Sleep Disorders

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Pre-Lecture Exam Question 1

1. **The most common cause of insomnia is**

A. Use of sleeping pills

B. Poor sleeping habits

C. Depression

D. Alcoholism

E. Sleep apnea

Question 2

2. **Hypnotic drugs are indicated**

A. for insomnia due to chronic medical conditions.

B. for insomnia due to depression.

C. for insomnia due to sleep breathing disorders

D. for transient problems lasting less than 30 days

E. All of the above

Question 3

3. A hypnotic which causes little daytime sedation is:

A. Lorazepam

B. Zolpidem

C. Temazepam

D. Flurazepam

E. Diphenhydramine

Question 4

4. The usual maximum dose of zolpidem for an elderly woman is

A. 5 mg

B. 10 mg

C. 15 mg

D. 20 mg

E. 25 mg

Question 5

5. A hypnotic which helps people fall asleep when taken at bedtime is:

A. Zaleplon

B. Temazepam

C. Lorazepam

D. Oxazepam

E. Ethchlorvynol

Question 6

6. The most popular drug for sleep complaints accompanying depression is:

A. Zolpidem

B. Zaleplon

C. Trazodone

D. Melatonin

E. Temazepam

Question 7

7. **Effective treatment for chronic insomnia may include:**

A. Zaleplon

B. Sleep restriction therapy

C. Zolpidem

D. Quazepam

E. Triazolam

Question 8

8. **The most common cause of excessive sleep is:**

a. Primary hypersomnia
b. Depression
c. Tricyclic antidepressants
d. Sleep apnea
e. Irregular habits

Question 9

9. Useful treatments for sleep apnea include:

A. Mandible and tongue appliances

B. Dieting

C. Sleep position training

D. Continuous positive airway pressure

E. All of the above

Question 10

10. To treat delayed sleep phase, use:

A. Vitamin B6

B. Bright light in the morning

C. Relaxation and sleep hygiene

D. Methylphenidate

E. Bright light just before bedtime

Sleep Disorders

- Primary
- Related to Another Mental Disorder
- Due to a General Medical Condition
- Substance-Related

Primary Sleep Disorders

- Dyssomnias
- Parasomnias

Dyssomnias

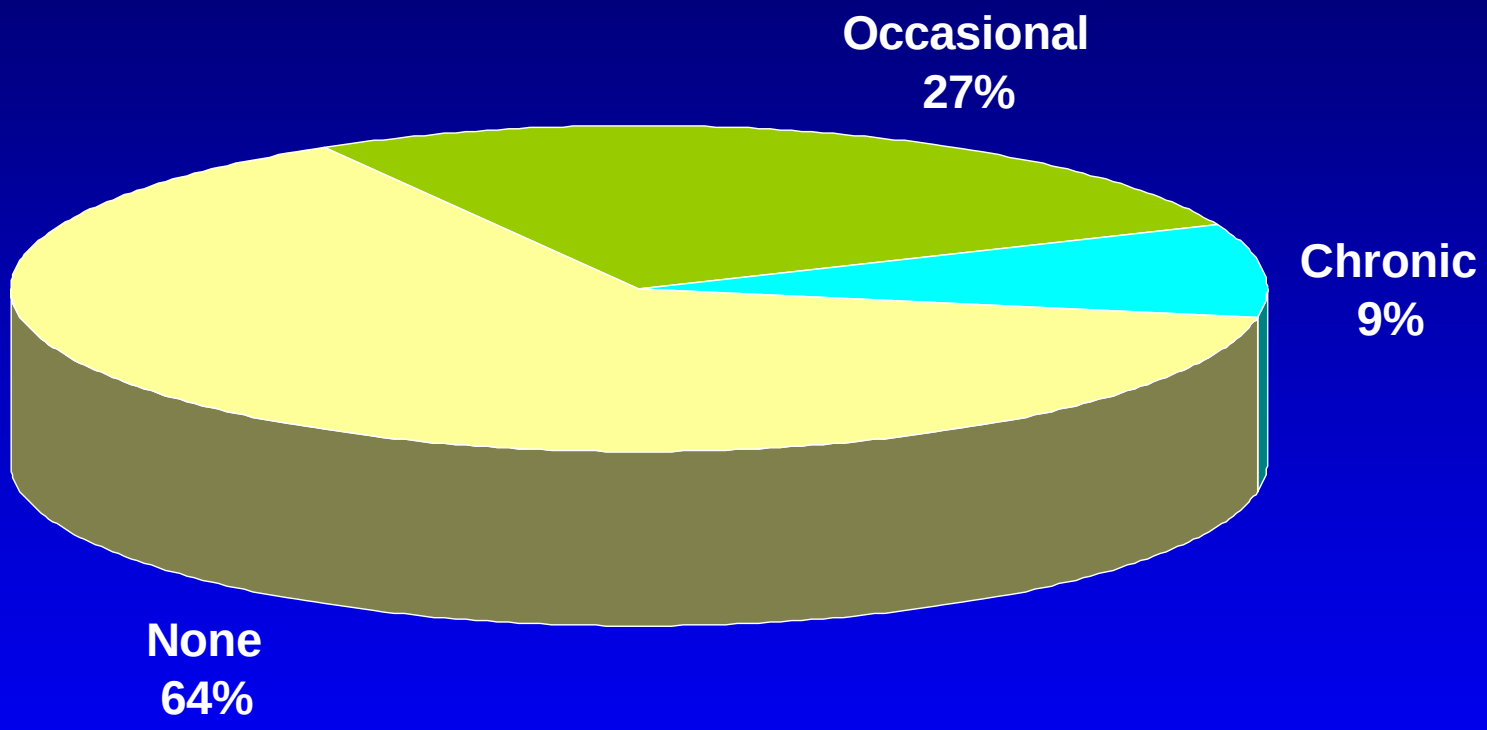
- Abnormalities in the
  - Amount
  - Quality
  - Timing of sleep

Dyssomnias

- Primary insomnia
- Primary Hypersomnia
- Narcolepsy
- Breathing-Related Sleep Disorder
- Circadian Rhythm Sleep Disorder
- Dyssomnia Not Otherwise Specified

- The most common cause of Insomnia complaints is depression
- The most common cause of excessive sleep is Sleep Apnea.

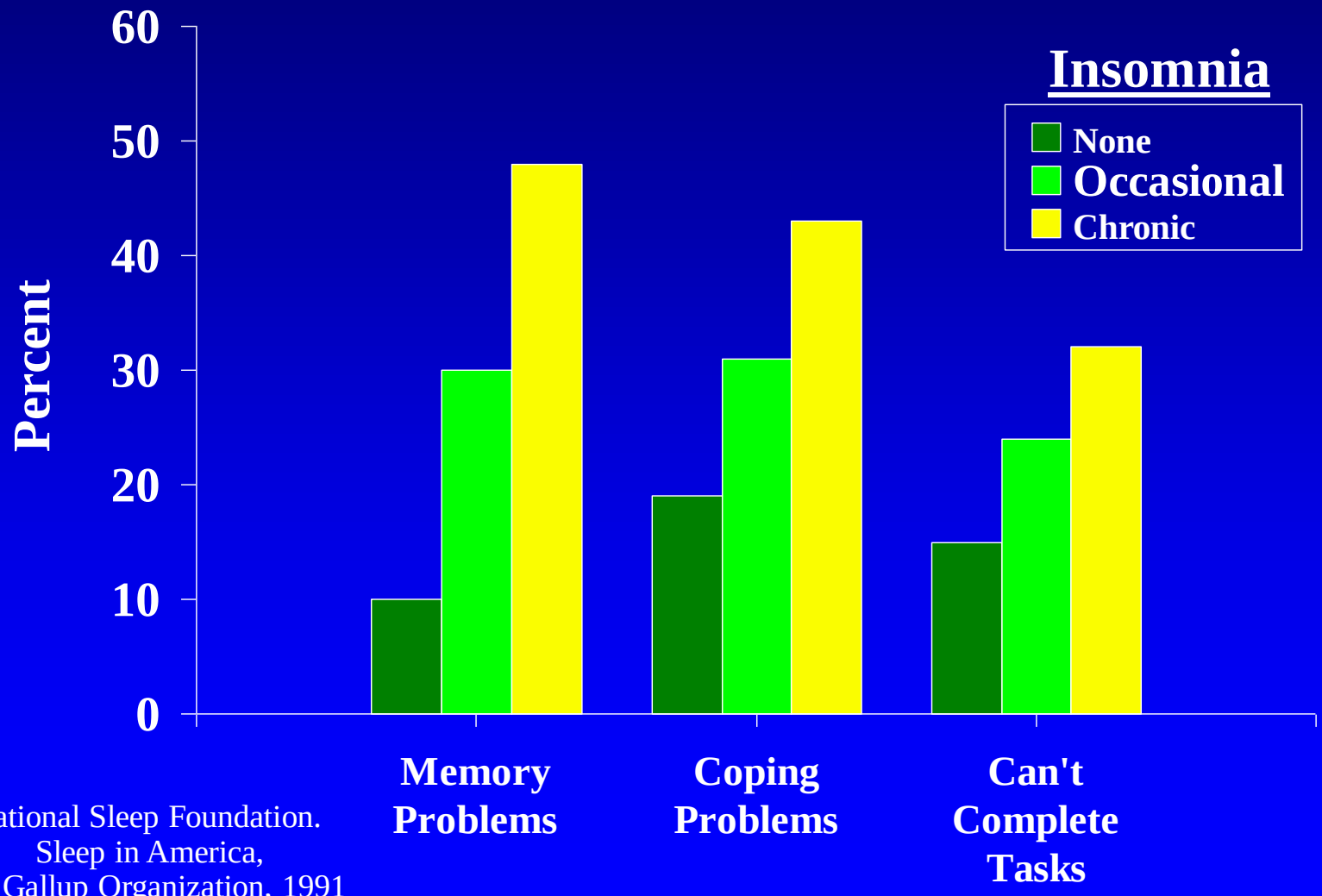
Prevalence of Insomnia in U.S.



National Sleep Foundation. Sleep in America, The Gallup Organization, 1991

- **Insomnia** due to depression or anxiety is more common than primary Insomnia.

Social Impact of Insomnia (might be related to depression)



National Sleep Foundation.
Sleep in America,
The Gallup Organization, 1991

Primary Insomnia

- Difficulty initiating or maintaining sleep or nonrestorative sleep for at least 1 month.
- Clinically significant distress or impairment in social, occupational, or other important areas of functioning
- Does not occur exclusively during the course of Narcolepsy, Breathing-Related Sleep Disorder, Circadian Rhythm Sleep Disorder or Parasomnia
- Does not occur exclusively during the course of another mental disorder
- Not due to the direct physiological effects of a substance or a general medical condition

Hypothesized Pathophysiology

DISORDER OF HYPERAROUSAL

Neurochemical or structural disorder involving neural networks governing sleep-wake states

DIAGNOSIS

- **Rule Out**
  - General medical condition that adversely affects sleep
  - Use of medications or substances able to disrupt sleep
  - Presence of another mental disorder able to disrupt sleep
  - Breathing-related sleep disorder
  - Parasomnia
- **Diagnose**
  - Primary insomnia if insomnia is not related to the above disorders and has persisted for more than a month

Treatment

- Hypnotics may be used up to 30 days
- Hypnotics are not recommended for chronic treatment

Hypnotics for Short-Term Use

Short Half - Life

Zolpidem: receptor specificity, low rebound, favorable kinetics, expensive

Triazolam: favorable kinetics, high rebound, strange behavioral and memory problems

Zaleplon: receptor specificity, half life too short

Medium Half - Life

Temazepam: Medium absorption, daytime sedation

Estazolam

Lorazepam: Medium absorption

Alprazolam

Medium absorption = onset of action ~ 1 hour

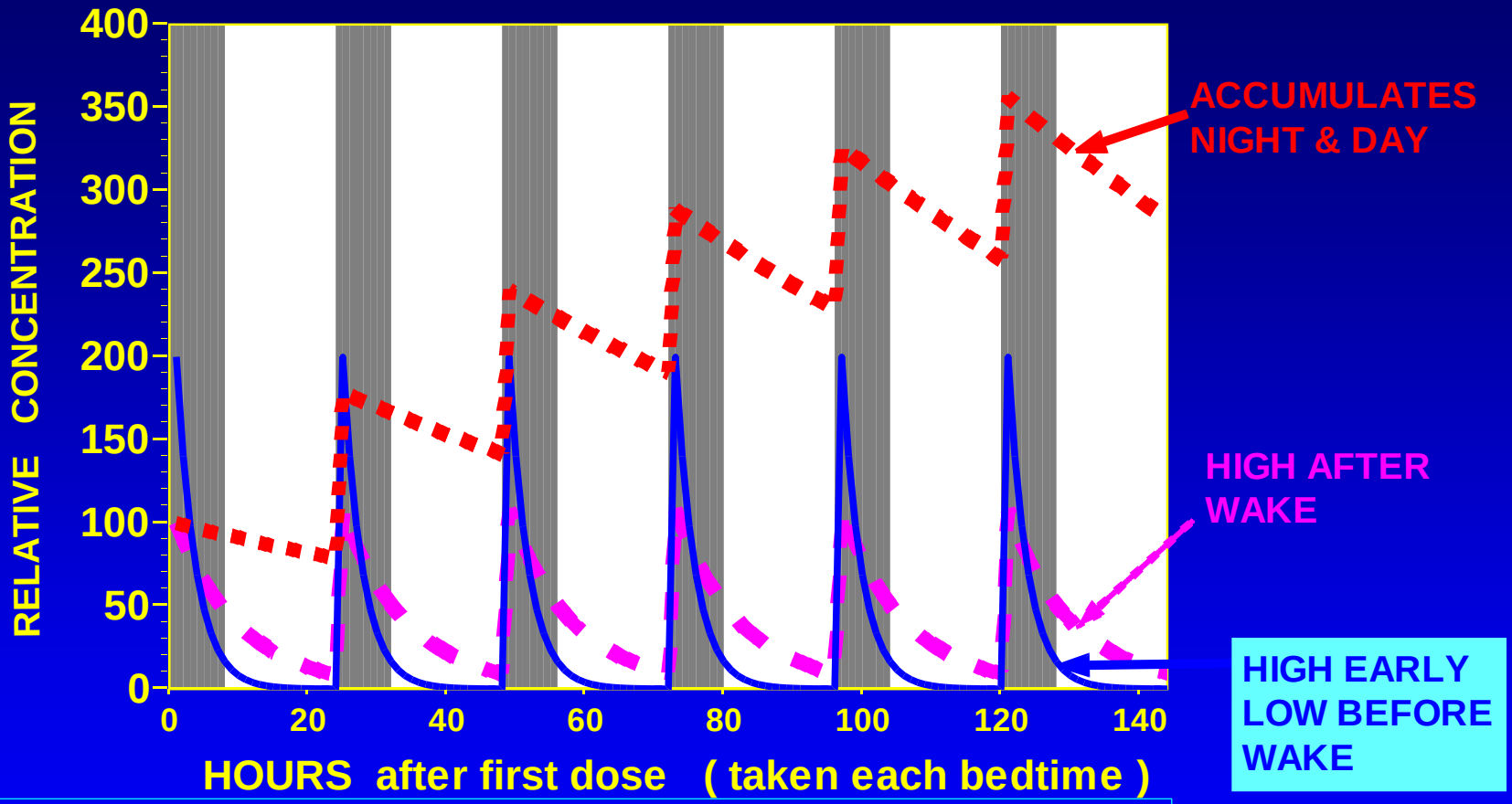
Benzodiazepine and Benzodiazepine-Like Hypnotics: Pharmacology

Drug	Onset of Action	Duration of Action	Active Metabolites
Estazolam	15 - 30 min	6 - 8 hr	Yes
Flurazepam	15 - 30 min	8 - 40 hr	Yes
Quazepam	15 - 30 min	8 - 40 hr	Yes
Temazepam	45 - 60 min	6 - 8 hr	No
Triazolam	15 - 30 min	3 - 4 hr	No
Zolpidem	15 - 30 min	4 - 7 hr	No?
Zaleplon	19 - 30 min	1 - 2 hr	No

Keck P. Modern Medicine 1992; 60:79-86

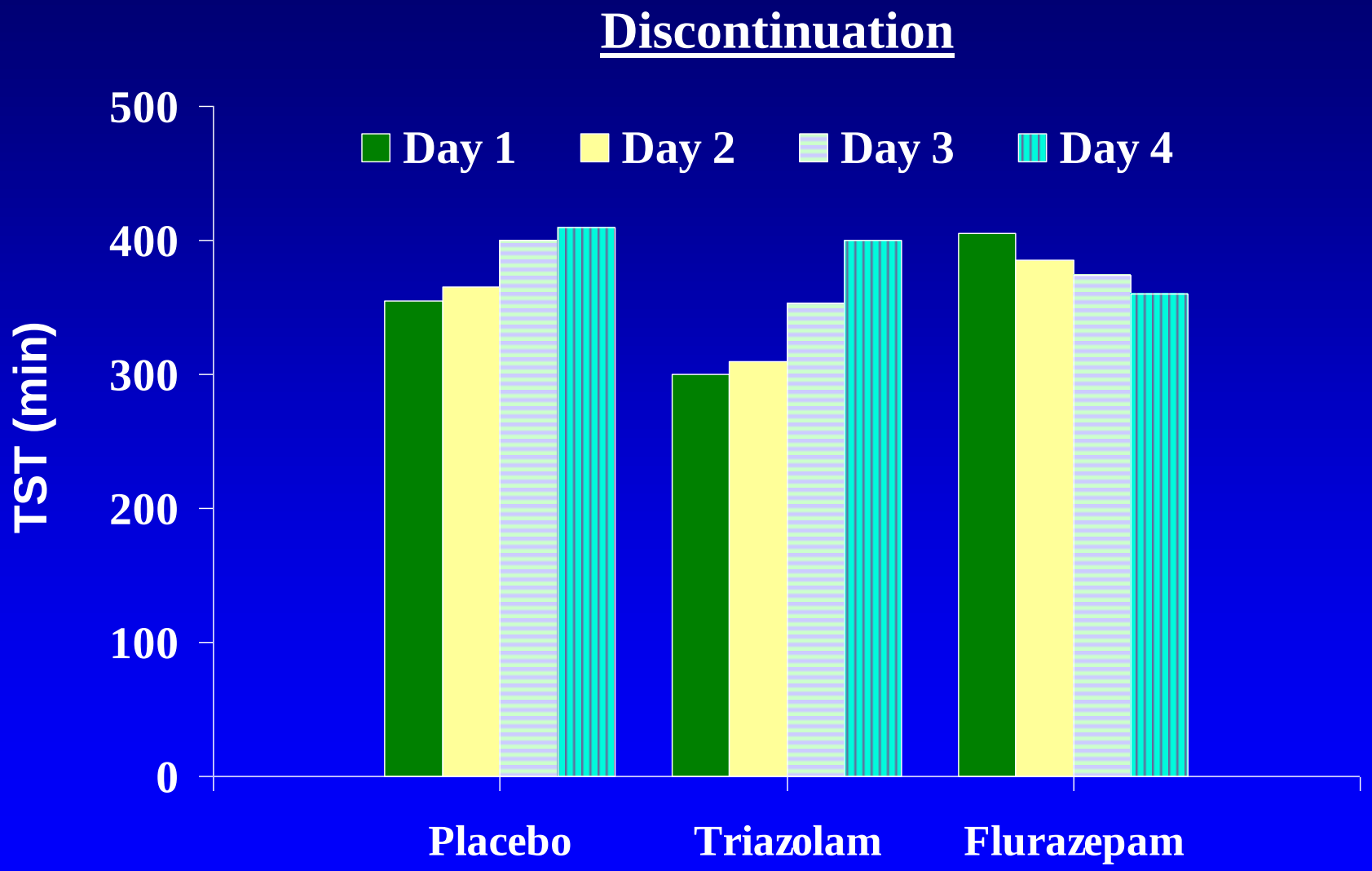
HALF-LIFE EFFECTS ON PLASMA LEVELS

NIGHT AND DAYTIME EFFECTS



Rebound Insomnia

Half-Life Effects on Total Sleep Time



Mitler MM et al. J Clin Psychopharmacol 1984; 4:2 - 13

Hypnotics for Short-Term Use
Medium Half-Life

All risk higher daytime sedation and falls in the elderly

- **Flurazepam**
- **Diazepam: rapid absorption, first-pass short half life, but metabolites accumulate**
- **Quazepam: little rebound**
- **Because delayed accumulation and elimination risks daytime sedation, increased falls, and confusion risk, long half-life hypnotics are not generally indicated**

Overdose

- Benzodiazepines alone rarely cause death
- Benzodiazepines combined with alcohol or other sedating drugs may be lethal
- Barbiturates, ethchlorvynol, glutethimide, etc. may be much more lethal

Zolpidem Pharmacokinetics

- Rapidly absorbed from GI tract (T_{max} 1.6 h)
- Short half - life (2.5 h)
- Usual dose is 10 mg
- Increased C_{max} and T_{max} in elderly, but no accumulation
- Recommended dose in elderly is 5 mg
- No dosage adjustment in patients with renal dysfunction
- Reduce dosage in patients with hepatic dysfunction

Zolpidem (Ambien)
Doses ≤ 20 mg

- Selectively binds to omega$_1$ (AKA BZ$_1$) receptor of GABA complex
  - Does not effectively bind to omega$_2$ and omega$_3$ receptor
- Does not have respiratory depressant, myorelaxant, or anticonvulsant effects
- Behaves more like a benzodiazepine in doses over 20 mg
  - Also over 20mg, risks of nausea and diarrhea increase
- Not usually recommended in doses above 10mg

Zolpidem Pharmacokinetics

Most Commonly Observed Adverse Events Seen at Statistically Significant Differences from Placebo

Short -term

- **Drowsiness 2%**
- **Dizziness 1%**
- **Diarrhea 1%**

Long-term

- **Dizziness 5%**
- **Drugged feelings 3%**

Zolpidem (Ambien) Clinical Effects

- Rapid onset of action
  - Often under 30 minutes
  - Take just prior to going to bed
- Hypnotic effect precedes myorelaxant effect
  - Most patients don't feel sleepy first, so they can fall asleep anywhere without warning
- Prolongs total sleep only average of 20 - 45 min.
  - May not treat early AM insomnia
- Better quality of sleep and feeling of refreshment reported more often than increased sleep time

Zolpidem (Ambien) Clinical Effects

- No daytime sedation in young adults
- Occasional, mild first-night rebound insomnia
- Preserves stages 3/4 sleep

Potential Problems with Zolpidem (Ambien)

- Higher doses (≥20 mg) may look like
  - Halcion: REM ⇓ etc.
- Acute effects
  - Increased postural sway
    - perhaps more falls
  - Memory and task difficulty
    - could be problem in dementia
  - Will not cover benzo hypnotic withdrawal
- Might produce dependence or tolerance

Trazodone for Insomnia

- Sleep lab studies report efficacy
- Dose: 25 - 50mg; low adipose patients usually require less
- Onset of action: 20-60 minutes
  - Average peak level in 23 minutes
- Effect on sleep stages:
  - Increases stage 4
  - Slight decrease in REM

Trazodone for Insomnia

- Advantages
  - Rapid onset of action
  - Usually minimal or no tolerance develops
  - May augment other antidepressants
- Disadvantages
  - Hypotension, dizziness
  - Daytime sedation ~20% of patients
  - GI disturbance
  - Priapism in men (1:800 to 1:10,000)
- If effective for sleep but complicated by side effects, consider nefazodone instead
  - Dose 100 - 300mg qhs

Nonbenzodiazepine Hypnotics

- Chloral hydrate
  - Onset - 1 hour
  - Half-life 4 - 10 hours
- EEG - Little effect
- Side effects
  - Gastric irritation - use milk or antacid
  - Organ toxicity - avoid in hepatic, renal or cardiac disease
- Decreased hepatic metabolism
- LD_{50} - 10gm
- Habituation and dependence - > 1 week

Pharmacological Treatment of Insomnia

Sedating TCA Antidepressants: Side Effects

- Not generally recommended for insomnia
- Orthostatic hypotension
- Sedation
- Anticholinergic effects
  - Dry mouth
  - Blurred near vision
  - Urinary retention
  - Constipation
  - Confusion

PDR 1993; Salzman C. J. Clin Psychiatry 1993; 54 (2 suppl):23-27;
Walsh JK et al. Am J Med 1990 88; (suppl 3A) 34s-38s

Antihistamines for Insomnia

- Both OTC and prescription agents used to treat insomnia
- Most contain hydroxyzine, diphenhydramine, or doxylamine
- May cause insomnia or worsen existing insomnia
- All risk negative effects on next-day functioning

Antihistamines for Insomnia Effects

- Onset 45 min - 1 hour
- Duration variable - frequently longer than 8 hours
- Decreases REM sleep

Antihistamines for Insomnia Side Effects

- Confusion - especially in elderly
- Anticholinergic - e.g., urinary retention
- AM sedation
- Habituation
- REM rebound on withdrawal
  - Causes and/or worsens insomnia
  - Can result in chronic use when acute treatment was planned

Considerations for Pharmacologic Treatment

- Elderly
  - Altered pharmacokinetics / accumulation
  - Increased incidence of sleep apnea
  - Effects on daytime performance
- History of heavy snoring
- Renal, hepatic, or pulmonary disease
- Concomitant therapy/potential interactions
- Psychiatric illness
- Occupation

Treatment

- B) OTHER APPROACHES
  - Sleep hygiene (education and counseling)
  - Relaxation therapies (e.g. hypnosis, deep breathing, meditation, muscle relaxation)
  - Sleep restriction therapy (limitation of wake time spent in bed)
  - Sleep deprivation
  - Other

Good Sleep Hygiene

- Sleep hygiene
  - consistent bedtime and waketime
  - Do not spend more hours in bed to make up for lost sleep time
  - No long daytime naps (e.g. 90 min)
  - Can try 15 - 40 min naps and closely follow sleep logs to decide if naps are OK
  - Don’t go to bed unless sleepy
- Avoid caffeine from mid afternoon on
- Avoid alcohol in the evening
- Use bedroom only for sleeping and sex
  - No work
  - No TV, etc.

Measures That Can Decrease Sleep Latency

- Daytime vigorous exercise, not evening
- Decreased stimulation prior to bedtime (avoid “action” movies, arguments, etc.)
- Sexual intercourse (good sex, not bad sex)
- Light bedtime snack (perhaps with tryptophan increasing foods, e.g., carbohydrates, dairy products)
- Tension-release relaxation exercises

Primary Hypersomnia

- Excessive sleepiness for at least 1 month (or less if recurrent). Prolonged sleep episodes or daytime sleep episodes that occur almost daily
- Clinically significant distress or impairment in social, occupational, or other important areas of functioning
- Not better accounted for by insomnia, does not occur exclusively during the course of another sleep disorder, and cannot be accounted for by an inadequate amount of sleep
- Does not occur exclusively during the course of another mental disorder
- Not due to the direct physiological effects of a substance or a general medical condition

Hypothesized Pathophysiology

DISORDER OF HYPOAROUSAL

Neurochemical or structural disorder involving limbic and hypothalamic function

Diagnosis of Primary Hypersomnia

- Rule Out
  - Sleep apnea
  - Depression
  - General medical condition that may adversely affect sleep
  - Use of medications or substances able to disrupt
  - Presence of another mental disorder (including insomnia) able to disrupt sleep
- Diagnose
  - Primary hypersomnia if hypersomnia is not related to the above disorders and has persisted for more than a month
- Treat: Stimulants

Narcolepsy

- Irresistible attacks of refreshing sleep that occur daily over at least 3 months that occur almost daily
- Cataplexy and/or recurrent intrusions of elements of rapid eye movement sleep into the transition between sleep and wakefulness, as manifested by either hypnopompic or hypnagogic hallucinations or sleep paralysis at the beginning or end of sleep episodes
- Not due to the direct physiological effects of a substance or a general medical condition

Pathophysiology:
Disorder of hypocretin/orexin neurotransmission

HERITABLE TRANSMISSION

Chromosome 6: HLA DQB1*0602

Treatment

A. Modafinil: rarely associated with substance dependence

B. Stimulants
   - Methylphenidate
   - Amphetamine: Tolerance more common; highest potential for illicit use
   - Pemoline

C. Rem Suppressing Agents, e.g.:
   - Tryciclic antidepressant
   - γ-hydroxybutyrate

Treatment

D. Other medications, e.g.:
   - Codeine
   - Propranolol
   - Bromocriptine
   - L-tyrosine
   - Selegiline:
   - Methysergide

E. Other approaches: scheduled naps throughout the wake period

Breathing-Related Sleep Disorders

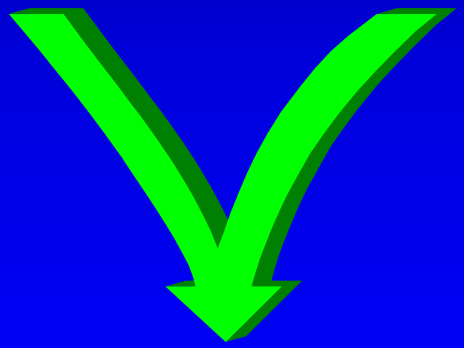
- Sleep disruption, leading to excessive sleepiness or insomnia, that is judged to be due to a sleep-related breathing condition (e.g. obstructive sleep apnea)
- Not better accounted for by another mental disorder and not due to the direct physiological effects of a substance or another general medical condition (other than a breathing-related disorder)

Sleep Apnea Detection

- Other person in room notices intervals when patient stops breathing 10 or more seconds
- Patient notices times waking up unable to breathe or gasping for air
- All night finger oximetry shows oxygen levels intermittently decreasing $\geq 4\%$
- Sleep lab studies show multiple, brief, not remembered awakenings

Pathophysiology:

- impairment in central respiratory drive malfunctioning in neurologic regulation of the set of muscles that dilate the upper airway during inspiration
- anatomic factors that reduce lumen size (e.g., **obesity**)
- reduction of phasic muscle activity (e.g, sedative-hypnotics)
- genetic factors



collapse of upper airway during respiration

Consequences

- Insomnia (occasionally)
- Daytime somnolence
- Impaired intellectual functioning
- Impaired concentration
- Depression

Diagnosis

- Electroencephalogram
- Electromyogram
- Respiratory Tracing
  - (e.g., measurements of oral and nasal airflow with thermistors)
- Oximetry
  - (oxygen saturation)
- Always Useful:
  - Electrocardiogram (possibly 24-hour-monitoring)

Associated Features

- loud snoring
- obesity
- hypertension (systemic and pulmunary)
- cardiac arrhythmias
- nocturnal cardiac ischemia
- myocardial infarction

Sleep Apnea Epidemiology

- Almost all obstructive sleep apneics snore
- Pure central sleep apneics don’t snore
- 50 - 60% of hypersomniacs have mixed or obstructive types
- 10% of persistent insomniacs have the central variety

Sleep Apnea Epidemiology In Normal Populations

- 30 - 60% y.o. workers
  - 2 - 4 % in women
  - 4 - 8 % in men
- 40 - 64 y.o. males
  - Median had 10 events/hr
  - No significant correlation between sleep apnea and daytime well being was seen in this “normal” population

Kripke et al. 1997

Sleep Apnea Epidemiology In At-Risk Populations

- Mild apnea in > 50% of adults < age 65
- Mild apnea in 80% > 65 years

Treatment

- Behavioral
  - abstinence from sedative-hypnotics
  - sleep position training (avoid supine position)
  - weight loss
- Mechanical
  - orthodontic appliances
  - tongue-retaining devices
  - nasal continuous positive airway pressure
- Surgical
  - e.g. uvulopalatopharyngoplasty; laser palatoplasty

Treatment of Sleep Apnea
Mild Obstructive

- Weight loss
- Avoid sedative-hypnotics including alcohol
- Sleeping on side
  - To train, sleeping with a rubber or tennis ball sewn into back of patient's night-garment
  - Cost of this medical procedure < $2

Treatment of Sleep Apnea Moderate to Severe Obstructive

- Continuous positive airway pressure
- Surgery (less proven)
  - Soft-palate surgery may decrease apneic episodes
- Mandibular and tongue advancement devices

Treatment of Central Apnea

- Low-flow nasal oxygen
- Diaphragmatic pacing
- Medications
  - Estrogen
  - Stimulating antidepressants (protryptyline, desipramine)
  - Stimulants
  - Acetazolamide
- CPAP

Sedative Hypnotics and Sleep Apnea

- Can push snorer into sleep apnea
- Can worsen sleep apnea
- Can worsen COPD

Periodic Limb Movement Disorder Insomnia (PLMDI) and Restless Leg Syndrome

Diagnosis

- RLS:
  - Legs squirm before sleep; not all day like akathisia
  - Patient complains of onset insomnia
- PLMDI:
  - Periods of rhythmic kicking during sleep
  - Bed partner more likely to report it
  - Patient complains of hypersomnia and fatigue
- 50 - 80% of patients with RLS have PLMDI

Periodic Limb Movement Disorder Insomnia (PLMDI) and Restless Leg Syndrome

- Treatment
- Benzodiazepines are palliative, not curative
  - Soothes RLS discomfort
  - Increases sleep continuity in PLMDI
- Carbidopa-levopoda for:
  - RLS - reduces discomfort
  - PLMDI - exacerbates and sometimes causes

Circadian Rhythm Sleep Disorder

- Delayed Sleep Phase Type
- Advanced Sleep Phase Type
- Jet Lag Type
- Shift Work Type
- Unspecified Type

Pathophysiology:

misalignment between sleep and biological rhythms

due to external demand
due to a diminished capacity to respond to external zeitgebers (e.g., blind subjects)

Treatment

A. Promote sleep hygiene

B. If the disorder is due to a diminished capacity to respond to external zeitgebers:

- Melatonin
- Phototherapy

Symptoms of Delayed Sleep Phase

- Can’t get to sleep at night
- Can’t get up in the morning
- Tired most of the day
- More alert in the evening

Treatment of Delayed Sleep Phase

- Bright light in the morning: as soon after arising as possible
- Vitamin B12: 1-3mg orally daily
  - Some evidence that it phase advances
  - Might augment light treatment

Ohta et al. 1992

Symptoms of Advanced Sleep Phase

- Drowsy or falls asleep early in the evening
- Awakens too early in the morning
- Most energetic in the morning

Treatment of Advanced Sleep Phase

- Use brighter light in the evening
  - 1-3 hours before bedtime
- Often 50 - 100 watts fluorescent is sufficient
  - Usually best near the television
  - Torchieres have good acceptance

Melatonin

A night hormone which makes
gonads atrophy
and can turn fur white

Melatonin Risks

- Long-term safety in humans not established:
  - Probably causes gonadal suppression in young men and women and may cause infertility
  - Suspected risks of seizure, myocardial infarction, or stroke
  - Purity and potency of over-the-counter preparations is variable
  - Might cause or protect against cancer

Melatonin for Insomnia

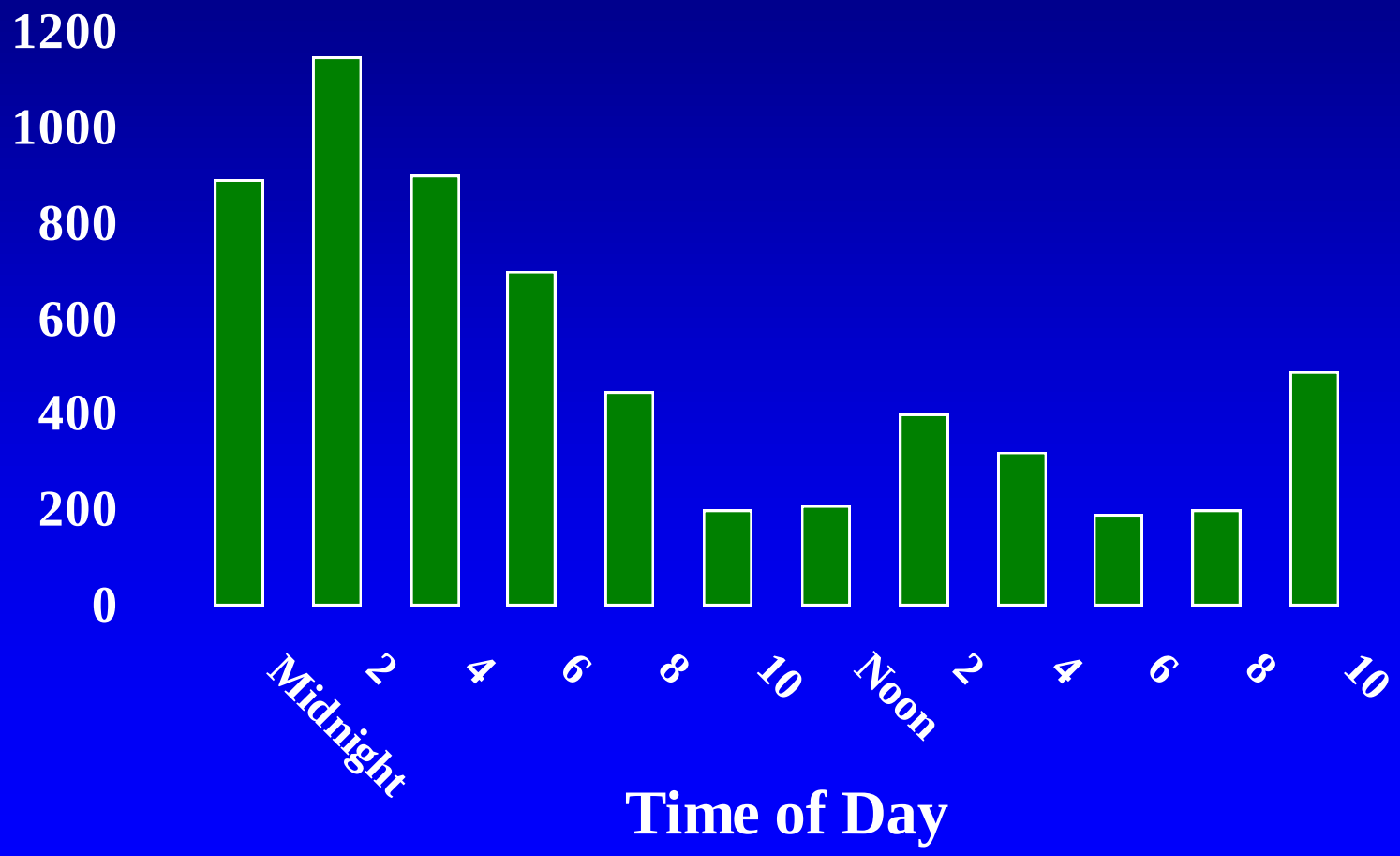
- Effectiveness and safety not demonstrated for chronic insomnia
- Some evidence of minor short-term benefits

Uses of Melatonin

- Jet lag: weak efficacy (some, not all studies), but not without side effects
- Shift work: weak efficacy in some studies. No studies beyond a few days

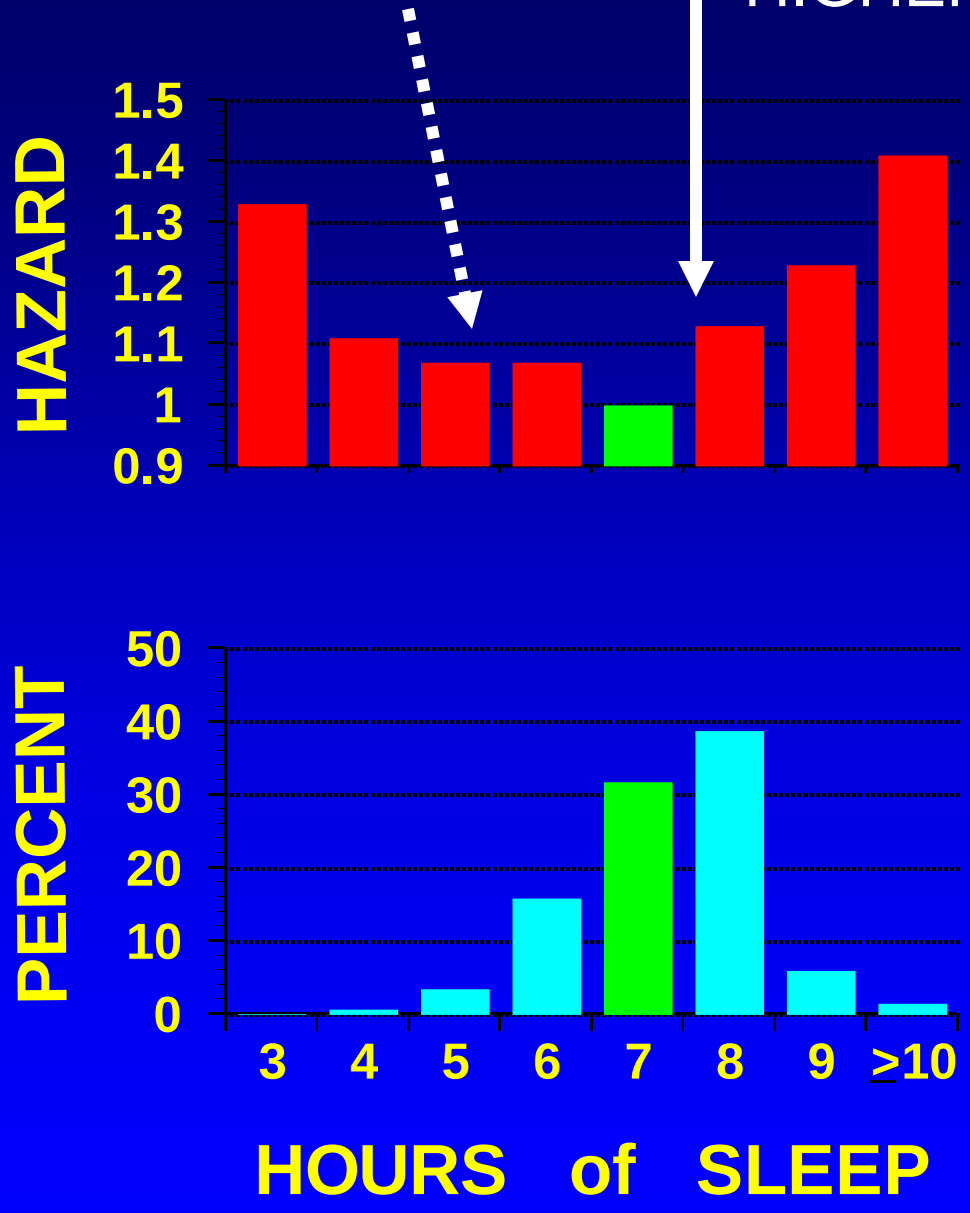
Fatigue-Related Auto Accidents

Compiled Data



NOT MUCH RISK TO SLEEPING 5-6 HOURS

8 HOURS SLEEP HIGHER MORTALTIY



It is safe not to sleep 8 hours, as long as patient is not too sleepy:

Kripke et al., *Arch. Gen. Psychiatry* 2002;59:131-136

Post Lecture Exam Question 1

1. **The most common cause of insomnia is**

A. Use of sleeping pills

B. Poor sleeping habits

C. Depression

D. Alcoholism

E. Sleep apnea

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C. Relaxation and sleep hygiene

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Answers to Pre & Post Competency Exams

1. C
2. D
3. B
4. A
5. A
6. C
7. B
8. D
9. E
10. B