeine
- CNS depressants
- CNS stimulants
- MAO inhibitors
- Nicotine
- Steroids
- Theophylline
- Thyroid preparations

CNS - central nervous system; MAO - monoamine oxide
## Diagnosing Insomnia: Differential Diagnosis

<table>
<thead>
<tr>
<th>Medical Etiologies</th>
<th>Psychiatric Etiologies</th>
<th>Other Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac disease</td>
<td>Mood disorders</td>
<td>Primary insomnia</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>Anxiety disorders</td>
<td>Circadian rhythm disorders</td>
</tr>
<tr>
<td>Pain secondary to a medical condition (eg, cancer)</td>
<td>Substance abuse disorders</td>
<td></td>
</tr>
<tr>
<td>Neurologic degenerative disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergies/asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restless leg syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep apnea</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Types of Insomnia: Duration

Transient Insomnia
- Several days

Short-term Insomnia
- ≤ 3 weeks

Chronic Insomnia
- > 3 weeks

CASE

“I wake up every hour to go to the bathroom.”
Sleep Hygiene Education

- Maintain a regular schedule for going to bed and arising
- Avoid excessive time in bed
- Avoid taking naps during the day and early evening
- Use the bed only for sleeping and sexual relations
- Do not watch the clock while in bed
- Do something relaxing before bedtime

**Sleep Hygiene Education (cont’d)**

- Make the bedroom as quiet and comfortable as possible
- Avoid taking the troubles of the day to bed
- Avoid consumption of alcohol or caffeinated beverages, especially within 6 hours of bedtime
- Get exercise, but early in the day (not within 2 hours of bedtime)
- Avoid going to bed hungry - eat a light snack in the evening if necessary

Increase Activity During the Daytime
Sleep Restriction

- Restrict time in bed (TIB) to actual sleep time
- Establish TIB based on sleep efficiency (SE) averaged over a 5 day period
- Increased TIB by 15 minutes if average SE over 5 days >90% (85% for elderly); decrease if SE <85% (80% for elderly)
- Be aware that daytime sleepiness is a potential side effect

Characteristics of the Ideal Hypnotic

- No effect on memory
- No respiratory depression
- No interaction with ethanol
- No tolerance
- No physical dependence
- No rebound insomnia
- No residual effects
- Rapid absorption
- Mechanism other than general CNS depression
- Rapid sleep induction
- Induction of physiological sleep pattern
- Optimal half-life
- No formation of active metabolites

Table 1—The 16 drugs with the most “drug occurrences” with a desired action of “hypnotic,” “promote sleep,” or “sedate night” in 2002 from the Verispan Physician Drug and Diagnosis Audit

<table>
<thead>
<tr>
<th>Rank</th>
<th>Drug</th>
<th>Occurrences (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Trazodone</td>
<td>2.730</td>
</tr>
<tr>
<td>2</td>
<td>Zolpidem</td>
<td>2.074</td>
</tr>
<tr>
<td>3</td>
<td>Amitriptyline</td>
<td>0.774</td>
</tr>
<tr>
<td>4</td>
<td>Mirtazapine</td>
<td>0.662</td>
</tr>
<tr>
<td>5</td>
<td>Temazepam</td>
<td>0.558</td>
</tr>
<tr>
<td>6</td>
<td>Quetiapine</td>
<td>0.459</td>
</tr>
<tr>
<td>7</td>
<td>Zaleplon</td>
<td>0.405</td>
</tr>
<tr>
<td>8</td>
<td>Clonazepam</td>
<td>0.394</td>
</tr>
<tr>
<td>9</td>
<td>Hydroxyzine</td>
<td>0.293</td>
</tr>
<tr>
<td>10</td>
<td>Alprazolam</td>
<td>0.287</td>
</tr>
<tr>
<td>11</td>
<td>Lorazepam</td>
<td>0.277</td>
</tr>
<tr>
<td>12</td>
<td>Olanzapine</td>
<td>0.216</td>
</tr>
<tr>
<td>13</td>
<td>Flurazepam</td>
<td>0.205</td>
</tr>
<tr>
<td>14</td>
<td>Doxepin</td>
<td>0.199</td>
</tr>
<tr>
<td>15</td>
<td>Cyclobenzaprine</td>
<td>0.195</td>
</tr>
<tr>
<td>16</td>
<td>Diphenhydramine</td>
<td>0.192</td>
</tr>
</tbody>
</table>
NIH Statements About Agents Not Approved for Insomnia Treatment

• Dietary supplements/herbal remedies
  – Valerian: Limited evidence shows no benefit beyond placebo
  – No systematic evidence for efficacy; there are significant concerns about risks
• Antihistamines
• Melatonin
  – Little evidence exists for efficacy in the treatment of insomnia
• Antipsychotics
  – Studies demonstrating the usefulness…are lacking; use in chronic insomnia is not recommended
• Antidepressants
  – All antidepressants have potentially significant adverse effects, raising concerns about the risk-benefit ratio
Approved Pharmacologic Treatment Options for Insomnia

• BZDs
  – Estazolam
  – Flurazepam
  – Quazepam
  – Temazepam
  – Triazolam

• Non-BZD agents affecting GABA/BZD complex
  – Eszopiclone
  – Zaleplon
  – Zolpidem
  – Zolpidem CR

• MT receptor agonist
  – Ramelteon
GABA Reuptake
Usual Half-Life Range of Benzodiazepine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-Life Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triazolam</td>
<td>1.5 - 5.5 h</td>
</tr>
<tr>
<td>Temazepam</td>
<td>8 - 20.0 h</td>
</tr>
<tr>
<td>Estazolam*</td>
<td>20 - 30.0 h</td>
</tr>
<tr>
<td>Quazepam*</td>
<td>15 h + 35.0 h</td>
</tr>
<tr>
<td>Flurazepam*</td>
<td>36 h +</td>
</tr>
</tbody>
</table>

*Includes active metabolites

### Table 9:1. Relative Risk of Hip Fracture

<table>
<thead>
<tr>
<th>Long-acting Benzodiazepines</th>
<th>Relative Risk</th>
<th>Short-acting Benzodiazepines</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlordiazepoxide</td>
<td>2.3</td>
<td>Oxazepam</td>
<td>1.4</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>1.9</td>
<td>Lorazepam</td>
<td>1.0</td>
</tr>
<tr>
<td>Diazepam</td>
<td>1.5</td>
<td>Triazolam</td>
<td>1.0</td>
</tr>
<tr>
<td>Overall</td>
<td>1.7</td>
<td>Overall</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Adapted from *JAMA* 1989;262:3303-3307
## Polysomnographic Findings†

<table>
<thead>
<tr>
<th>Stage</th>
<th>Barbiturates, Nonbarbiturates</th>
<th>Benzodiazepines</th>
<th>Zolpidem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 sleep</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Stage 2 sleep</td>
<td>↑</td>
<td>↑</td>
<td>√</td>
</tr>
<tr>
<td>Stages 3 &amp; 4 sleep</td>
<td>↓</td>
<td>↑</td>
<td>√</td>
</tr>
<tr>
<td>REM sleep</td>
<td>↓</td>
<td>↑</td>
<td>√</td>
</tr>
<tr>
<td>Latency</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Time in</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Number of cycles</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Total sleep time</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>

† Clinical significance unknown
* Not consistent among benzodiazepines
[1] No significant effects

**Proposed Specificity of Action**

Differences in pharmacologic response between drugs may be due to drug selectivity for GABA\textsubscript{A} receptor subtypes

**Animal Models**

![Graph showing response (%)](image)

Adapted from Sanger DJ, Zivkovic B. *Psychopharmacology*. 1966: 89:317-322
Rapid Clearance in Relation to Sleep Onset and Time Slept

- **Zaleplon 10 mg: Cp**
- **Zaleplon 10 mg: TSO-TTS**
- **Zolpidem 10 mg: Cp**
- **Zolpidem 10 mg: TSO-TTS**

![Graph showing the percentage of C_max over time for different medications.]

- TSO: Time to Sleep Onset
- TTS: Time to Sleep Through the Sleep Cycle

**Percentage of C_max**

- Time (h): 0, 1, 2, 3, 4, 5, 6, 7, 8

- Graph indicates the percentage of C_max at various time points for each medication.
CASE

“I cannot fall asleep until 2 A.M. and I am always late for appointments.”
Delayed and Advanced Sleep Phase Syndromes

- **Sample Desired Sleep Time**
  - able to remain awake to desired bedtime
  - able to wake up at desired risetime

- **Advanced Sleep Phase Syndrome**
  - cannot remain awake until desired bedtime
  - cannot remain asleep until desired risetime

- **Delayed Sleep Phase Syndrome**
  - cannot fall asleep until late in night
  - cannot awaken until midmorning
Diagnostic Criteria for RLS

- A desire to move the limbs usually associated with paresthesias or dysesthesias
- Motor restlessness during wakefulness
- Symptoms are worse at rest and are alleviated with activity
- Symptoms are worse in the evening or night

International RLS study Group 1995
Pharmacological Treatment of RLS

Dopaminergic Agents
levodopa/carbidopa
pergolide
pramipexole
ropinirole

Opiods
hydrocodone
propoxyphene
Pathophysiology of Apnea
Pathophysiology of Sleep Apnea

Awake: Small airway + neuromuscular compensation

- Loss of neuromuscular compensation
- Decreased pharyngeal muscle activity
- Airway collapses

Sleep Onset

- Apnea
- Hypoxia & Hypercapnia
- Increased ventilatory effort

Hyperventilate: correct hypoxia & hypercapnia

Airway opens

Pharyngeal muscle activity restored

Arousal from sleep
Clinical Consequences

Sleep Apnea →
Sleep fragmentation, Hypoxia/Hypercapnia

Excessive daytime sleepiness

Cardiovascular Complications

Morbidity Mortality
Prevalence of Sleep Apnea

30-60 year olds

Percent of Population

AHI > 5
SAS
Asthma

Male
Female
U.S. Pop

Young et al. NEJM, 1993;328
## Prevalence of Sleep Apnea in the Elderly

<table>
<thead>
<tr>
<th>RDI</th>
<th>Community Dwelling</th>
<th>VAH Inpatients</th>
<th>Nursing Home Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥5</td>
<td>81%</td>
<td>84%</td>
<td>70%</td>
</tr>
<tr>
<td>≥10</td>
<td>62%</td>
<td>65%</td>
<td>58%</td>
</tr>
<tr>
<td>≥20</td>
<td>44%</td>
<td>45%</td>
<td>38%</td>
</tr>
<tr>
<td>≥40</td>
<td>25%</td>
<td>21%</td>
<td>15%</td>
</tr>
</tbody>
</table>
Consequences: Excessive Daytime Sleepiness

- Increased motor vehicle crashes
- Increased work-related accidents
- Poor job performance
- Depression
- Family discord
- Decreased quality of life
Consequences: Cardiovascular

- Systemic hypertension
- Cardiac arrhythmias
- Myocardial ischemia
- Cerebrovascular disease
- Pulmonary hypertension / cor pulmonale
FIG. 1. Estimates of survival (with sample sizes and percent mortality) for elderly with AI < 5, AI = 5–20 and AI ≥ 20.
Sleep Apnea Risk Factors

- Obesity
- Increasing age
- Male gender
- Anatomic abnormalities of upper airway
- Family history
- Alcohol or sedative use
- Smoking
- Associated conditions
Risk Factor: Anatomic Abnormality

Suratt, et al. Chest 1986;90
Risk Factor: Sedatives

Graph showing peak integrated activity (% control) over minutes after diazepam injection for Phrenic Nerve and Hypoglossal Nerve.

Kryger et al. Prin. Pract. of Sleep Med. ©1994 W.B. Saunders
Risk Factor: Alcohol

BEFORE ALCOHOL

PHRENIC  

HYPOGLOSSAL  

BLOOD ALCOHOL = 83 mg/dl

PHRENIC  

HYPOGLOSSAL  

BLOOD ALCOHOL = 134 mg/dl

Bonara et. al.  
Am Rev Resp Dis 1984;130
Exam: Tonsillar Hypertrophy

Behavioral Interventions

- Encourage patients to:
  - Lose weight
  - Avoid alcohol and sedatives
  - Avoid sleep deprivation
  - Avoid supine sleep position
  - Stop smoking
Positive Airway Pressure
Positive Airway Pressure
Positive Airway Pressure: Problems

- Mask Discomfort
- Air leak
- Rhinitis Congestion
- Patient Acceptance
  - Claustrophobia
  - Aerophagia
  - Chest Discomfort
Oral Appliance: Mechanics
Table 1. Clinical and polygraphic criteria to diagnose REM sleep behavior disorder proposed by Mahowald and Schenck (1994)

Clinical findings
1. History of sleep behavior and any polysomnographic abnormalities listed
2. No history of sleep behavior and
   - any polysomnographic abnormalities listed and
   - any videotape behavioral abnormality listed

Polysomnography: at least one of the following findings during REM sleep:
- excessive augmentation of chin EMG tone
- excessive chin or limb EMG twitching irrespective of chin EMG tone

Videotaping of abnormal behavior during REM sleep
- excessive limb or body jerking
- complex movements
- vigorous or violent movements