SLEEP DISORDERS

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★ ←marks important slides. See notes for explanations.

Pre-Lecture Exam Question 1

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

A. Use of sleeping pills

B. Poor sleeping habits

C. Psychiatric disturbance

D. Alcoholism

E. Sleep apnea

Question 2

2. Effective treatment for chronic insomnia may include:

A. Zaleplon

B. Sleep restriction therapy

C. Zolpidem

D. Quazepam

E. Triazolam

Question 3

3. Benefits of hypnotics outweigh risks:

A. For insomnia due to medical conditions

B. For hospice care

C. To prevent depression

D. To improve daytime alertness

E. All of the above

Question 4

4. **A hypnotic which causes little daytime sedation is:**

A. Lorazepam

B. Zolpidem

C. Temazepam

D. Flurazepam

E. Diphenhydramine

Question 5

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

A. 6.25 mg

B. 10 mg

C. 15 mg

D. 20 mg

E. 25 mg

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

A. Zaleplon

B. Temazepam

C. Lorazepam

D. Oxazepam

E. Ethchlorvynol

Question 8

8. The most common cause of excessive sleepiness 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. Relaxation and sleep hygiene

C. Methylphenidate

D. Bright light in the morning

E. Bright light just before bedtime

OUTLINE

- Sleep disorders: definitions
- Insomnia
- Hypnotics: risks and choices
- Cognitive behavioral therapy (CBT)
- Sleep apnea
- Narcolepsy
- PLMD (periodic limb movements)
- Circadian rhythm sleep disorders

KEY POINTS

- Cognitive-behavioral therapy is best for chronic insomnia
- Hypnotics risks usually outweigh benefits
- Sleep apnea is the most common cause of excess sleepiness
- Circadian rhythm disorders can be treated using the light phase response curve

SLEEP DISORDERS

- Primary
- Comorbid:
  - Related to Another Mental Disorder
  - Due to a General Medical Condition
  - Substance-Related
- Often can’t be distinguished

SLEEP DISORDERS

- Insomnia
- Breathing disorders
- Hypersomnia & narcolepsy
- Circadian disorders
- Parasomnias
- Movement disorders

INSOMNIA: 1) Sleep Difficulty

- Complaints of disturbed sleep in the presence of adequate opportunity and circumstance for sleep
  - (1) difficulty in initiating sleep
  - (2) difficulty in maintaining sleep or
  - (3) waking up too early
  - ? nonrestorative or poor-quality sleep

- NIH conference on chronic insomnia

  http://consensus.nih.gov/2005/2005InsomniaSOS026html.htm

INSOMNIA: 2) Daytime Hyperarousal

Some patients with chronic insomnia have daytime hyperarousal and are not able to fall asleep in the day. They might be fatigued, but they are not sleepy.

INSOMNIA:
3) Functional Impairment Associated

- Several studies show decreased quality of life and impaired daytime function associated with insomnia.

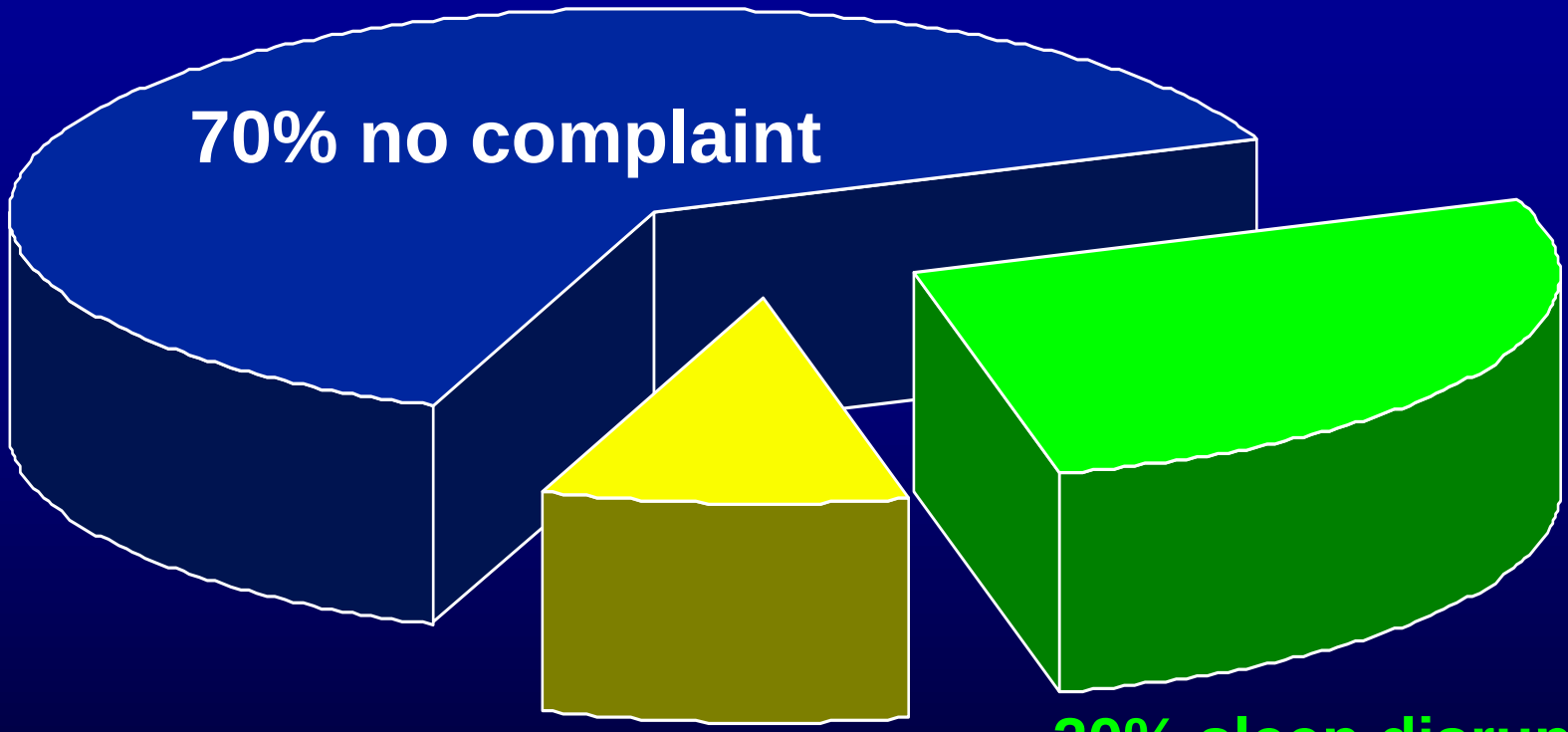
- However, it is difficult to distinguish any causal effects of insomnia from effects of comorbidities such as depression and anxiety.

- **Most insomnia is comorbid with other disorders, most commonly depression, substance abuse and anxiety.**
- **In comorbid insomnia, it is unclear when treatment focus should be on comorbidities.**
- **Primary insomnia is insomnia without comorbidities.**

MENTAL ILLNESS & INSOMNIA

- About half of all insomnia is comorbid with a mental illness.
- There is no doubt that mental illnesses, especially depression, anxiety, and substance use, sometimes cause insomnia.
- Some argue that insomnia may be a cause of depression or other mental illness, but the proof is not yet available.

Prevalence of Insomnia in U.S.



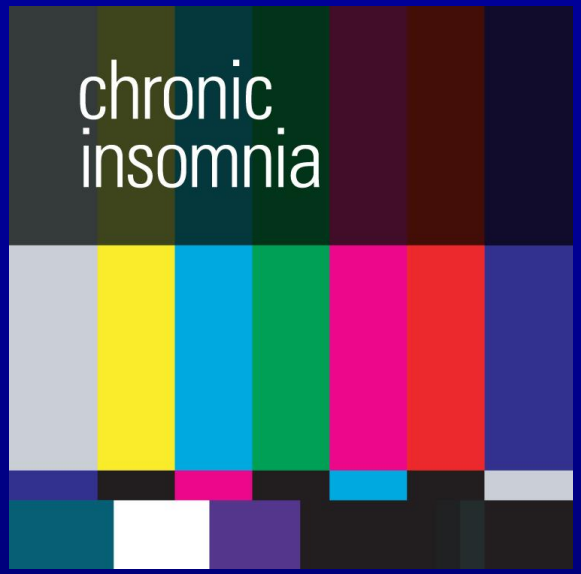
National Institutes of Health State of the Science Conference statement on Manifestations and Management of Chronic Insomnia in Adults, June 13-15, 2005. *Sleep* 2005;28(9):1049-57

INSOMNIA TREATMENTS

- Cognitive-behavioral therapy: best demonstrated long-term efficacy and least side effects
- Hypnotics: most hypnotics not recommended for more than 1 month's use
- Sedative antidepressants: little data

CHRONIC INSOMNIA

- Most insomnia is chronic
- Lasts for years
- Natural history not well studied
- Primary and comorbid insomnia hard to distinguish



NIH conference on chronic insomnia found better evidence for cognitive-behavioral treatments than for long-term pharmacologic agents.

- http://consensus.nih.gov/2005/2005InsomniaSOS026html.htm

COGNITIVE-BEHAVIORAL TREATMENT of INSOMNIA

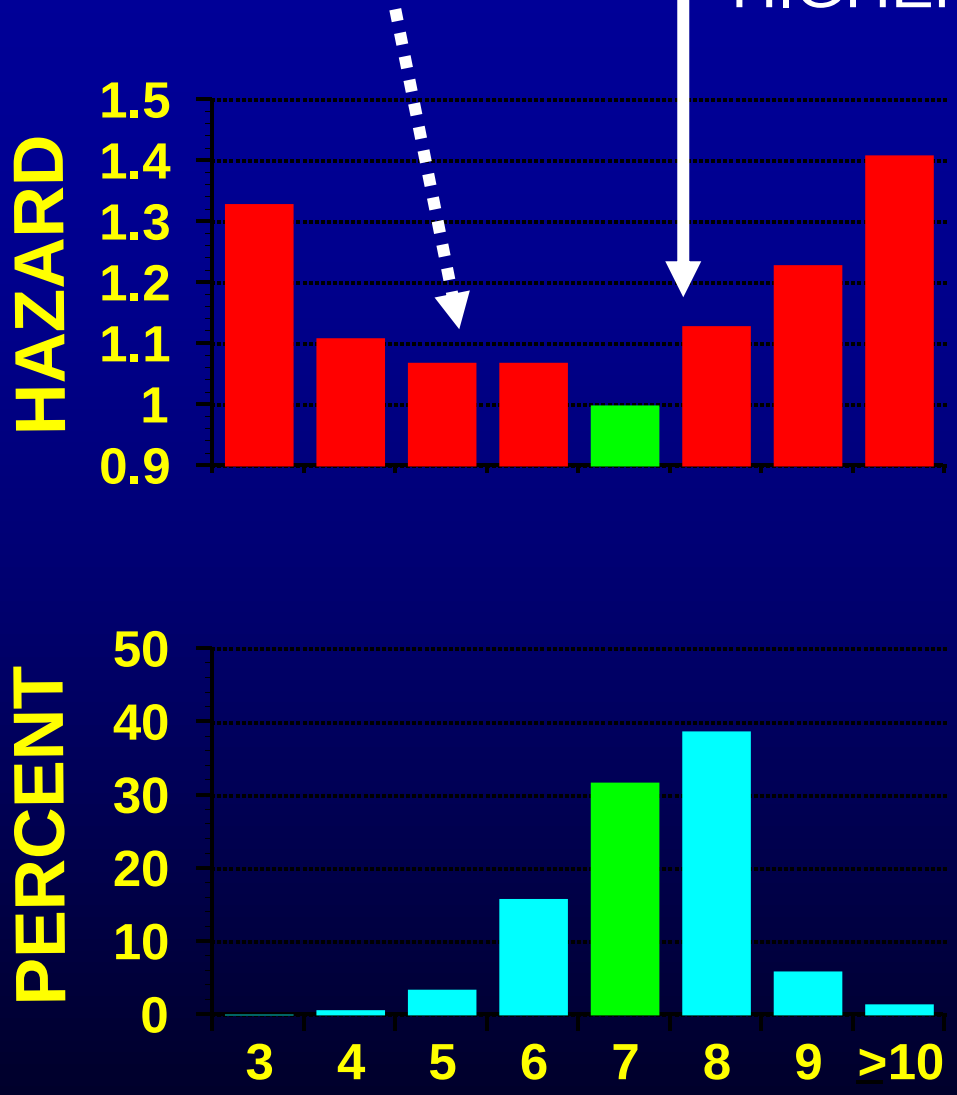
- Cognitive treatment (why “Not to worry!”)
- Sleep hygiene (education and counseling)
- Relaxation therapies (e.g., deep breathing, meditation, muscle relaxation)
- Sleep restriction therapy (limitation of time spent in bed)

COGNITIVE ELEMENT:

- The healthiest people sleep 6.5 – 7.5 hours. It is safer to sleep 5-6 hours than 8-10 hours.
- The average adult in the U.S. sleeps 6.5 hours: most do not need 8 hours.
- It is normal for older people to awaken often at night.
- People with insomnia live longer than people without insomnia: Not to worry!
- It is harmful to spend longer in bed than you can sleep.

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

GOOD SLEEP HYGIENE

- Sleep hygiene
  - consistent bedtime and wake time
  - Do not spend extra hours in bed to make up for poor sleep
  - 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
- Limit alcohol in the evening
- Use bedroom only for sleeping and sex

AVOID ALERTING IN BED

- If patient needs to spend time worrying, do it in a worry chair
- Mystery books and watching TV should be avoided in bed.
- Where possible, do alerting activities outside the bedroom

Measures That Can Decrease Sleep Latency

- Tension-release relaxation exercises: meditative, autogenic, Jacobsonian, etc.
- Decreased stimulation prior to bedtime (avoid “action” movies, arguments, etc.)
- Light bedtime snack (perhaps milk or other tryptophan-increasing foods, e.g., carbohydrates, dairy products)

SLEEP RESTRICTION

- **Reducing time-in-bed has powerful and lasting benefits for insomnia.**
- **E.g., a patient who says she only sleeps 6 hours should reduce time-in-bed to 6 hours.**
- **Correct negative conditioning to the bedtime experience: RELEARN that when you go to bed, you habitually go to sleep.**

SLEEP RESTRICTION

- If patient is sleeping >85% of time in bed, may increase time in bed by 15 min. per week
- If patient reports sleeping <85% of time in bed, then time in bed should be reduced
- Maintain a regular get-out-of bed time

Hypnotics:

Only 3 for Long-Term Use

FDA-approved based on 6-month studies with subjective data for efficacy:

- **Eszopiclone**
- **Zolpidem tartrate extended release**
- **Ramelteon**

Hypnotics for Short-Term Use

SHORT Half - Life

Zolpidem: receptor specificity, low rebound, favorable kinetics, strange behaviors

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

Zaleplon: receptor specificity, half life too short

Hypnotics for Short-Term Use

MEDIUM Half - Life

Temazepam: onset ~1 hour, daytime sedation

Lorazepam: onset ~1 hour

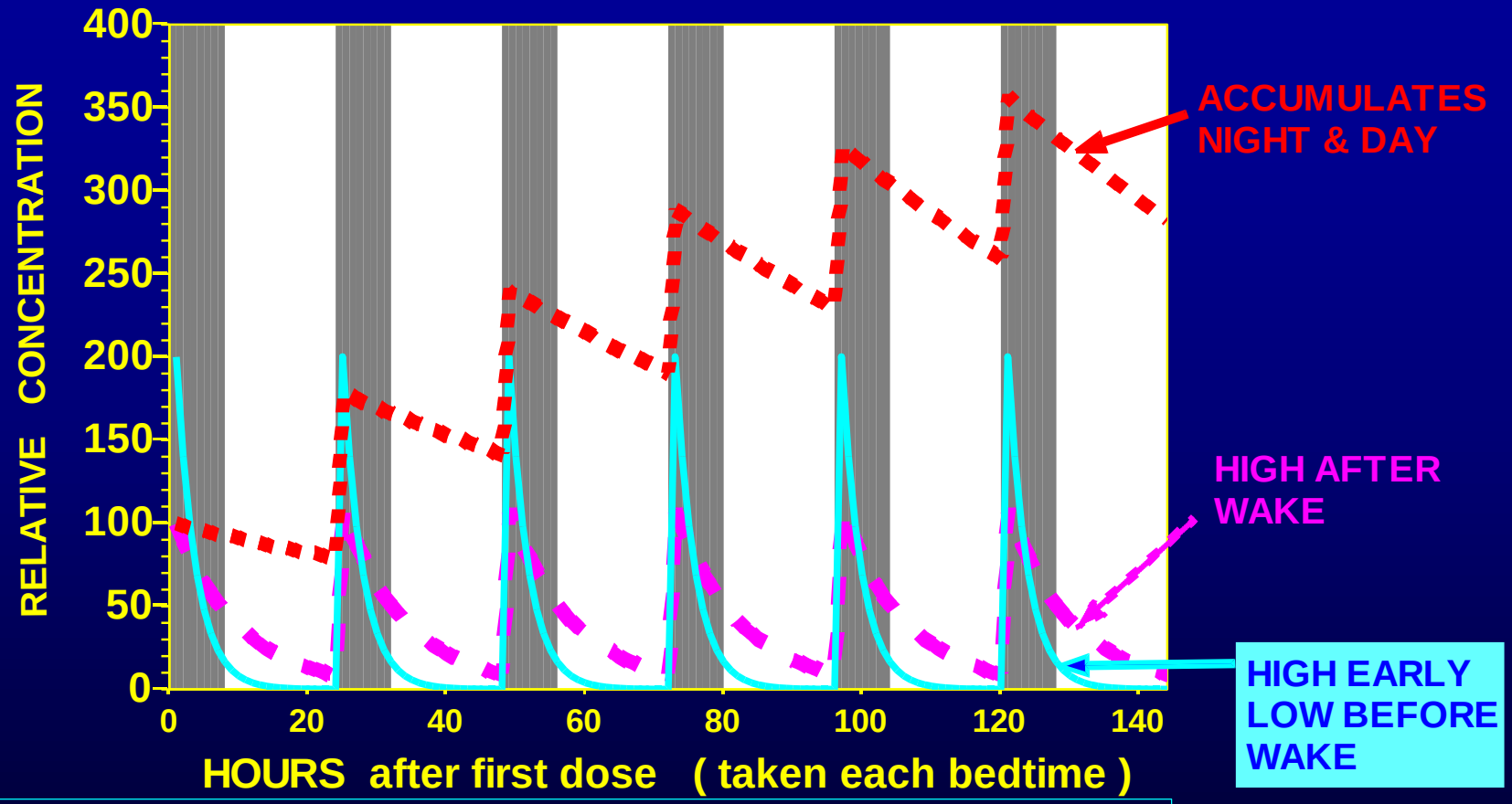
Estazolam

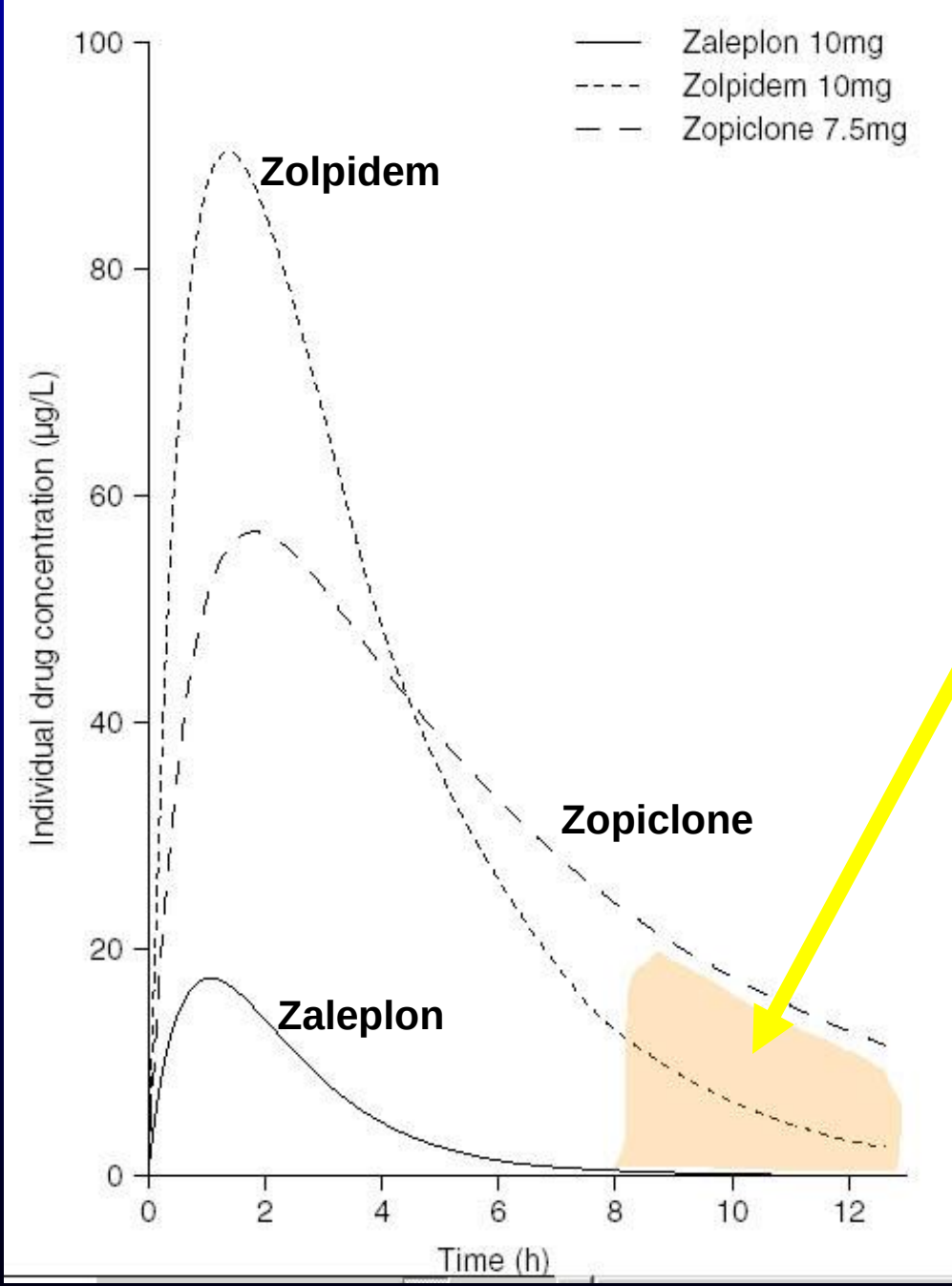
Alprazolam?

Long Half-Life Hypnotics for Short-Term Use:

- Flurazepam and quazepam
- Diazepam: rapid absorption, first-pass short half life, but active metabolites accumulate
- Because of delayed accumulation and delayed elimination risk, **daytime sedation, increased falls, and confusion,** long half-life hypnotics are <u>not generally indicated</u>, especially for elders

HALF-LIFE EFFECTS ON PLASMA LEVELS





Predicted HANGOVER. Zolpidem sustained release ? similar to eszopiclone

Adapted from:
Drover, D.R.
Clin. Pharacokinet.
2004;43:227-238.

	Drug	Brand	Dosage	Half-life	Absorption
Z drugs	zolpidem	Ambien or generic	5-10 mg	2.2-2.9 hr	fast
	zolpidem extended	Ambien CR	6.25-12.5 mg	2.2-2.9 hr	1/2 fast, 1/2 slower
	eszopiclone	Lunesta	2-3 mg	6-9 hr	fast
	zaleplon	Sonata	5-10 mg	1 hr	fast

	Drug	Brand	Dosage	Half-life	Absorption
Benzodiaze-pines	quazepam	Doral	7.5-15 mg	25+ hr	fast
	triazolam	Halcion or generic	.125-.25 mg	1.5-5.5 hr	fast
	flurazepam	Dalmane or genetic	15-30 mg	4 days + (metabolites)	fast
	estazolam	ProSom	1-2 mg	10-24 hr	fast-moderate
	temazepam	Restoril or generic	15-30 mg	8-20 hr	inconsistent information
	lorazepam	Ativan or generics	0.5-2 mg	9-16 hr	slow
	oxazepam	Serax	10-15 mg	4-14 hr	slow

	Drug	Brand	Dosage	Half-life	Absorption
Other	ramelteon	Rozerem	8 mg	2-5+ hr (metabolites)	rapid
	secobarbital	Seconal	100 mg	15-40 hr.	rapid
	trazodone	Desyrel	25-100	3-9 hr	rapid

META - ANALYSIS

A new NIH-sponsored meta-analysis has raised a question whether the new benzodiazepine agonists ("Z" drugs) produce any significant increase in objective (EEG) total sleep time for chronic insomnia.*

*Buscemi N, Vandermeer B, Friesen C et al. The Efficacy and Safety of Drug Treatments for Chronic Insomnia in Adults: A Meta-analysis of RCTs. *J Gen Intern Med* 2007;22:1335-50.

META - ANALYSIS

Advantage of Benzodiazepine Agonists (Z drugs) vs. Placebo

	OBJECTIVE	SUBJECTIVE
Total Sleep Time	11.4 min (-0.5, 23.2)[NS]	31.5 min (25.6, 37.5)
Sleep Onset Latency	-12.8 min (-17, -9)	-17.0 min (-20, -14)
Wake After Sleep Onset	-7.0 min (-14.6, 0.7)[NS]	-15.0 min (-19.1, 4.9)[NS]
Sleep Efficiency	4.7% (3.1, 6.2)	5.0% (1.5, 8.6)

The numbers represent benefits of drug versus placebo (mean and 95% confidence limits). For Total Sleep Time and Sleep Efficiency, a positive increase was desirable, but for Sleep Onset Latency and Wake After Sleep Onset, a negative decrease indicated benefit.

Objective benefits for Total Sleep Time and Wake After Sleep Onset were NOT significant = NS. Subjective benefits were greater but not impressive.

META - ANALYSIS

- This new meta-analysis found that the drug groups had a “significantly higher risk of harm” than placebo, that is, participants taking “Z” drugs experienced more adverse symptoms.

- There was strong evidence for publication bias, that is, unpublished results were quite likely worse than the results published and analyzed.

ANOTHER META - ANALYSIS: OVER AGE 60, RISKS > BENEFITS: Hypnotics Not Recommended

- Number needed to treat for improved sleep quality was **13**.
- Number needed to harm for any adverse event was **6!**

Glass J, Lanctot KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ 2005 November 11*.

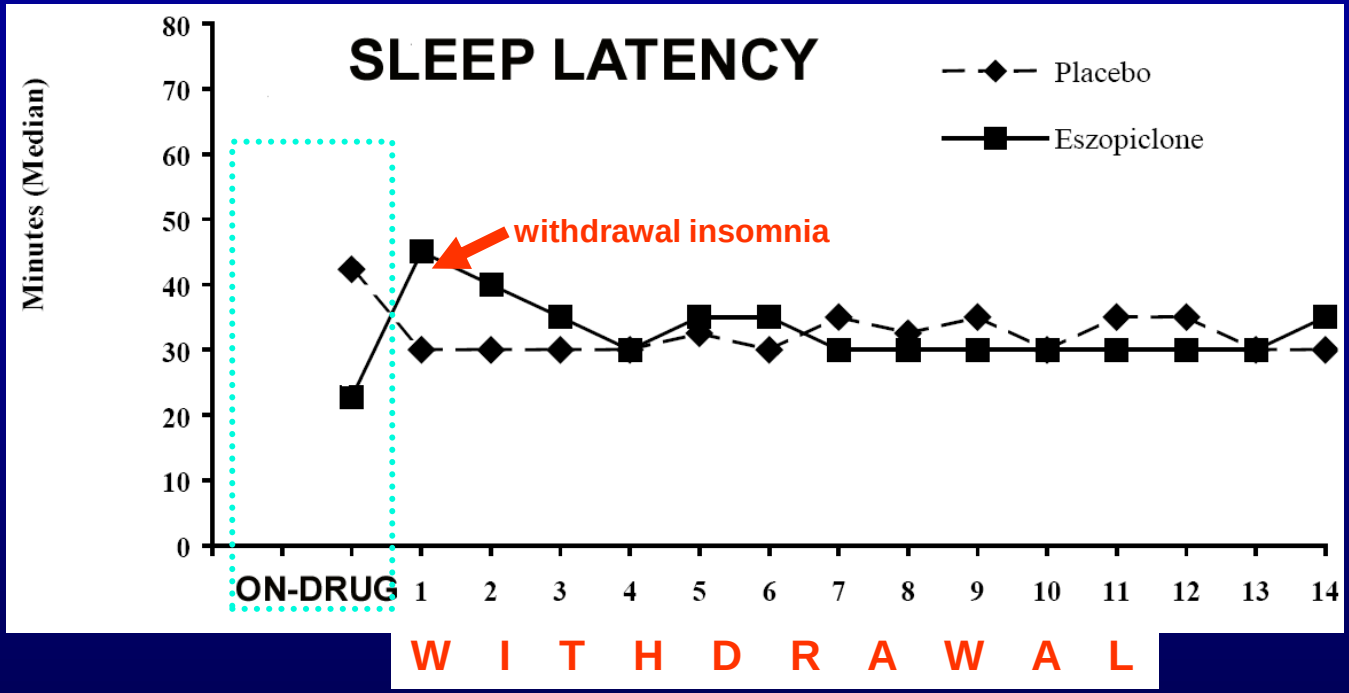
DAYTIME IMPAIRMENT

- Preponderance of objective evidence that all hypnotics result in daytime impairment, NOT improved function.
- However, recent trials have demonstrated subjectively reported improvements in function.
- Note the disjunction between objective and subjective measures of benefit.

DAYTIME IMPAIRMENT

- Daytime impairment is much worse from hypnotics with half-life >>4 hours.
- Risks include increased automobile accidents, falls, memory loss, and confusion.

REBOUND INSOMNIA



After 6 months eszopiclone 3 mg., on the first withdrawal night, the hypnotic group slept WORSE than the placebo group. Adapted from Walsh JK, Krystal AD, Amato DA et al. Nightly treatment of primary insomnia with eszopiclone for six months: effect on sleep, quality of life, and work limitations. *Sleep* 2007;30(8):959-68.

REBOUND INSOMNIA

Likewise, a patient taking zolpidem a few times a week sleeps worse on nights skipping medication than after skipping placebo.

***Walsh JK*. Zolpidem "as needed" for the treatment of primary insomnia: A double-blind placebo-controlled study. *Sleep Medicine Reviews* 2002;6(Suppl. 1):S7-S11. See correction pp. 195-196.**

OVERDOSE

- Acute ingestion of benzodiazepine agonists alone rarely causes death.
- Benzodiazepines combined with alcohol or other sedating drugs may be lethal.
- Barbiturates, ethchlorvynol, glutethimide, etc. may be much more lethal.

Over a Dozen STUDIES FOUND

INCREASED MORTALITY

ASSOCIATED WITH HYPNOTICS USE*

Kripke et al 1979
Allgulander et al 1987
Allgulander et al 1990
Rumble and Morgan 1992
Thorogood et al 1992
Merlo et al 1996
Sundquist et al 1996
Kojima et al 2000
Kripke et al 2002
Mallon et al 2002
Ahman & Bath 2005
Hausken et al 2007
Mallon et al, 2009

* Causality unproven. Most data for older hypnotics.

QUESTION of DEPRESSION RISK

	SUBJECTS	DEPRESSED
TOTAL OF 4 HYPNOTICS	5535	109 (2.0%)
TOTAL OF 4 PLACEBO GROUPS	2318	21 (0.9%)

In randomized trials of zolpidem, zaleplon, eszopiclone, and ramelteon, depression was reported more often in drug than placebo groups:

Chi Square = 10.39, p<0.002, risk ratio = 2.2

Kripke DF. *BMC Psychiatry* 2007;7:42.

Question of Infection

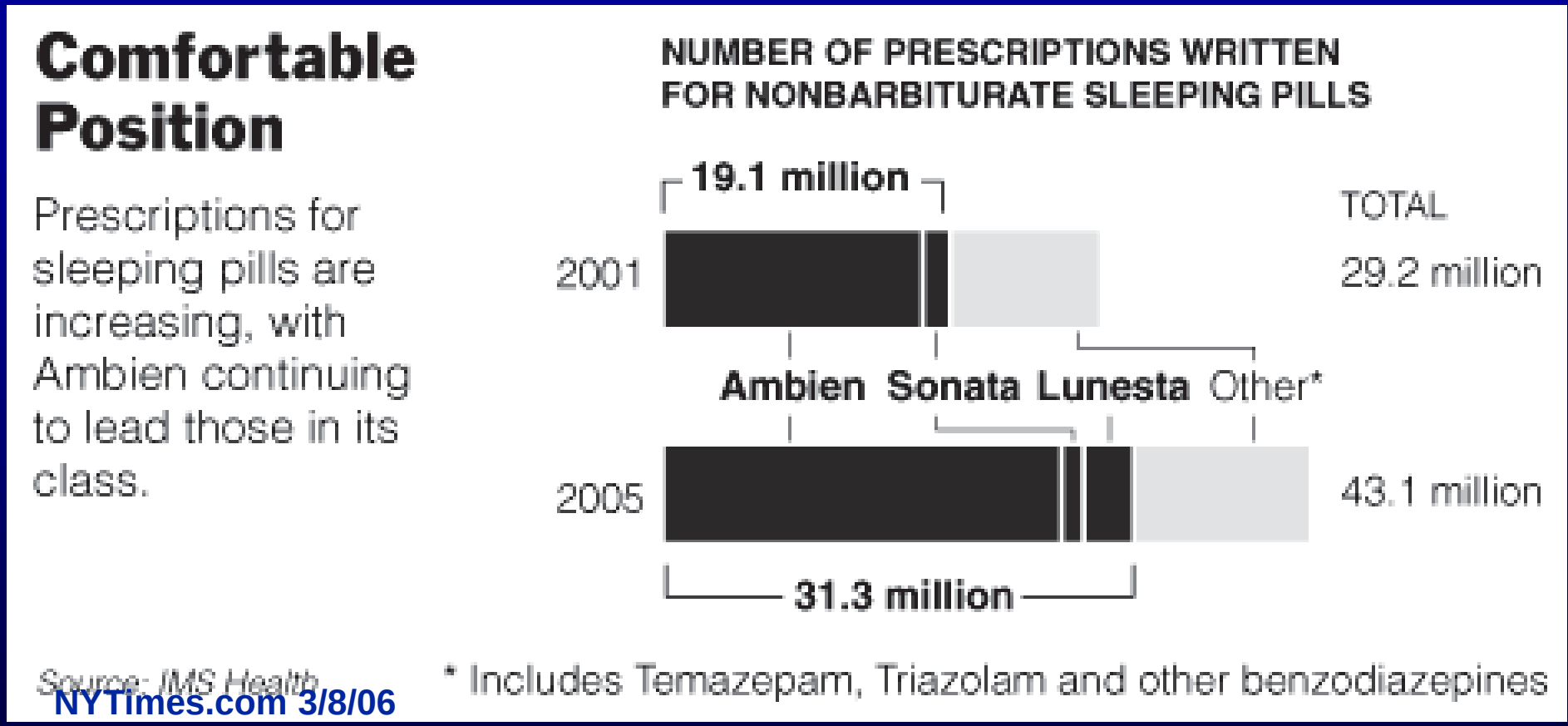
- In controlled trials of zolpidem, zaleplon, eszopiclone, and perhaps ramelteon, more frequent infections were reported in drug than in placebo groups.
- Overall, there were 44% more infections reported among those randomized to drug than to placebo
- The medical import is not yet understood. Possibly, some of the symptoms were due to gastro-esophageal reflux.

- Joya, F. et al. J. Clin. Sleep Med. *2009*;5:377-383

Question of Cancer

- In controlled trials of zolpidem, zaleplon, eszopiclone, and ramelteon, there were 13 cancers (9 skin cancers) in those randomized to hypnotic and none among those randomized to placebo. Kripke, D.F. J. Sleep Res. 2008;17:245–250
- Some experts do not believe these data indicate that hypnotics cause cancer. Friedman, G.D. J. Sleep Res. 2008;17:243-244.

Zolpidem the market leader



NYTimes.com 3/8/06

Sales are up in 2009 due to generic zolpidem.

Trazodone and antihistamines are also frequently used as hypnotics.

Zolpidem Clinical Effects

- Rapid onset of action
  - Often under 30 minutes
  - Take just prior to getting into bed
- Hypnotic effect precedes myorelaxant effect
  - Most patients don't feel sleepy first, so they can fall asleep anywhere without warning
  - Bad accidents happen when zolpidem is taken too long before bedtime

Zolpidem Clinical Effects

- Prolongs total sleep 20 - 45 min. or less
  - May make early AM insomnia worse
- Maximum dosage:
  - Adults: 10 mg or 12.5 mg (extended release)
  - Elderly: 5 or 6.25 mg (extended release)
- Beyond the recommended maximum, zolpidem causes more severe daytime impairment, more addiction, and more behavioral disturbances.

	Eszopiclone	Zolpidem
HALF LIFE	6 hours (9 hours in elderly)	2.6 hours (? 3 hours in elderly)
RECEPTOR SPECIFICITY	Medium	High

ESZOPICLONE

- FDA permitted an indication for long-term use, 2005
- Several studies have claimed improved functioning with long-term use, based on subjective data.*
- However, severe adverse effects were 3 times as common with eszopiclone as with placebo.*
- Dropouts for depression were 12 in the eszopiclone group and 0 in the placebo group.*

* Krystal AD, Walsh JK, Laska E et al. *Sleep* 2003;26(7):793-9.

ESZOPICLONE

- Likely to produce more hangover than zolpidem or zaleplon
- Impairs morning digit symbol substitution as compared to placebo
- Same active ingredient as zopiclone, which was associated with excess auto accidents in Europe
- Maximum dosage 3 mg. (2 mg. elderly)

WEIRD ADVERSE EFFECTS OF "Z" DRUGS

- Hallucinations
- "Zombie driving"
- Somnambulistic night eating
- Confusion & amnesia
- Combined incidence may exceed 1%

RAMELTEON

- FDA approved long-term use indication, 2005
- Melatonin agonist
- Does not bind to benzodiazepine-GABA receptor: no cross-tolerance
- Complex metabolism, active metabolites

RAMELTEON

- **Little benefit:** Appears to reduce sleep latency 7 – 16 min, but has little or NO value for maintaining sleep—similar to melatonin
- Little dose-response: 8 mg. for all

RAMELTEON BANNED!

- **The European Committee for Medicinal Products for Human Use (CHMP) has issued a negative opinion on the use of the melatonin receptor agonist ramelteon in insomnia, due to its unfavourable risk-benefit balance. In France, melatonin itself is licensed for use in this indication. --*Prescrire Int* 2009 June;18(101):114.**

RAMELTEON

- Likely to have no risk of dependency and less other risks than benzodiazepine agonists

- Possible affects on reproductive endocrinology, e.g., prolactin, testosterone

META – ANALYSIS of ANTIDEPRESSANTS*

- According to meta-analysis of a very small number of studies, antidepressants may produce more benefit for sleep than benzodiazepine agonists.

*Buscemi N, Vandermeer B, Friesen C et al. The Efficacy and Safety of Drug Treatments for Chronic Insomnia in Adults: A Meta-analysis of RCTs. *J Gen Intern Med* 2007;22:1335-50.

TRAZODONE for INSOMNIA

- 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 be antidepressant or augment other antidepressants
- Disadvantages
  - Hypotension, dizziness
  - Daytime sedation ~20% of patients
  - GI disturbance
  - Priapism in men (1:800 to 1:10,000)
  - Cardiac rhythm risks

TRAZODONE

- Very little study of hypnotic efficacy beyond 2 weeks
- May have more adverse effects than benzodiazepine agonists
- Probably does not cause dependency

TCA ANTIDEPRESSANTS

- Not generally recommended for insomnia without depression
- Orthostatic hypotension
- Daytime 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

DOXEPIN

- Doxepin is possibly effective in lower doses than other tricyclics (6 mg.), due to antihistaminic properties. An NDA is pending.

NonBENZODIAZEPINE HYPNOTICS

- **Chloral hydrate**
  - Onset - 1 hour
  - Half-life 4 - 10 hours
- EEG - Little distortion
- 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

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

SLEEP APNEA

The most common cause of complaints of excessive sleepiness (falling asleep in the day)

SLEEP APNEA DETECTION

- Observed patient stops breathing 10 or more seconds
- Patient notices waking up unable to breathe or gasping for air
- All night finger oximetry shows O2 saturation intermittently dipping

- Snoring, a common sign

APNEA SYMPTOMS

- Daytime somnolence
- Snoring, often loud
- Insomnia Sx (occasionally)
- Impaired intellectual functioning
- Impaired concentration
- Depression
- Hypertension

ASSOCIATED FEATURES

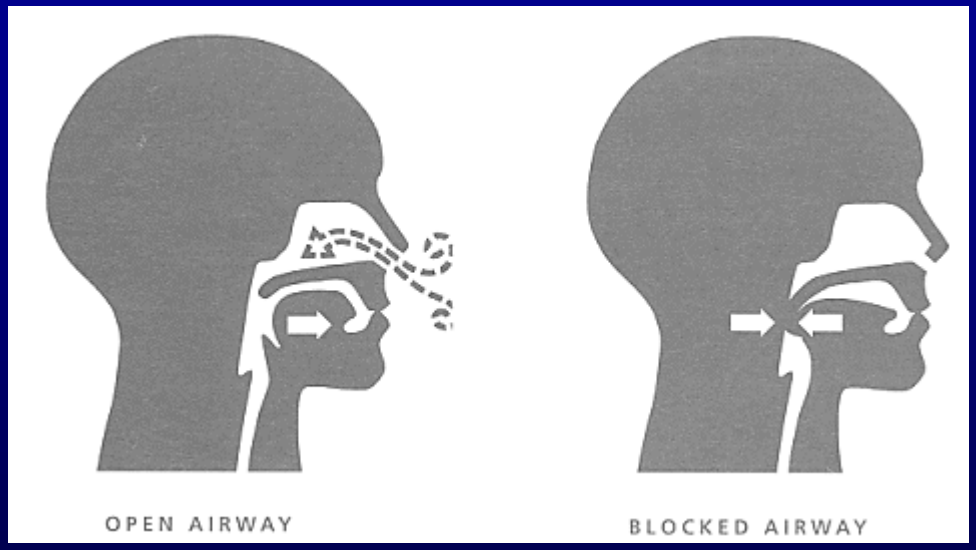
- obesity
- automobile accidents due to sleepiness
- hypertension (systemic and pulmonary)
- cardiac arrhythmias

Pathophysiology:

- anatomic factors that reduce airway lumen size (e.g., obesity, poor dental development)
- impairments in central respiratory drive: malfunctioning in neurologic regulation of the muscles that dilate the upper airway during inspiration
- disordered respiratory feed-back loops
- relaxation of phasic muscle activity (e.g, sedative-hypnotics, alcohol)

collapse of upper airway during inspiration

APNEA



Sleep Apnea Epidemiology In Normal Populations

- Workers age 30 – 60 years (hypersomnia with apnea)
  - 2 - 4 % in women
  - 4 - 8 % in men

  Young et al, *NEJM*, 1993
- Population age 40 - 64 years males
  - Median had 10 sleep breathing events/hr
  - No significant correlation between apneas and daytime well-being was seen in this representative sample

  Kripke et al., S*leep* 1997
- Over age 65, 80% have at least some mild apneas

  Ancoli-Israel et al., *Sleep* 1981

APNEA 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)

TREATMENT of MILD OBSTRUCTIVE SLEEP APNEA

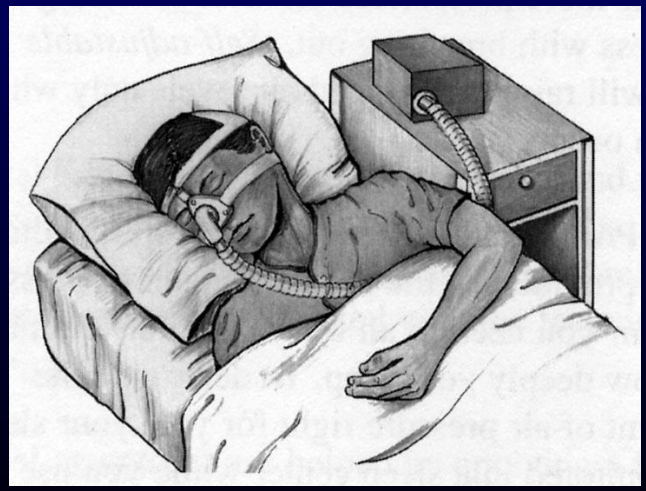
- Weight loss
- Avoid sedative-hypnotics including alcohol at night
- Avoid sleeping supine
  - A rubber ball sewn into back of patient's night-garment is an effective reminder
- Nose spray if there is an allergic component

TREATMENT of MODERATE or SEVERE SLEEP APNEA

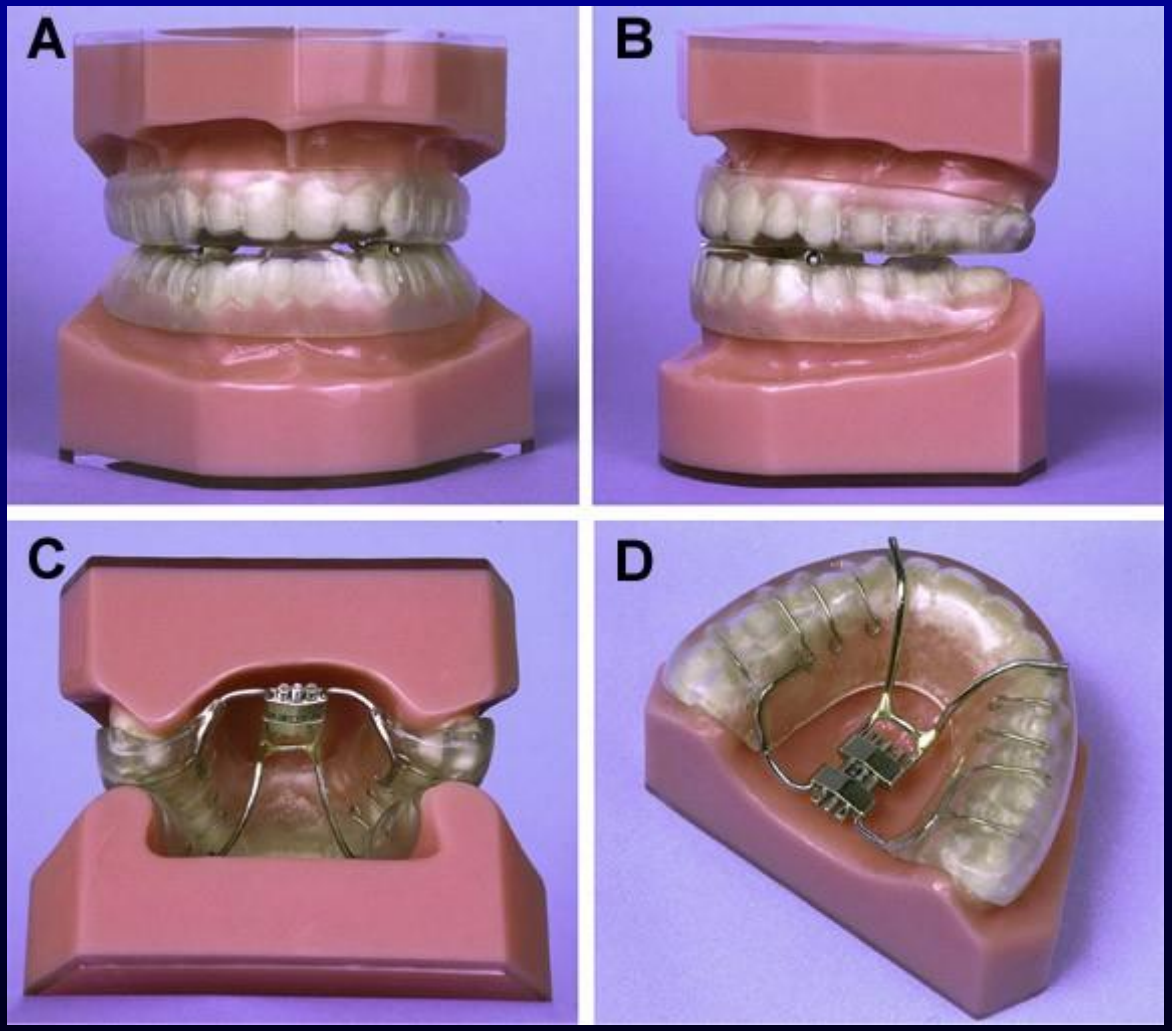
- **C**ontinuous **P**ositive **A**irway **P**ressure (sometimes bi-level or self-adjusting)
- Mandibular and tongue advancement oral appliances
- Surgeries (less proven)
  - Uvulopalatoplasties
  - Mandibular or maxillary advancement

Continuous Positive Airway Pressure

CPAP TREATMENT



MOUTH APPLIANCES



TREATMENT of CENTRAL SLEEP APNEA

- CPAP: ? risks/benefits
- Low-flow nasal oxygen
- Diaphragmatic pacing
- Medications
  - Estrogen
  - Stimulating antidepressants (protryptyline, desipramine)
  - Acetazolamide

SEDATIVE HYPNOTICS and SLEEP APNEA

- Can push snorer into sleep apnea
- Can worsen sleep apnea
- Can worsen COPD
- Same risks with alcohol
- BUT, there may be situations where a sedative may help

NARCOLEPSY

- Irresistible attacks of refreshing sleep that occur almost daily over at least 3 months
- Cataplexy
- 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
- Nocturnal sleep disturbed

NARCOLEPSY ETIOLOGY

Largely due to destruction of hypocretin/orexin neurons

HERITABLE PREDISPOSITION to Autoimmune damage

Chromosome 6: HLA DQB1*0602
T cell receptor alpha locus:
Hallmeyer et al. *Nat Genet* 2009;41(6):708-11.

NARCOLEPSY TREATMENT

A. Modafinil: rarely associated with substance dependence

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

C. Anti-cataplexy agents
   - Trycyclic or SSRI antidepressants
   - Sodium oxybate (special prescribing rules)

NARCOLEPSY TREATMENT

- Education
- Counseling
- Planned naps
- Careful sleep hygiene
- Group support

Restless Legs Syndrome (RLS) & Periodic Limb Movement Disorder (PLMD)

- **RLS:**
  - **Legs squirm before sleep; not all-day like akathisia**
  - **Patient complains of onset insomnia**
- **PLMD: rhythmic limb movements in sleep**
- **50 - 80% of patients with RLS have PLMD**
- **Genetic factors discovered in 2007**
- **Low iron stores a factor**

Periodic Limb Movement Disorder (PLMD) and Restless Legs Syndrome

- Benzodiazepines or narcotics
  - Palliative, not curative
  - Soothes RLS discomfort
  - Increases sleep continuity in PLMD
- Dopaminergic drugs such as ropinirole and pramipexole palliative
- Iron supplementation when ferritin<50

CIRCADIAN RHYTHM SLEEP DISORDERS

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

CIRCADIAN PATHOPHYSIOLOGY

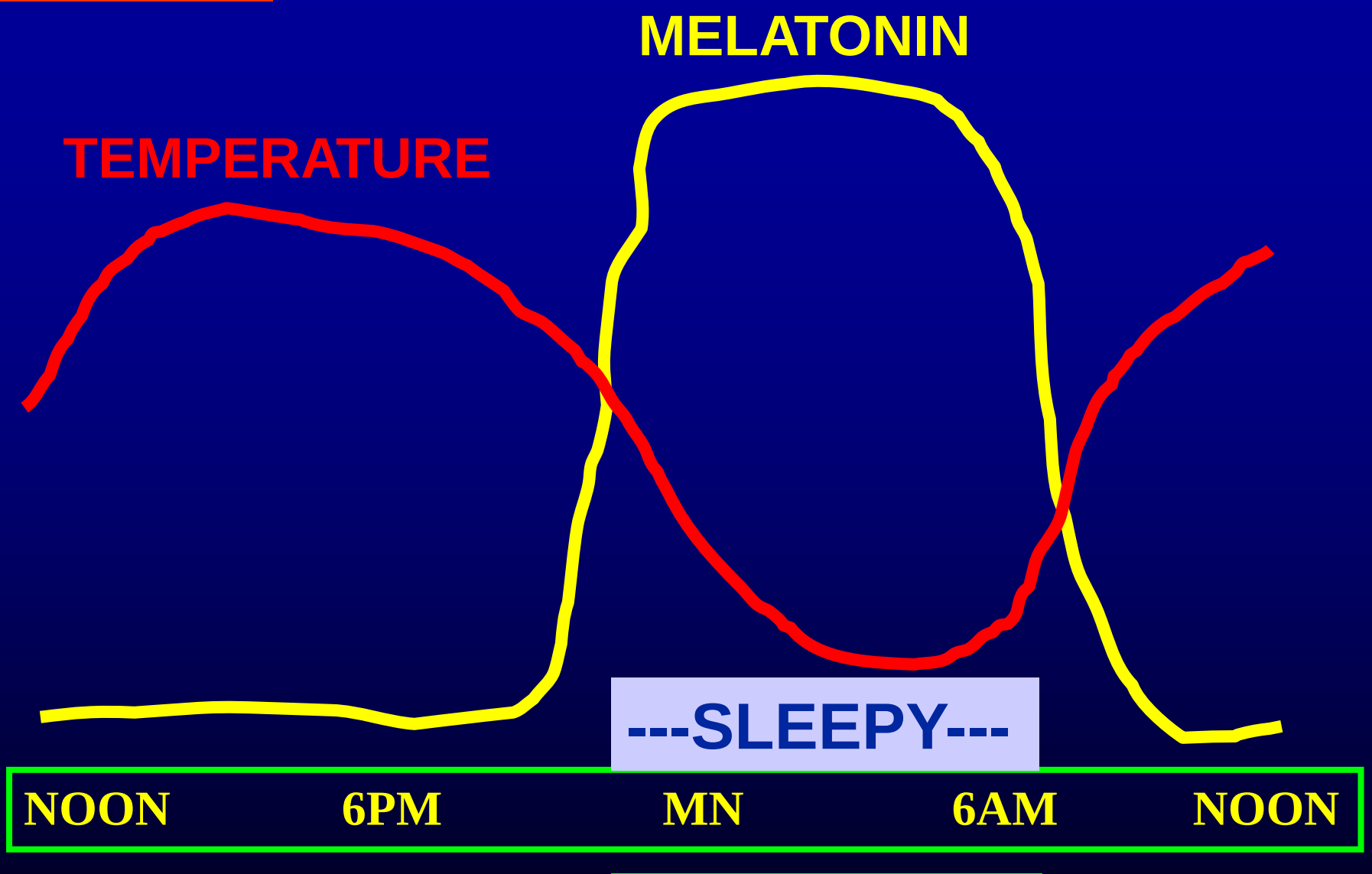
MISALIGNMENT between sleep and biological rhythms

- due to external demands, e.g., night shift
- due to a diminished capacity to respond to rhythm synchronizers (e.g., blind subjects)
- genetic defects in the body clock

SYMPTOMS of DELAYED SLEEP PHASE

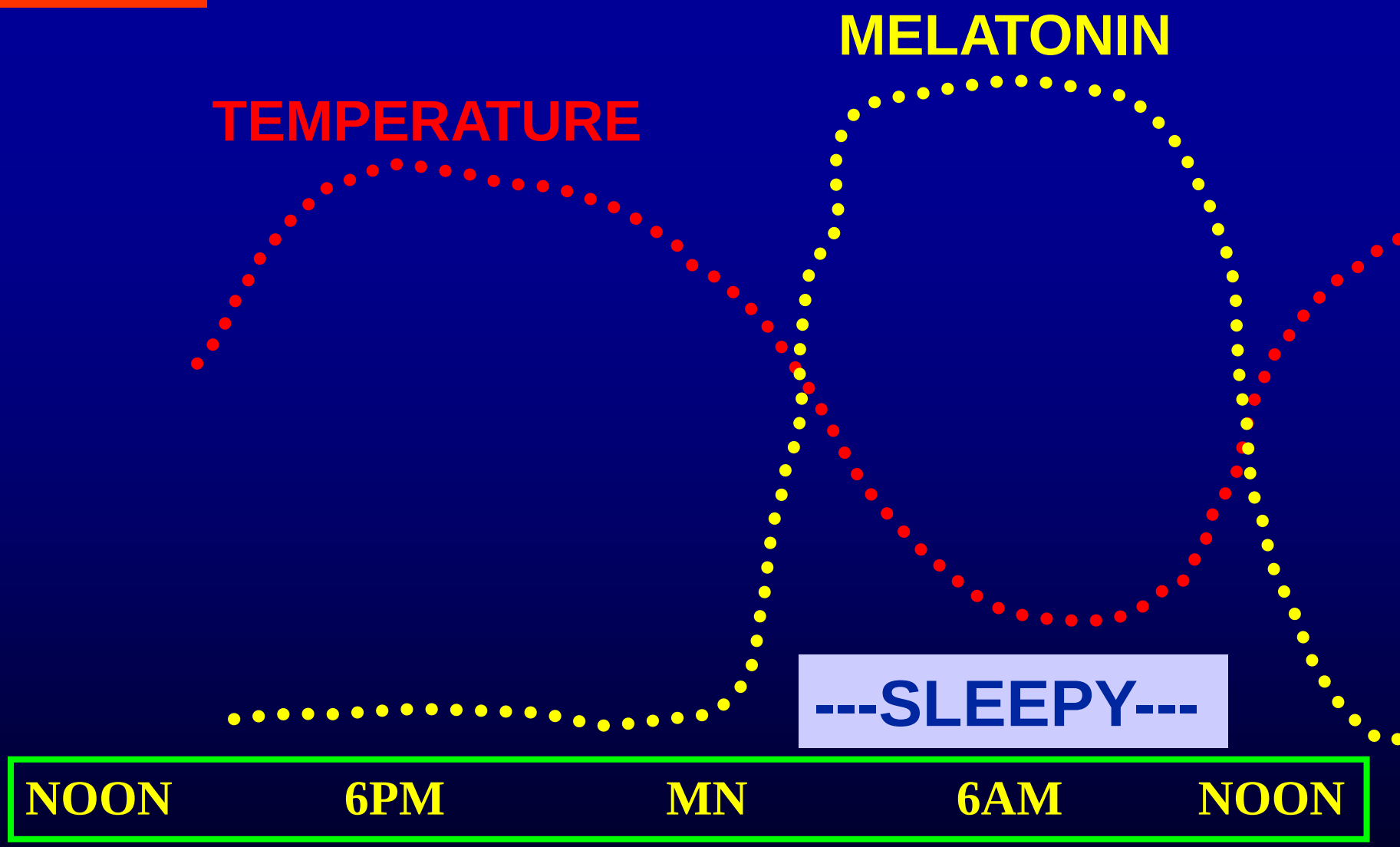
- Can’t get to sleep at night
- Can’t get up in the morning
- Tired most of the day
- More alert in the evening

NORMAL:



Sleep and Preferred sleep time aligned

DSPD:



Preferred sleep time and sleepy time misaligned

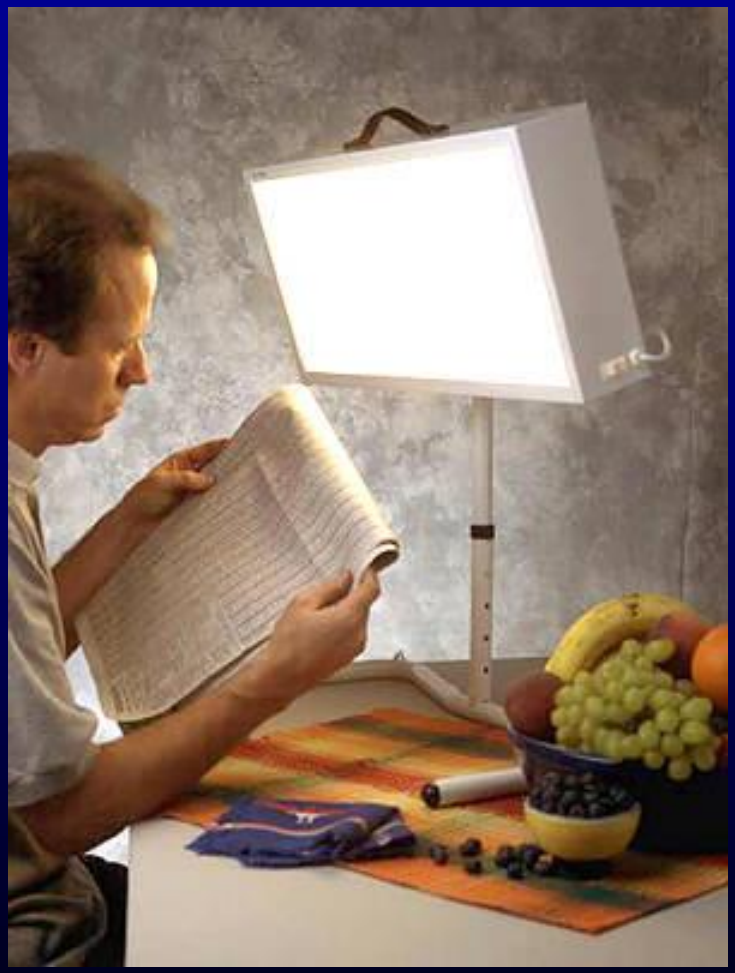
Treatments for Delayed Sleep Phase

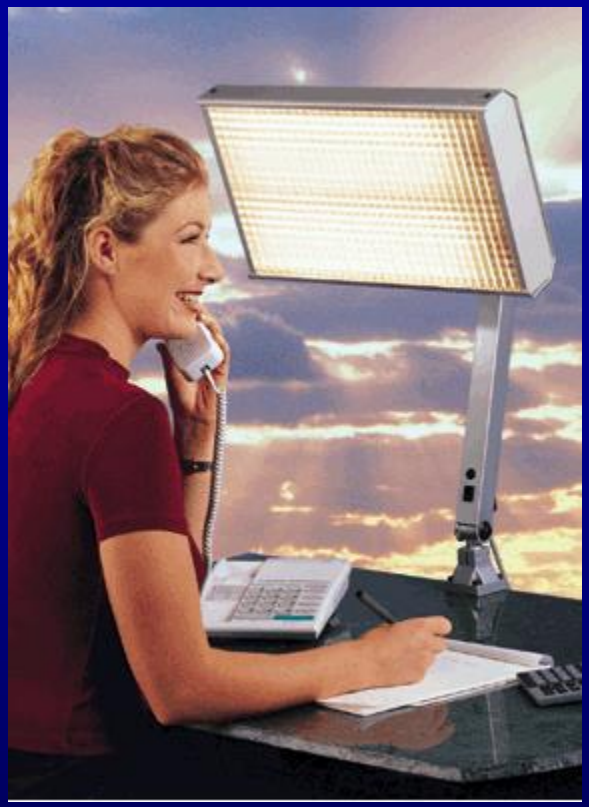
- **Bright light in the morning:**

  as soon after arising as possible

- **Vitamin B12: 1-3mg orally daily**
  - **Some evidence that B12 phase advances**
  - **Might augment light treatment**
- **Melatonin 0.02-0.20 mg. ~10 hours after arising**

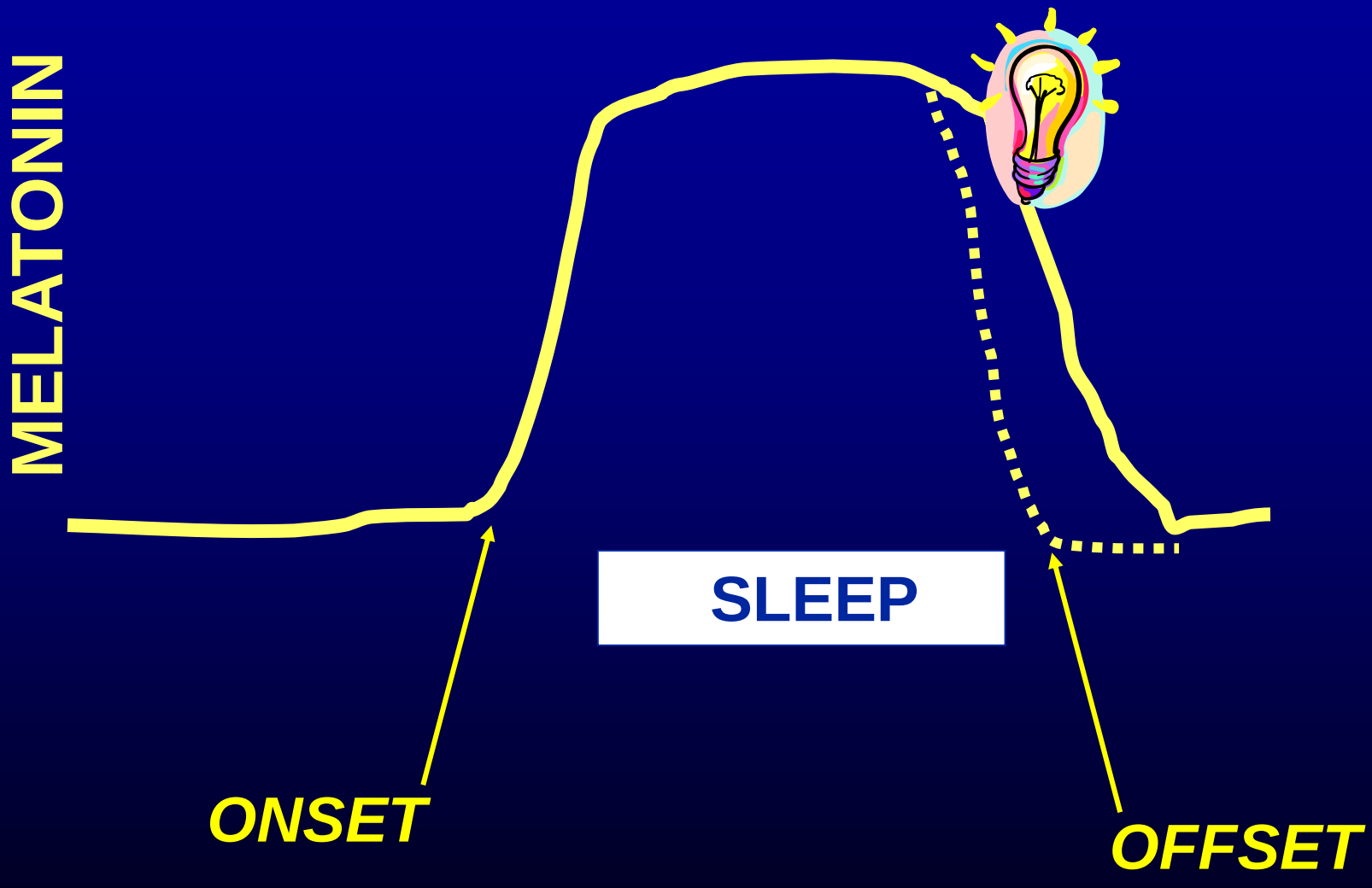
Fluorescent Light Boxes





Light just after waking advances melatonin secretion

and makes sleepiness earlier:



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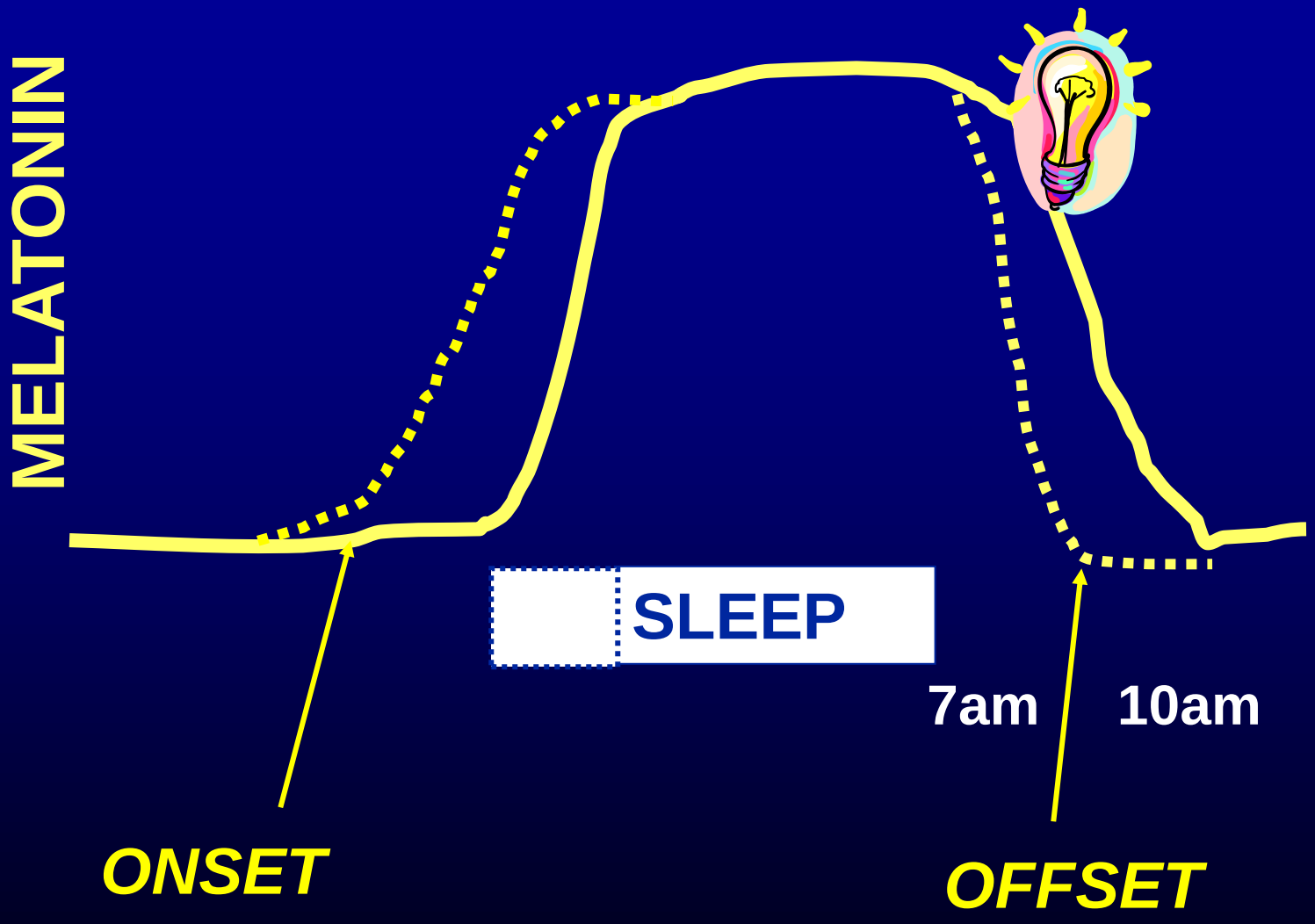
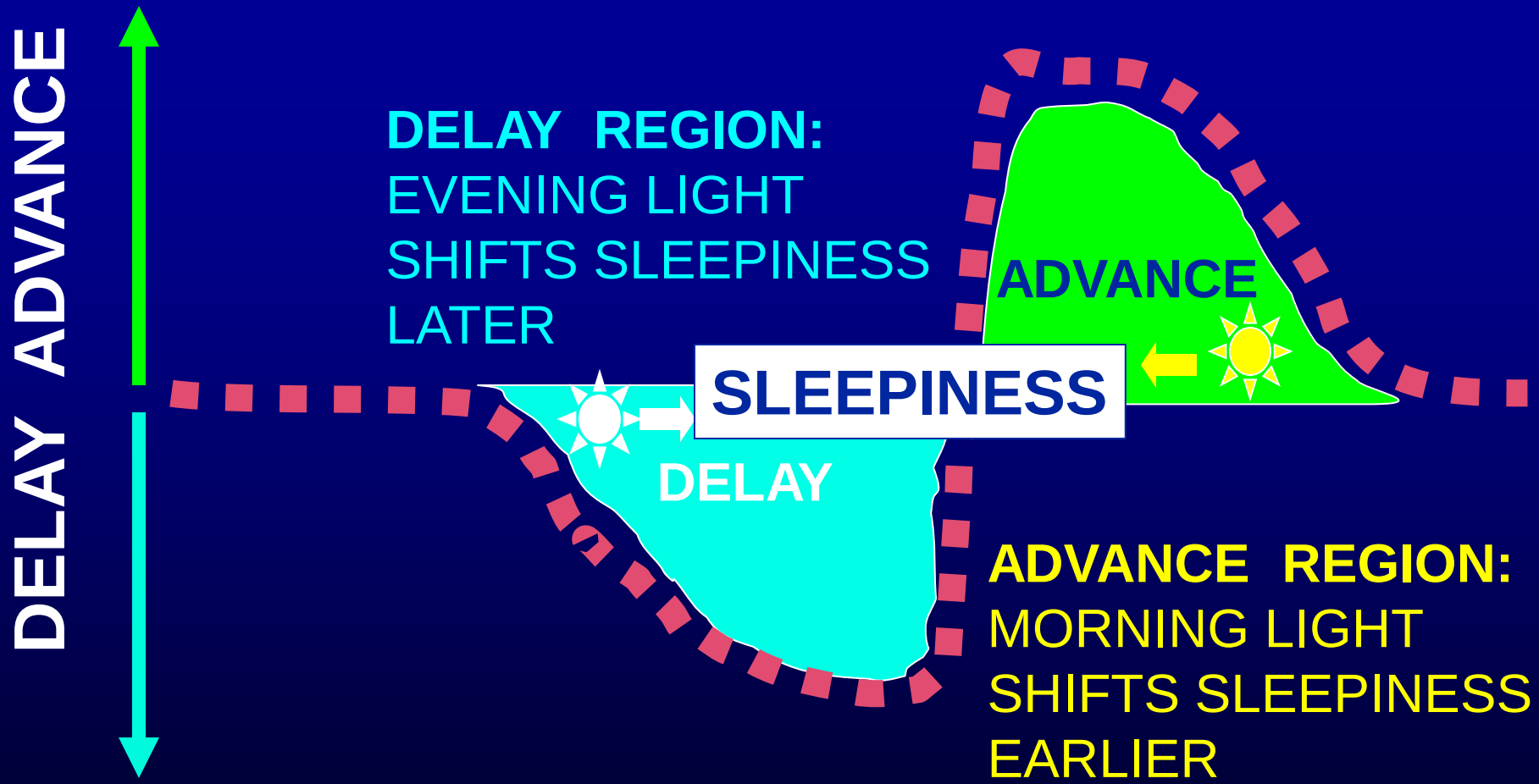


PHASE RESPONSE CURVE



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
  - just before bedtime

- Sometimes 50 - 100 watts fluorescent is sufficient
  - Usually best near the television

MELATONIN:

Used by 5% of the population

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

Melatonin is not hypnotic: nocturnal rodents have high melatonin when they are most alert.

MELATONIN RISKS

- **Long-term safety in humans not established:**
  - **Possibly 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 protect against or cause cancer**

MELATONIN for INSOMNIA

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

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

SHIFT WORK

- An increasing percentage of the population
- Impairs sleep and night performance
- Possibly associated with depression and shortened life
- Accidents

SHIFT WORK TREATMENT

- Melatonin is not as effective as bright light for treatment of night shift work (<1 week studies)
- Long-term studies not available
- Adjustment to night shifts is helped by wearing orange (blue-block) glasses when driving home in the morning.

FATIGUE – RELATED AUTO ACCIDENTS

RESIDENTS!

- GET PLENTY OF SLEEP!
- AFTER NIGHT SHIFTS, BE CAREFUL DRIVING HOME!

Post Lecture Exam Question 1

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

A. Use of sleeping pills

B. Poor sleeping habits

C. Psychiatric Disturbance

D. Alcoholism

E. Sleep apnea

Question 2

2. Effective treatment for chronic insomnia may include:

A. Zaleplon

B. Sleep restriction therapy

C. Zolpidem

D. Quazepam

E. Triazolam

Question 3

3. Benefits of hypnotics outweigh risks:

A. For insomnia due to medical conditions

B. For hospice care

C. To prevent depression

D. To improve daytime alertness

E. All of the above

Question 4

4. A hypnotic which causes little daytime sedation is:

A. Lorazepam

B. Zolpidem

C. Temazepam

D. Flurazepam

E. Diphenhydramine

Question 5

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

A. 6.25 mg

B. 10 mg

C. 15 mg

D. 20 mg

E. 25 mg

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

A. Zaleplon

B. Temazepam

C. Lorazepam

D. Oxazepam

E. Ethchlorvynol

Question 8

8. The most common cause of excessive sleepiness 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. Relaxation and sleep hygiene

C. Methylphenidate

D. Bright light in the morning

E. Bright light just before bedtime

Answers to Pre & Post Competency Exams

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