Sleep Disorders

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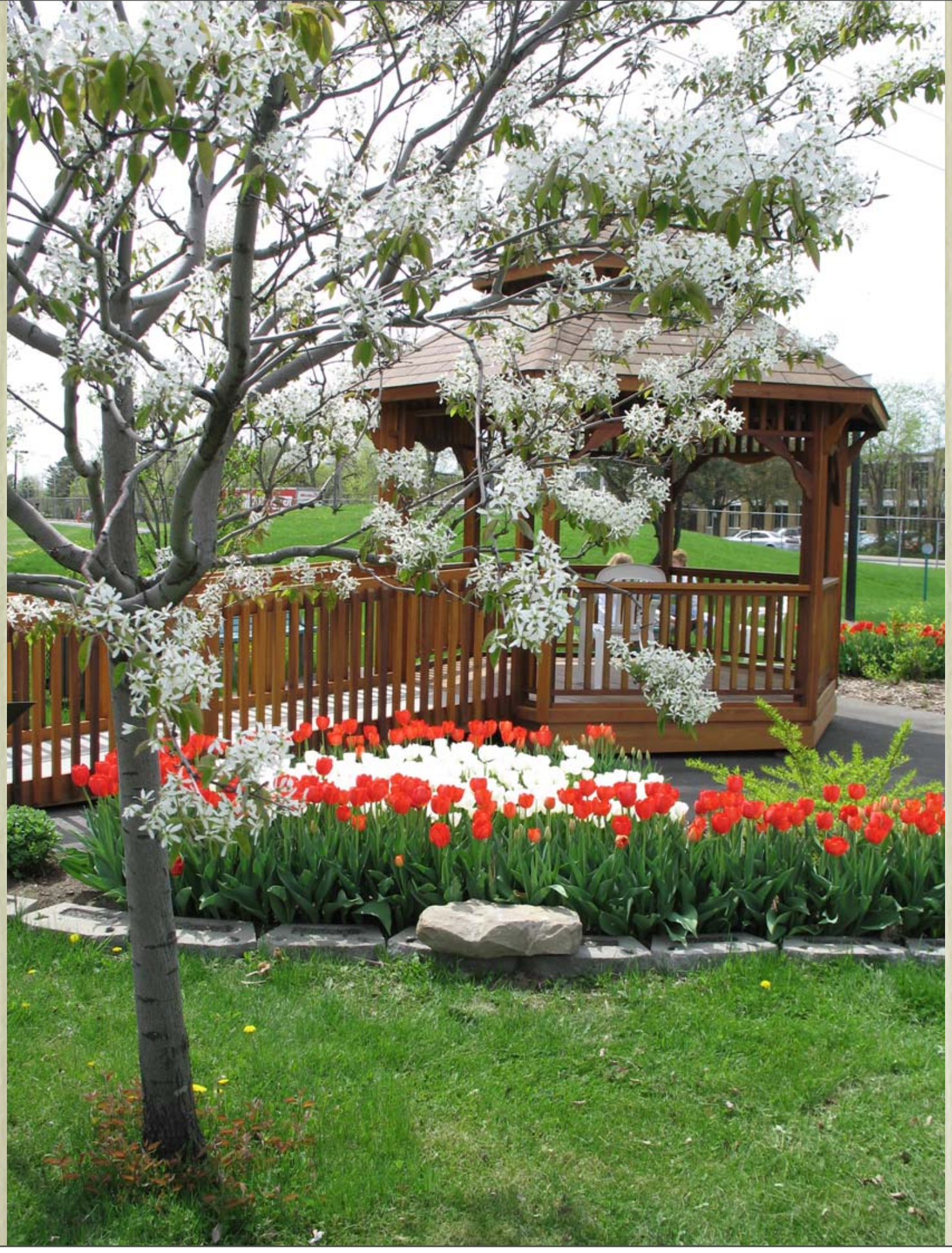


A Proverb

"Earley to bed and earley to rise,
makes a man healthy, wealthy,
and wise."

—John Clarke (1596-1658):
proverb collection Paroemiolgoia Anglo-Latina, 1639

You've all heard this proverb, usually attributed to Benjamin Franklin.

It was actually cited by John Clarke more than a hundred years before Franklin.

Outline

- Sleep:
  - Characteristics of sleep
  - Sleep complaints
  - Epidemiology & Importance of Sleep Disorders
  - Approach to the patient

Outline - 2

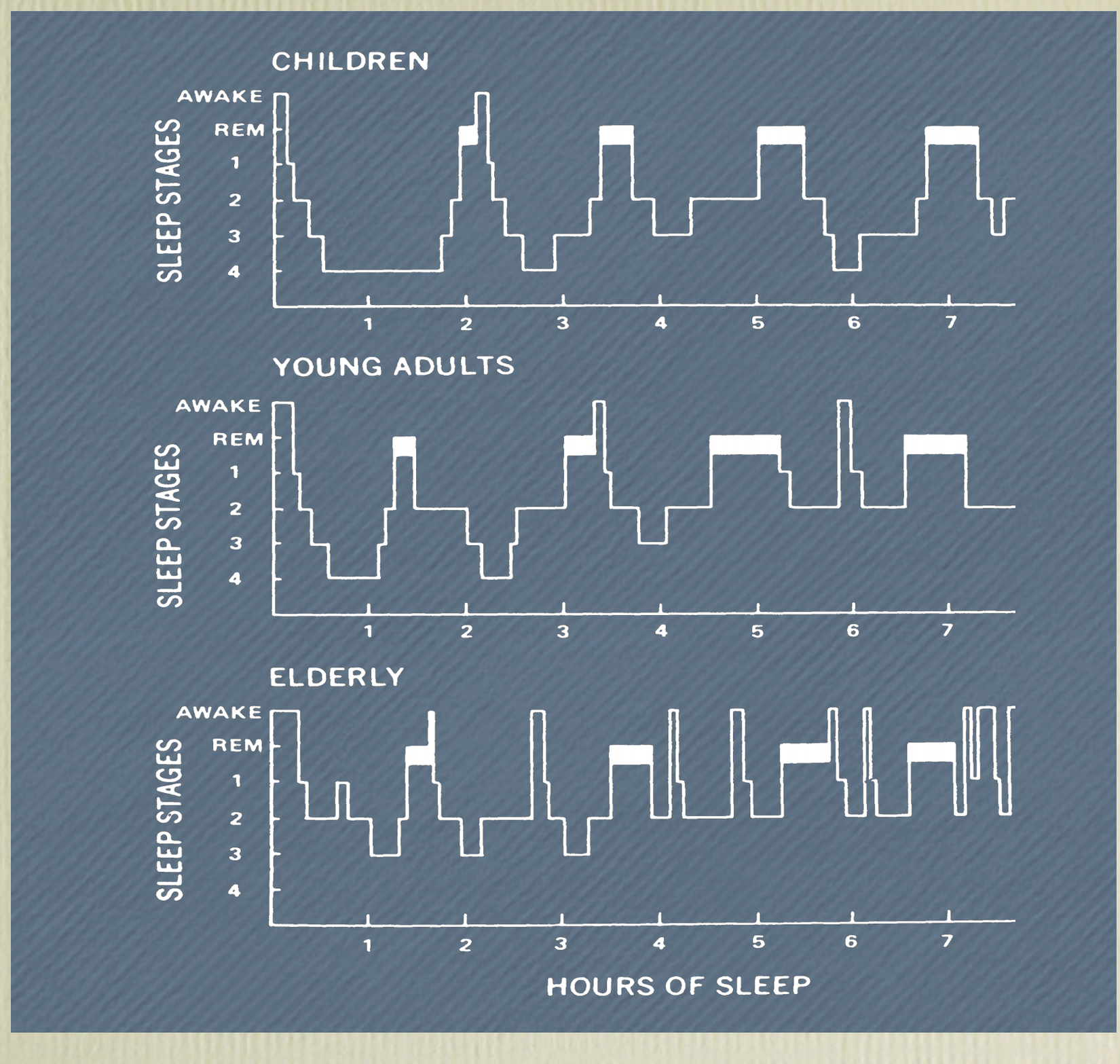
- Hypersomnia
  - Manifestations, causes, treatments
  - OSA
  - Narcolepsy
- REM sleep behaviour disorder
- Restless Legs Syndrome (RLS)
- Insomnia
- Advanced & Delayed Sleep Phase Syndrome

Characteristics of Sleep

- 2 independent states: NREM and REM sleep
- REM sleep: 20-25%
  - First cycle: 60-90 min after sleep onset
  - Recurs every ~90 min
  - Successive stages generally get longer
- NREM sleep: 4 stages (based on EEG)
  - Stage 1: 3-8%
  - Stage 2: 45-55%
  - Stage 3 & 4 (Slow wave sleep, delta sleep): 15-20%

EEG Stages of Normal Sleep

- Note decrease in stage 3 and 4, and increase in awakenings, with aging
- REM sleep occurs every 90 minutes, and increases through the night



Common sleep complaints

- Cannot sleep
    - Trouble falling asleep and staying asleep
- Cannot stay awake
    - Falling asleep during the day
- Cannot sleep at the right time
- Thrash and move about in bed and experience repeated leg jerking

Sleep problems in the elderly

- Alameda County Study
  Roberts RE, Shema SJ, Kaplan GA. Prospective data on sleep complaints and associated risk factors in an older cohort. Psychosom Med. 1999;61:188-196.
  - Insomnia: 23.4% one-year prevalence
    - Predicted by: gender, mood disturbance, chronic health problems
  - Hypersomnia: 6.8%
    - Predicted by: life events, mood disturbance, chronic health problems
  - Thus, increase of insomnia/hypersomnia with age due to increase in depression and health problems, not age per se.

Sleep in America: the 2002 Poll

- 1010 adults, 20 min telephone interview
  - Over-65s sleep longer on weekdays (average 7.3 hrs)
  - Over-65s reported fewer symptoms of insomnia and sleep disorders in general
  - more of the elderly reported their mood as "very positive"

www.sleepfoundation.org

The National Sleep Foundation sponsors a yearly poll, with the imposing title "Sleep in America". An executive summary of the 2002 report is available online.

The poll surveys a sample of about 1000 adults from all over the US, in a 20-minute telephone interview.

Findings related specifically to the elderly:

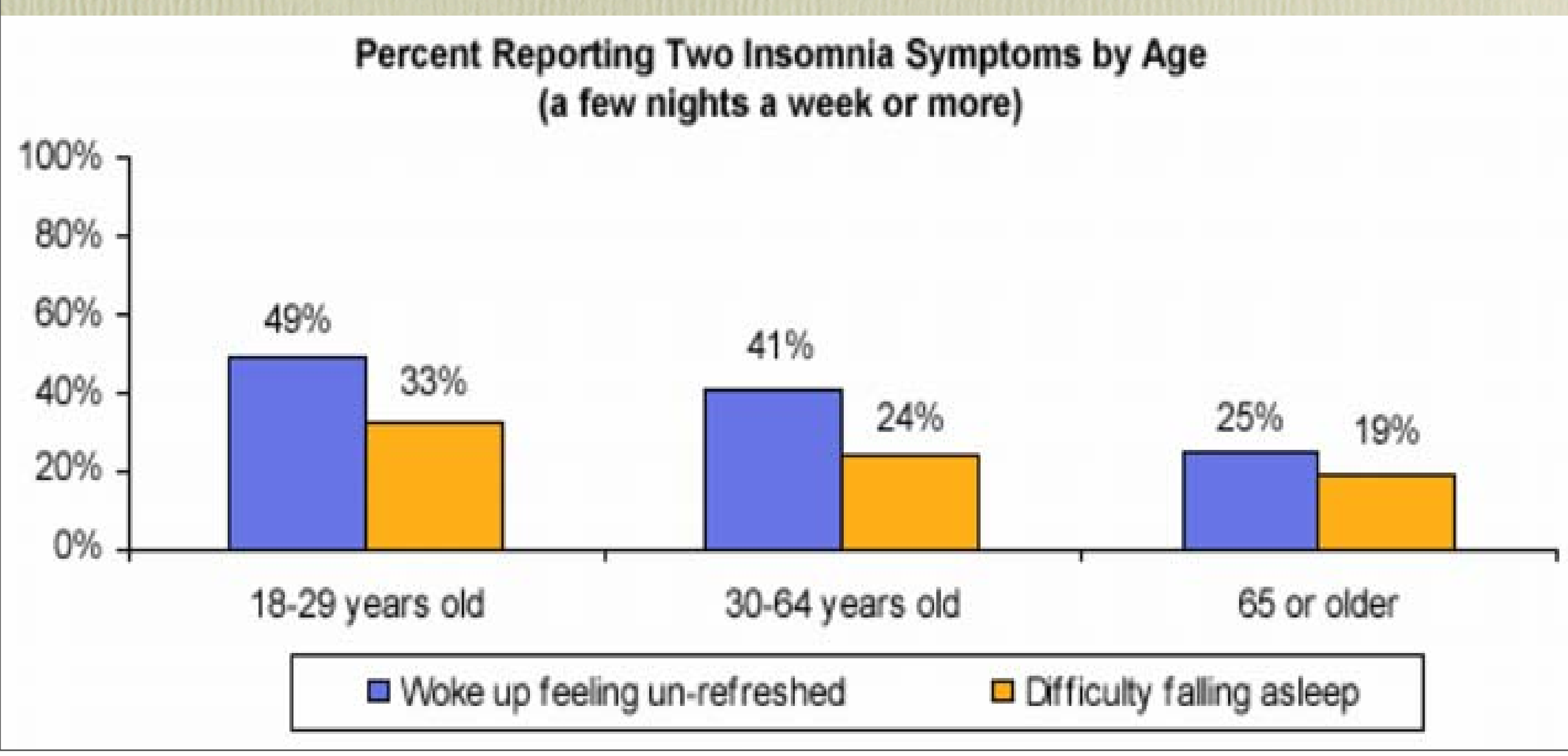
Unsurprisingly, over-65s sleep longer, on average 7.3 hours, on weekdays, compared to younger adults;

They reported fewer symptoms of insomnia and sleep disorders in general, and more of the elderly reported their mood as "very positive".

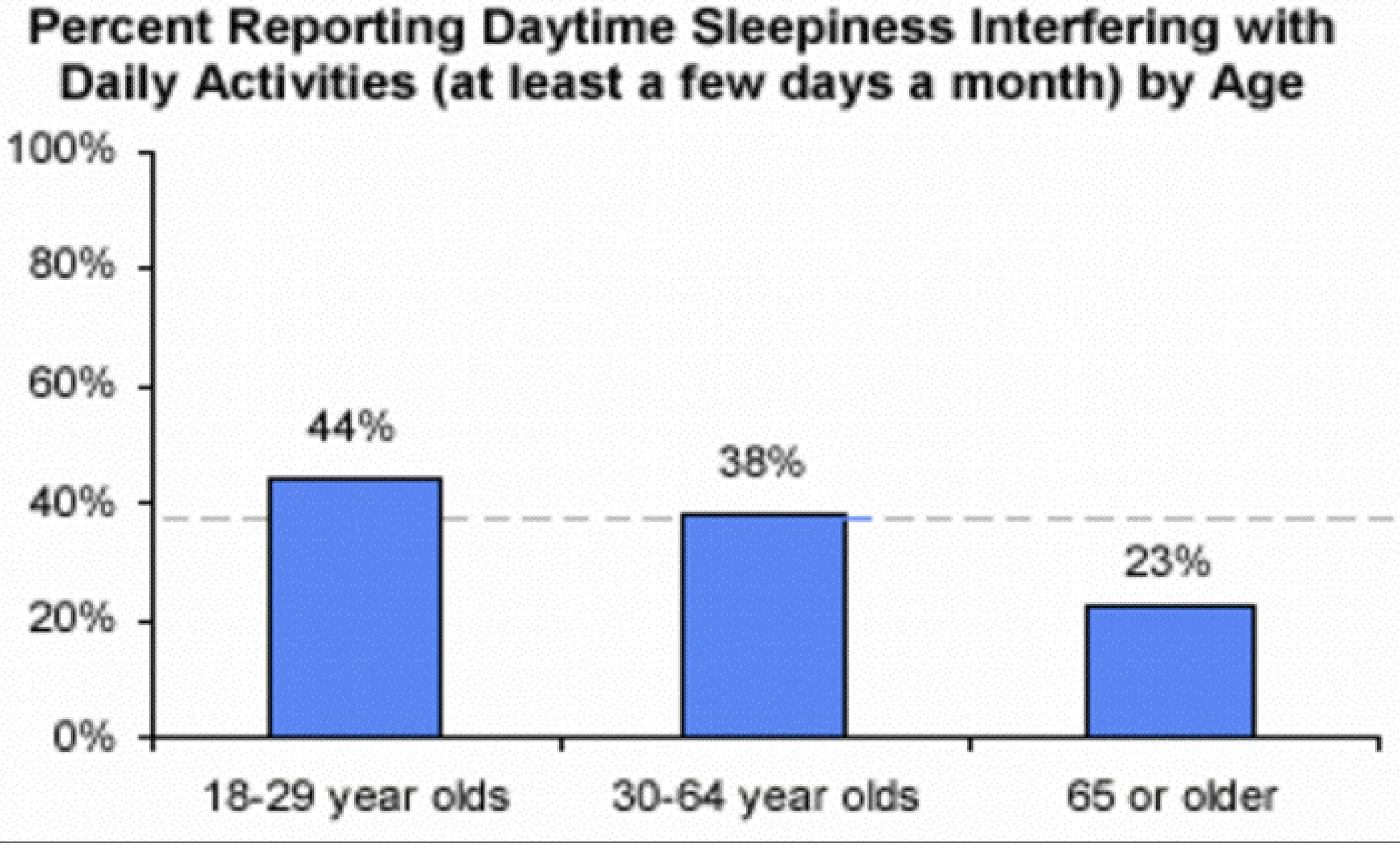
Risk factors for insomnia:

- Low socio-economic status
- Female, elderly
- Low marital satisfaction
- Having children under age 18
- Sleeping with your children
- Medical or psychiatric illness
- Shift workers

Feeling unrefreshed, difficulty falling asleep, by age



Daytime sleepiness, by age



Sleep problems: Approach to the patient

- Screening for sleep disorders
- History
- Laboratory

GSAQ: Global Sleep Assessment Questionnaire

- 11 questions
- 4 possible responses -- never, sometimes, usually, or always -- during past 4 weeks

1. Did you have difficulty falling asleep, staying asleep, or feeling poorly rested in the morning?
2. Did you fall asleep unintentionally or have to fight to stay awake during the day?
3. Did sleep difficulties or daytime sleepiness interfere with your daily activities?
4. Did work or other activities prevent you from getting enough sleep?
5. Did you snore loudly?
6. Did you hold your breath, have breathing pauses, or stop breathing in your sleep?
7. Did you have restless or "crawling" feelings in your legs at night that went away if you moved your legs?
8. Did you have repeated rhythmic leg jerks or leg twitches during your sleep?
9. Did you have nightmares, or did you scream, walk, punch, or kick in your sleep?
10. Did the following things disturb you in your sleep: pain, other physical symptoms, worries, medications, or other (specify)?
11. Did you feel sad or anxious?

- 212 adults at 5 sleep centers and 2 primary-care clinics
- Diagnoses confirmed by sleep specialists

Disorder	*Sensitivity*	*Specificity*
Primary insomnia	79	57
Insomnia associated with a mental disorder	83	51
Obstructive sleep apnea	93	58
Periodic limb movements	93	52
Restless legs syndrome	96	50

Roth T, Zammit G, Kushida C, et al. A new questionnaire to detect sleep disorders. Sleep Med. 2002;3:99–108.

Sleep History

- Quality of sleep
- Times of day:
  - Going to bed
  - Waking
  - Out of bed for the day
- Waking during the night:
  - why, frequency, duration
- Daytime drowsiness
  - How often
  - Time of day, evening
  - Distressing?
  - Accidents, near-accidents

If the patient complains of a sleep disturbance, I ask about those aspects of sleep shown on this slide. I want to emphasize how important it is to correctly identify daytime drowsiness or sleepiness. If we fail to pick up on these cases and do not make the appropriate referrals, for example to a sleep laboratory to assess for sleep apnea or narcolepsy, we could be sued or even charged with criminal negligence if the person is involved in an accident.

Sleep History -2

- Daytime fatigue
- Daytime naps:
  - Frequency, time, duration
- Sleeping aids
  - Rx, OTC, EtOH
- Sleep problems
  - Frequency
  - Distressing?
- Stimulants
- Attitudes towards sleep
- Sleep log

When asking about the use of medication or alcohol to help sleep, don't forget to include over the counter medication, or to find out whether medication is being borrowed from someone else's prescription. Long-acting medications can cause daytime drowsiness, while short-half-life drugs, including alcohol, can worsen sleep in the second half of the night because of rebound or withdrawal insomnia.

Stimulants which affect sleep, besides medications such as theophylline, include caffeine in coffee, tea, or many carbonated soft drinks.

Attitudes and beliefs about sleep are extremely important because they affect behaviour so powerfully. Many people believe that their fatigue means that they need more sleep. They may also believe that it's essential to make up for poor sleep by sleeping late or taking a long nap, even if this means going to work late or calling in sick.

Finally, if the sleep habits seem incompatible with the clinical presentation, asking the individual to keep a sleep log or diary for one or two weeks can be instructive.

Laboratory

- For secondary sleep disturbances: work up the primary condition
- Polysomnography (PSG)
- Multiple sleep latency test (MSLT)
- Maintenance of wakefulness test
- Actigraphy
- Video-PSG

Polysomnography measures the electroencephalogram, the electro-oculogram, and the submental electromyogram. In addition, when obstructive sleep apnea is suspected, a thermocouple under the nose is used to monitor air flow; a tracheal microphone picks up snoring, effort belts around the chest and abdomen measure respiratory effort, and a finger oximeter measures oxygen saturation. For sleep movement disorders, leg electromyograms and wrist actigraphs may also be used.

The Multiple Sleep Latency Test involves having the subject lie down in a dark, quiet room for 20 minutes, at 2-hour intervals during the day. The time to fall asleep is measured.

The Maintenance of Wakefulness test aims to assess the ability of the individual to resist falling asleep, again during 20-minute periods, at least 4 times during the day.

Actigraphy involves a wristwatch sized device, worn on the wrist of the dominant hand, which measures accelerations and stores the data for downloading into a computer. There, a computer program predicts whether the person is awake or asleep during the course of monitoring. This technique is often used for ambulatory sleep monitoring.

Hypersomnia: cardinal manifestations

- Excessive daytime somnolence (EDS)
- Falling asleep in inappropriate places and circumstances
- Lack of relief of symptoms after additional sleep
- Daytime fatigue
- Inability to concentrate
- Impairment of motor skills
- Cognitive impairment

  Ohayon MM, Vecchierini MF. Daytime sleepiness and cognitive impairment in the elderly population. Arch Intern Med. 2002;162:201-208.
- Symptoms specific to etiology

Causes of EDS

- Sleep deprivation & sleepiness related to lifestyle
- Obstructive sleep apnea (OSA)
- Central sleep apnea
- Narcolepsy
- Jet lag
- Delayed sleep phase syndrome
- Shift work
- Non-24 hour sleep-wake disorders
- Medications
- Withdrawal from stimulant medications

People may be sleepy because they're not sleeping enough - working two jobs, studying, or online gambling.

Obstructive sleep apnea is a common cause.

Jet lag, of course, is temporary.

Delayed sleep phase syndrome is something that afflicts younger people. The elderly are much more likely to have advanced sleep phase syndrome, where they can't stay awake in the evening.

Medications as a cause of sleepiness should always be considered. Ask if the person uses any over-the-counter stuff, or someone else's prescription meds.

Caffeine withdrawal is also a cause of daytime sleepiness, but of course it's temporary.

Causes of EDS: psychiatric

- Bipolar depression
- Seasonal affective disorder

Causes of EDS: neurologic

- Thalamus, hypothalamus, brainstem lesions
- Multiple sclerosis
- Encephalitis (eg encephalitis lethargica)
- Trypanosomiasis (African sleeping sickness)
- Neurodegenerative disorders:
    - Alzheimer's
    - Parkinson's
- Neuromuscular disorders causing sleep apnea

Causes of EDS: medical

- Hepatic failure
- Renal failure
- Respiratory failure
- Electrolyte disturbances
- Cardiac failure
- Endocrine: hypothyroidism, diabetes, etc.
- Severe anemia
- Vitamin B12 deficiency

Just to round out the differential diagnosis, here are some medical causes of excessive daytime sleepiness.

Let’s look at two causes in more detail, narcolepsy and sleep apnea.

Breathing-Related Sleep Disorder (BRSD) - Sleep Apnea

- 3 types: obstructive sleep apnea; central; mixed
- Increases with age
- Most common Sx: daytime sleepiness, snoring, morning headaches

Breathing-related sleep disorder is very common, and is likely becoming more so, as the prevalence of obesity is increasing.

I want to draw attention to morning headaches as a presenting symptom; something you need to ask your patient about.

Breathing-Related Sleep Disorder (BRSD) - 2

- Why important to psychiatry:
  - May first present to psychiatry, eg with memory problems
  - Failure to recognize and refer may entail legal liability
  - Relative contraindication for hypnotics, alcohol
  - BDZ may induce an iatrogenic sleep apnea
  - CPAP treatment improves BDI scores

Generally, the diagnosis is made by sleep specialists using overnight sleep monitoring. These people will also provide treatment, or refer to other specialists. So why should we in psychiatry be concerned?

Some of the daytime symptoms of sleep apnea, such as memory loss, decreased mental function, lethargy, or automatic behaviour, or nighttime symptoms such as impotence or confusion, might lead to psychiatric referrals.

If we fail to recognize daytime sleepiness as a safety hazard, we could be held liable for motor vehicle accidents and injuries. This can be an issue for daytime sleepiness due to any cause, not just sleep apnea.

Benzodiazepines are relatively contra-indicated in people with sleep apnea. Psychiatrists frequently prescribe these medications - we must rule out sleep apnea before doing so.

Finally, it is possible for benzos to cause sleep apnea. Monitor closely any patients you have on these medications.

Alcohol can also cause sleep apnea. This is where morning headache may be mistakenly believed to be a hangover symptom, when it could be due to the sleep apnea induced by alcohol in the evening.

Treatment of OSA with CPAP has been shown to significantly improve BDI scores, whether or not patients were taking antidepressants.

Obstructive Sleep Apnea

- intermittent airway closure due to pharyngeal muscle relaxation during sleep
- causing oxygen saturation to fall until an arousal from sleep (typically imperceptible) occurs
- the arousals are thought to cause:
  - sleep fragmentation, thus daytime sleepiness;
  - sympathetic activation, thus hypertension;
  - hypoxemia may lead to pulmonary hypertension and CHF

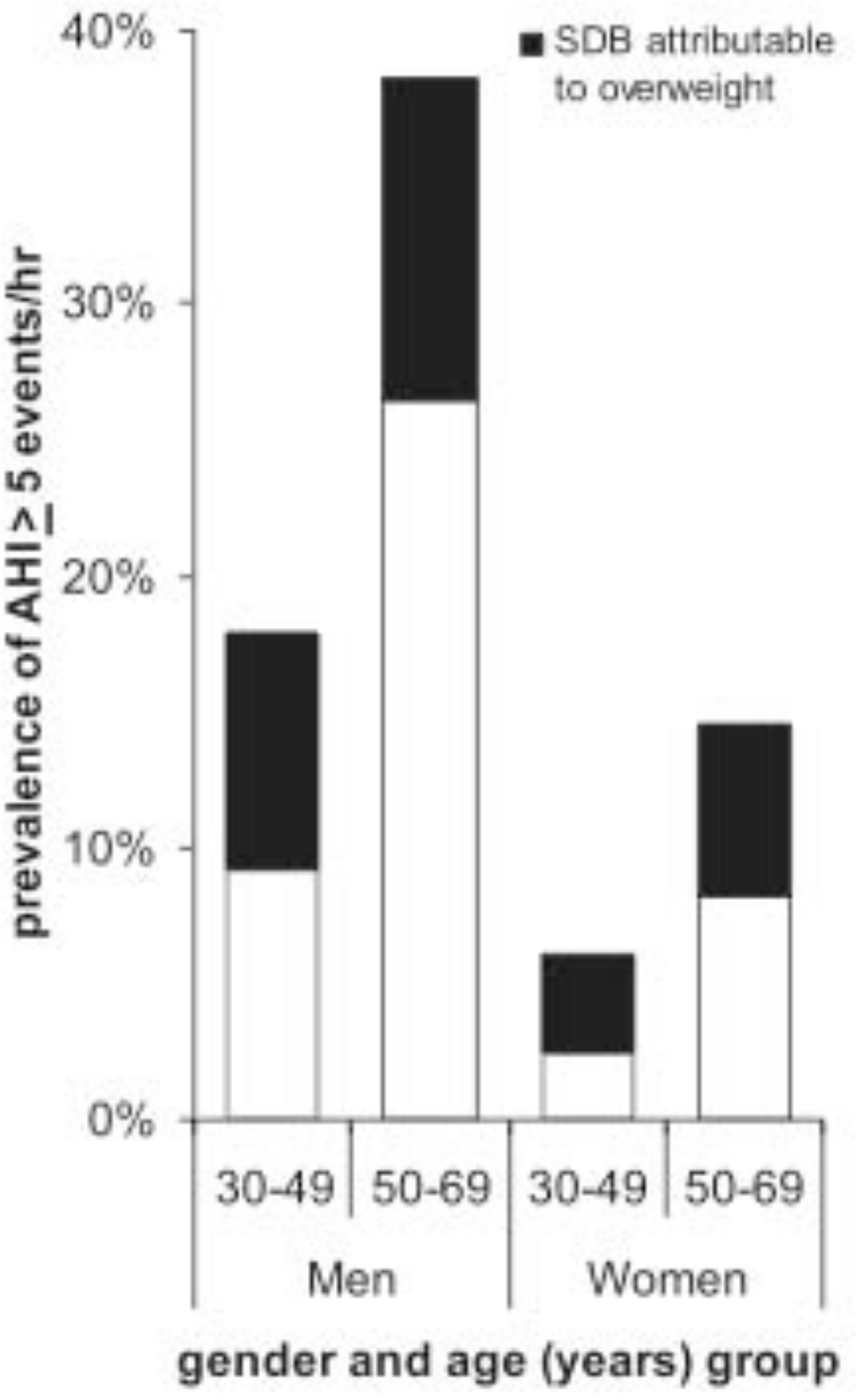
Grades of OSA

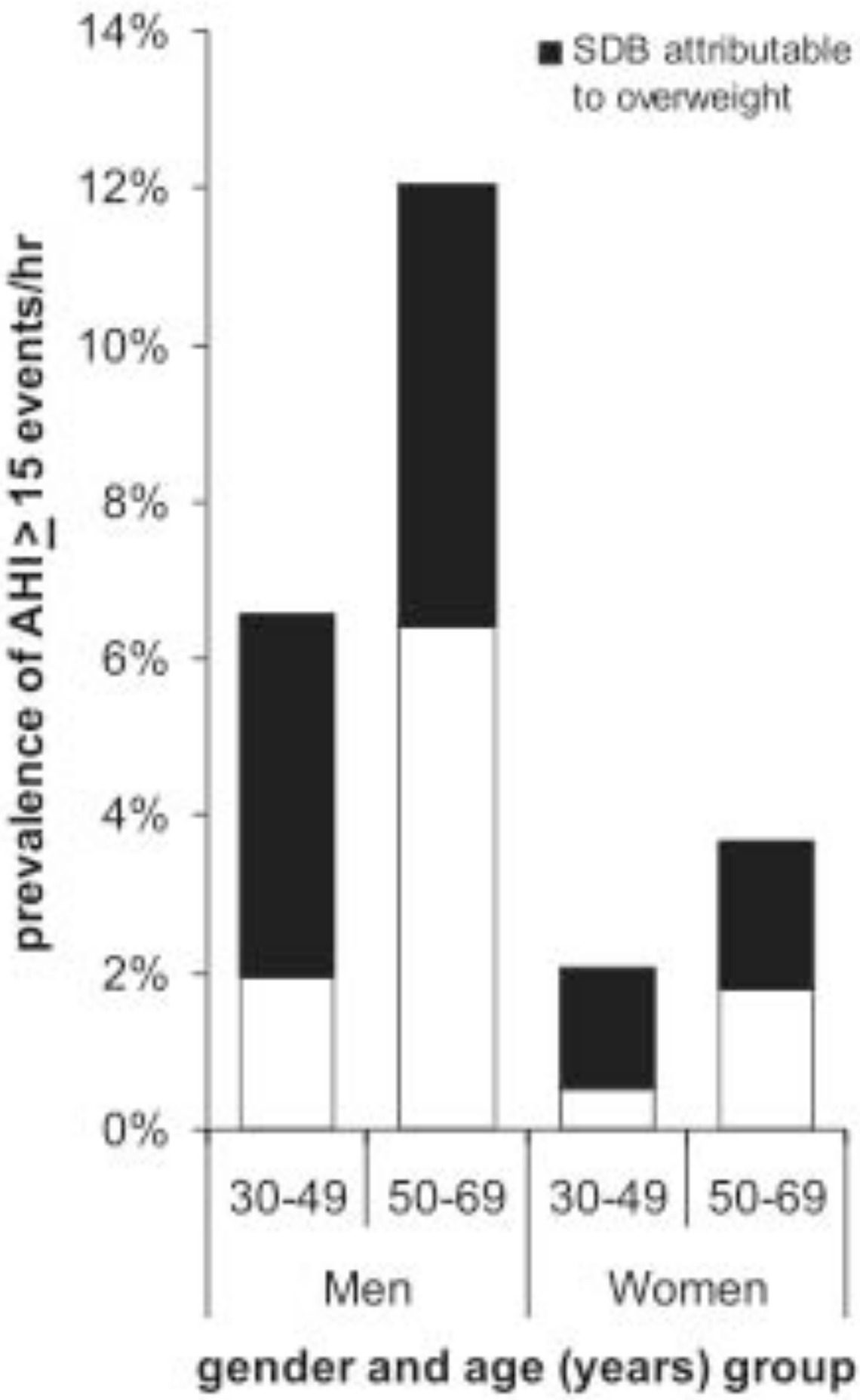
- AHI: apnea hypopnea index (number of events per hour)
  - mild: AHI 5 - 15
  - moderate: AHI 15 - 30
  - severe: AHI > 30

You may also come across the acronym RDI, which stands for Respiratory Disturbance Index. It's often taken to be the same as the AHI.

Prevalence of OSA

- 2003 estimates for U.S. adults, ages 30-69 {Young et al., 2005, J Appl Physiol, 99, 1592-9}
  - AHI ≥ 5: 17% of adults
  - AHI ≥ 15: 5.7% of adults
  - about half are due to excessive weight





The graph on the left shows prevalences for all OSA, from mild on up, broken down by gender and age range. Older men are the most affected.

The same is true for the graph on the right which shows prevalences for moderate to severe OSA. Note the prevalence of 12% for men!

Screening for OSA

- **STOP**:
  - **S**: do you **S**nore?
  - **T**: are you **T**ired, or sleepy, or fatigued?
  - **O**: has anyone **O**bserved that you have apnea?
  - **P**: do you have high blood **P**ressure?
- yes answers on 2 out of 4: 70% chance of having sleep apnea {Chung et al., 2008, Anesthesiology, 108, 812-21}

Additional Risk Factors

- **BANG**:
  - **B** - is **B**MI over 35?
  - **A** - is **A**ge over 50?
  - **N** - is **N**eck size over 17 inches (43 cm)?
  - **G** - is the **G**ender male?
- STOP + BANG = 5/8, then 90% likelihood of sleep apnea

Screening for OSA

- overnight pulse oximetry
  - helps to rule out OSA if AHI < 5
  - does not replace polysomnography for diagnosis or for treatment titration
  - If it shows significant breathing disturbance, it can get your patient a faster appointment with the sleep specialist / sleep lab

The gold standard for diagnosing OSA is, of course, polysomnography in the sleep lab. Unfortunately, this is not available in many places, and the wait list can be months.

Some sleep specialists have the equipment to do home polysomnography.

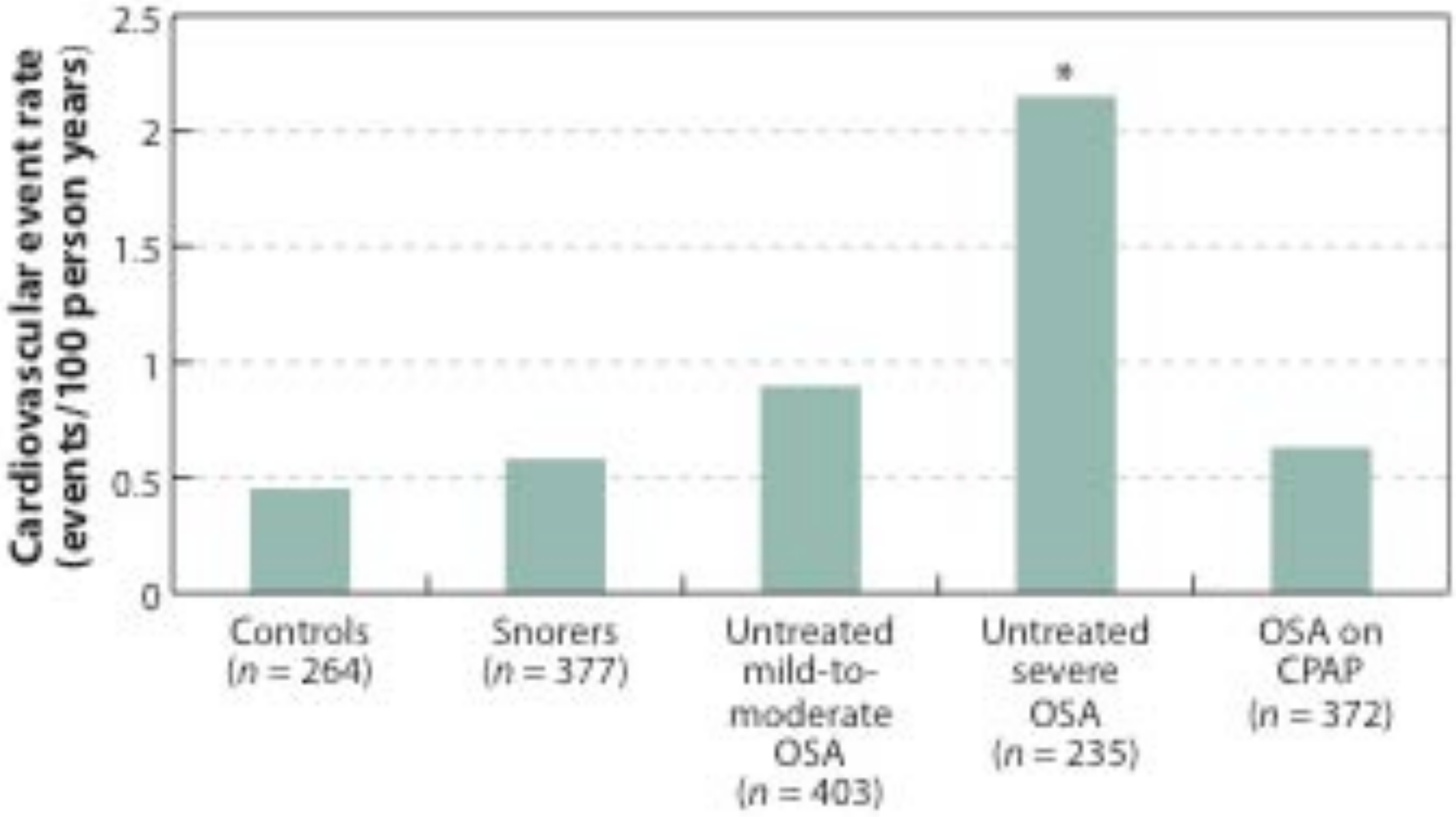
But if you suspect OSA, overnight pulse oximetry can be a useful screen.

I'll pass around a little device for this, available on the internet for $128 Canadian, including taxes and shipping. Try it out!

It stores data for 24 hours, and the data can then be downloaded to your computer for analysis and for printing out reports. Here is a report that I did for myself.

Why treat OSA?

- OSA is an independent risk factor for cardiovascular events
- CPAP reduces the risk



{Pack, 2006, Am J Respir Crit Care Med, 173, 7-15}

Show your patients who are reluctant to have their OSA investigated or treated this graph. These are groups of males, carefully matched for age and Body Mass Index, followed up over 10 years.

Patients with severe OSA treated with CPAP had event rates that were statistically no different than controls.

How does OSA increase cardiovascular event risk?

- At least 3 mechanisms:
  - sympathetic bursts at end of each apnea; also heightened daytime sympathetic state
  - ischemia-reperfusion leads to free radicals, oxidative stress, increase in pro-inflammatory cytokines, thus atherosclerosis
  - OSA may trigger acute MI {Kuniyoshi et al., 2008, J Am Coll Cardiol, 52, 343-6}

You can see on my overnight oximetry report, the increases in heart rate associated with apnea spells. This represents sympathetic nervous system activity.

the third mechanism is posited from the finding that OSA patients are more likely to have a myocardial infarct between midnight and 6 am, while non-OSA MI victims are more likely to have their MIs during the other 18 hours of the day.

OSA treatment

- sleep on one's side
- avoid bedtime alcohol, hypnotics
- methylphenidate for daytime sleepiness
- CPAP, biPAP, autoPAP
- dental appliances, surgery

Narcolepsy

- Inherited disorder of REM sleep regulation
- SOREMs: Sleep Onset REM periods
- Excessive sleepiness late teens/early 20s
- Other symptoms typically begin years later
- Occurs in mammals
- Prevalence: 0.03-0.16%
- GWAS suggest an autoimmune disorder {Pack and Pien, 2011, Annu Rev Med, 62, 447-60}

Narcolepsy is an inherited disorder, thought to be a physiologic dysregulation of REM sleep. Patients have an abnormally short or even non-existent first nonREM sleep period; that is, they often go directly into REM sleep.

It usually begins with excessive daytime sleepiness during young adulthood. Other symptoms follow several years later. It can occur in dogs and other mammals, which provides a useful animal model for research.

Its prevalence is about the same as that for multiple sclerosis.

Genome-wide association studies suggest that narcolepsy may be an autoimmune disorder. About 90% of narcolepsy patients have a particular HLA (human leukocyte antigen) gene variant which only occurs in 24% of controls. Postmortem studies of narcolepsy patients show marked reductions in orexin (hypocretin) cells in the lateral hypothalamus, presumably destroyed by an autoimmune process. Orexins are neuropeptides believed to control wakefulness, energy expenditure, and perhaps food intake.

Narcolepsy - 2

- Symptoms:
  - Excessive daytime sleepiness
  - Cataplexy
  - Disturbed nocturnal sleep
  - Hypnagogic hallucinations
  - Sleep paralysis
- Sleep lab:
  - SOREMs at night or with daytime naps

Narcolepsy is associated with a pentad of symptoms: 1) excessive daytime sleepiness, characterized by irresistible "attacks" of sleep in inappropriate situations, such as driving a car, talking to a supervisor, or social events; 2) cataplexy, which is sudden bilateral loss of muscle tone, usually lasting seconds to minutes, generally precipitated by strong emotions such as laughter, anger, or surprise; 3) poor or disturbed nocturnal sleep; 4) hypnagogic hallucinations, varied dreams at sleep onset or while awake; and 5) sleep paralysis, a brief period of paralysis associated with the transitions into and out of sleep.

Narcolepsy: medication

- For sleep attacks: use stimulants:
  - Methylphenidate (Ritalin, Concerta, Biphentin)
    - Start with 5 mg bid-tid
    - Go up to 50 mg or higher per day if necessary
  - amphetamine (Adderall)
  - dexedrine
  - Methamphetamine (Desoxyn - not available in Canada)
  - Modafinil (Alertec)
  - Sodium oxybate (Xyrem)

Narcolepsy: medication

- For cataplexy, sleep paralysis, hypnagogic hallucinations:
  - Tricyclic antidepressants
    - Protriptyline (Triptil): start 5 mg qd
    - Imipramine (Tofranil): 25-200 mg per day
    - Clomipramine (Anafranil): 10-200 mg per day
- SSRIs
  - Eg, fluoxetine (Prozac): 20-80 mg per day

REM Sleep Behaviour Disorder

- Associated with complicated behaviours during sleep, eg walking, running, singing, and talking
- Usually in 2nd half of night during REM sleep
- Apparently due to intermittent loss of muscle atonia that normally accompanies REM sleep, thus allowing pt to act out their dream
- Memory for the dream content is usually good
- Typically occurs in men in 50s or 60s

First described in 1986, this disorder, like sleepwalking, is associated with complicated behaviors during sleep, such as walking, running, singing, and talking. [92] In contrast to sleepwalking, which occurs during the first third of the night during delta sleep, REM sleep behavior disorder usually occurs during the second half of the night during REM sleep. It apparently results from an intermittent loss of the muscle atonia that normally accompanies REM sleep, thus allowing the patient to act out her or his dream. Also, in contrast to sleepwalking, memory for the dream content is usually good. Furthermore, the idiopathic form typically occurs in men during the sixth or seventh decade of life.

REM Sleep Behaviour Disorder - 2

- Cause or causes unknown
- Occurs in or during:
    - Various neurological disorders, eg dementia, subarachnoid hemorrhage, and degenerative disorders
    - withdrawal from sedatives or alcohol
    - treatment with TCAs or biperiden (Akineton)
- Rx: clonazepam 0.5 to 1.0 mg qhs
- Educate patients and families
- Warn to take precautions about injuring themselves or others

The cause or causes remain unknown. It has been reported in a variety of neurological disorders and during withdrawal from sedatives or alcohol; during treatment with tricyclic antidepressants or biperiden (Akineton); and in various neurological disorders, including dementia, subarachnoid hemorrhage, and degenerative neurological disorders.

Nocturnal administration of clonazepam, 0.5 to 1.0 mg, is usually remarkably successful in controlling the symptoms of this disorder. Patients and their families should be educated about the nature of the disorder and warned to take precautions about injuring themselves or others.

Restless Legs Syndrome (RLS)

- unpleasant sensations in the legs associated with an urge to move
- rest worsens symptoms
- movement lessens or relieves symptoms
- diurnal variation (symptoms worse in the evening and night)
- about 80-85% of RLS patients have periodic limb movements on overnight sleep studies

There are four features.

RLS -2

- marked differences in prevalence between countries and ethnic groups
- familial and sporadic forms
- causes:
  - pregnancy
  - renal failure on dialysis
  - iron deficiency
  - various medications {Sateia, 2009, Chest, 135, 1370-9} (handout)

RLS - treatment

- correct iron deficiency
- eliminate caffeine, nicotine, alcohol
- medications: carbidopa-levodopa, anticonvulsants, benzodiazepines, baclofen, bromocriptine, clonidine

When there are so many possible treatments, it's highly likely that none of them are very effective.

Insomnia: cardinal manifestations

- Difficulty falling asleep
- Frequent awakenings
- Early morning awakening
- Insufficient sleep
- Daytime fatigue or sleepiness
- Lack of concentration or irritability
- Anxiety, sometimes depression
- Forgetfulness
- Psychosomatic symptoms

How much sleep do we need?

- "Doctors suggest teenagers need about nine hours of sleep a night, and adults need at least eight. A recent Canadian poll found 35 per cent of youth aged 12 to 17, and 61 per cent of adults get less than eight hours of sleep a night. The poll showed an alarming 30 per cent of adults are getting fewer than six hours a night."

http://www.css.to/worldsleepday2011.html

Many people who suffer from insomnia, as well as many researchers, are convinced that they are not getting enough sleep. But there is considerable evidence that suggests that many insomniacs are trying to sleep more than they need, and that this is actually what causes their insomnia.

That of course raises the question, how much sleep do we need?

The news media, organizations like the National Sleep Foundation, as well as the Canadian Sleep Society, tell us we should have 8 hours or more of sleep. Here is a quote from the Canadian Sleep Society, who I think should know better, on their web page about World Sleep Day, which is on Friday, March 18.

Mortality and sleep duration

- numerous studies using self-reported sleep:
  - meta-analysis of 23 studies {Gallicchio and Kalesan, 2009, J Sleep Res, 18, 148-58}:
    - RR short sleep 1.10
    - RR long sleep 1.23
    - cf "normal" sleep of 7 -7.9 hrs

Mortality and actigraphic sleep

- < 300 min (< 5 hrs): 61% survival
- 300 - 390 min (5 - 6.5 hrs): 90% survival
- > 390 min (> 6.5 hrs): 78% survival

{Kripke et al., 2011, Sleep Med, 12, 28-33}

Of course, studies using self-reported sleep are prone to all sorts of biases, for example, people with insomnia tend to understate the actual amount of sleep they get.

This is a very recent study using actigraphic data - one week of recording of 444 women who were then followed for between 10 to 14 years.

So if we do best in terms of health, with a sleep duration of between 5 and 6.5 hours, then the recommendations of these sleep foundations and societies to get at least 8 hours are tantamount to promoting poor health.

I think that to promote such long sleep is also going to increase the number of insomniacs out there, which is certainly good for business, whether it's sleep foundations, sleep physicians, or drug companies.

What causes increased mortality with short or long sleep?

- both short and long sleep are associated with diabetes, hypertension, and obesity, as well as CVD

- for CVD, the association is independent of age, sex, race-ethnicity, smoking, alcohol intake, BMI, physical activity, diabetes, hypertension, and depression {Sabanayagam and Shankar, 2010, Sleep, 33, 1037-42}

The study looking at cardiovascular disease was a survey involving interviews of 31,428 US residents.

long sleep and mortality

- long sleep: depression, antidepressant use, and unemployment were identified as the major confounders or causal intermediates

{Patel et al., 2006, Sleep, 29, 881-9}

Other confounders or causal intermediates with lesser influence were benzodiazepine use, low societal status, sedentary lifestyle, and obesity.

Can we modify how much we sleep?

- Older adults who slept more than 8.5 hours, restricted their time in bed by 90 minutes for 8 weeks {Youngstedt et al., 2009, Sleep, 32, 1467-79}

- compared to controls:
  - restricters had improved sleep efficiency and sleep latency
  - no change in depression, sleepiness, health-related quality of life, or neurobehavioural performance
  - after one year, continued to restrict sleep voluntarily by ~1 hr

If sleeping too long increases mortality, can we decrease the amount of sleep we get? Here is a study touching on that question, in which 42 adults aged 50 to 70 years were screened and then randomized to a restricter group and a control group.

The restricters slept better, without negative effects, and voluntarily continued to restrict their sleep even after the study was over.

How to tell if we're getting the right amount of sleep

- should we wake up refreshed, ready to go?

Insomnia: treatment

- Early rising to reduce REM sleep
- Taper hypnotics
- Sleep hygiene
- Sleep restriction or compression
- Short naps
- Psychostimulants

The most useful single intervention for many people with fatigue or other depressive symptoms is to counsel them to get up earlier, for example at 6 am, or simply to go back to the sleeping pattern they followed when well.

For people taking sleep medication, getting up early may be extremely difficult. Hypnotics should be gradually tapered and eventually discontinued. When the side effects of benzodiazepines, which include increased car accidents, more falls especially in the elderly, memory problems, drug dependence, and a quadrupling of the risk for becoming depressed, are explained, patients are more receptive to the idea of giving them up. It is especially important to emphasize that behavioural treatments have been shown to be more effective than drugs for treating insomnia. If medication must be used, trazodone, which unfortunately is not very effective as an antidepressant, does promotes sleep.

Behavioural treatments for insomnia include sleep hygiene, which we'll get to in a minute. In my clinical experience, sleep hygiene approaches are not nearly as effective as the treatment which some people call sleep restriction, and others call sleep compression. The principle is the same: reduce the person's time in bed, initially to the person's own estimate of how much time they actually sleep. Increase the time in bed by a half-hour each week, as long as the patient continues to sleep well.

Because sleep restriction may actually produce some sleep deprivation, given that insomniacs underestimate their actual sleep time, I advise that daytime sleepiness be addressed by taking short naps, lying down for not more than 15 or 20 minutes.

Insomnia: treatment - 2

- Light {Leger et al., 2011, J Psychosom Res, 70, 29-36}
- Caffeine
- Exercise
- Deal with resistance
  - Address myths
  - Involve family or caregivers
- B_{12}

The value of natural daylight was demonstrated by a study of 13,296 employees of a single transportation company in France. Those exposed to natural light had less hypersomnia and insomnia.

Caffeine may actually help insomnia, by keeping people awake during the day. On the other hand, too much caffeine keeps people awake. I have two patients where we were unable to bring mania under control until the patients discontinued their consumption of caffeinated soft drinks. Interestingly, there is a study showing that in women, drinking no coffee was associated with a 2.9 times higher risk of suicide than for those consuming 2 to 3 cups of coffee daily, over a 10-year period.

Behavioural approach to insomnia

Olders H, Winningham ML. Select psychiatric and psychological considerations. In: Winningham ML, Barton-Burke M, editors. Fatigue in cancer: a multidimensional approach. Sudbury, MA: Jones & Bartlett; 2000. p. 197-242.

- Arise at the same time each day, whether you have slept well or not, or even if you have not slept at all.
- Limit daily in-bed time to "normal" amount. This depends on age, and on what worked for the individual when well. I usually recommend seven hours for middle-aged adults, six hours for people in their 60s or early 70s, and five to six hours for elderly clients.
- Limit or discontinue use of drugs that act on the central nervous system (eg, caffeine, nicotine, alcohol, and stimulants).

Behavioural approach to insomnia - 2

- Cut out daytime naps, if they exceed 15 or 20 minutes.
- Establish physical fitness with a routine of exercise early in the day, followed by other activity.
- Avoid evening stimulation; substitute either listening to the radio or leisure reading for watching television.
- Try a warm 20-minute body bath or soak near bedtime.
- Eat on a regular schedule; avoid large meals near bedtime.

Behavioural approach to insomnia - 3

- Practice an evening relaxation routine.
- Maintain comfortable sleeping conditions.
- Spend no longer than 20 minutes awake in the bed.
- Adjust sleep hours and routine to optimize your daily schedule and living situation.
- Use the bedroom only for sleeping or making love, so as to train yourself not to be in bed while awake.

Insomnia: Sleep restriction therapy

Tasman A, Kay J, Lieberman JA. Psychiatry. Philadelphia: Saunders; 1997:2 v. (xxxv, 1900 p.)

- Stay in bed for the amount of time you think you sleep each night, plus 15 min. In addition, get up at the same time each day. For example, if you report sleeping only 5 h a night and you normally get up at 6 AM, you are allowed to be in bed from 12:45 AM until 6 AM.

- Do not nap during the day.

- When sleep efficiency is 85% (i.e., sleeping for 85% of the time in bed), you can go to bed 15 min earlier. Repeat this process until you are sleeping for 8 h or the desired amount of time. (Tasman, 1997)

Generic name	*Trade name*	*Dose (mg)*	*Absorption*	*Active metabolite*	*Half-life*
chlor-diazepoxide	Librium	5 - 10	intermediate	yes	2 - 4 d
diazepam	Valium	2 - 10	fast	yes	2 - 4 d
flurazepam	Dalmane	7.5 - 30	intermediate to fast	yes	2 - 4 d
clorazepate	Tranxene	7.5 - 15	fast	yes	2 - 4 d
clonazepam	Rivotril	0.5 - 1.0	intermediate	yes	2 - 3 d
oxazepam	Serax	10 - 15	slow	no	8 - 12 h
lorazepam	Ativan	0.5 - 4	intermediate	no	10 - 20 h

Generic name	*Trade name*	*Dose (mg)*	*Absorption*	*Active metabolite*	*Half-life*
temazepam	Restoril	7.5 - 15	slow	no	10 - 20 h
alprazolam	Xanax	0.25 - 2	intermediate	no	14 h
triazolam	Halcion	.125 - .5	intermediate	no	2 - 5 h
midazolam	Versed	7.5 - 15	intermediate	no	2 - 3 h
zolpidem	Ambien	5 - 10	intermediate	no	2 - 5 h
zopiclone	Imovane	7.5 - 15	rapid	weak	4 - 7 h
zaleplon	Sonata; Starnoc	5 - 10	rapid	no	1 h

Alprazolam may trigger self-destructive behaviour, eg in borderline personality disorder patients [Gardner DL, Cowdry RW. Alprazolam-induced dyscontrol in borderline personality disorder. Am J Psychiatry. 1985;142:98-100.]

With triazolam, a dose of 0.5 mg can cause amnesia. However, a dose of one-half of the recommended geriatric dose, ie 0.0625 mg, is effective in adults.

Zolpidem has been approved for use in Canada, but is not actually being marketed.

Zopiclone may leave a metallic taste in the mouth.

Zaleplon can be prescribed as a “rescue” medication: rather than take it before bed in anticipation of an otherwise sleepless night, go to bed without medication; if you can’t sleep or wake up and can’t fall back asleep, you can take the medication if it’s 4 or more hours before your arising time.

Benzodiazepines and others

Generic name	*Trade name*	*Dose (mg)*	*Absorption*	*Active metabolite*	*Half-life*
chloral hydrate		500 - 1000	rapid	yes	4 - 12 h
propofol	Diprivan	2 - 2.5 mg/kg	intravenous	no	alpha: 1.8 - 8.3 min; beta: 34 - 66 min
valerian root		500			

Chloral hydrate is used very little these days, primarily because it is no longer available in capsules. The only formulation is a liquid which is very bitter and also quite irritating to the stomach.

Chloral hydrate is rapidly absorbed, and initially very rapidly metabolized to an active metabolite, trichloroethanol, which then undergoes a further metabolism for which the half-life is between 4 and 12 hours, as shown.

I included propofol for completeness, as it finds a lot of use in the ICU to keep patients asleep. Note the short alpha & beta half-lives, as given in the CPS.

A randomized, double-blind comparison of 600 mg valerian to 10 mg oxazepam in 202 adults 18-73, for 6 weeks: both groups had equal improvement in sleep [Ziegler G, Ploch M, Miettinen-Baumann A, Collet W. Efficacy and tolerability of valerian extract LI 156 compared with oxazepam in the treatment of non-organic insomnia--a randomized, double-blind, comparative clinical study. Eur J Med Res. 2002;7:480-486.]

melatonin

- Hormone derived from serotonin
- synthesized and released by the pineal gland
- Rises in evening, peaks between 3 and 5 am, decreases to low levels during the day
- In the elderly, levels do not rise as high
- In general, not useful as a hypnotic. May be helpful in treating jet lag, or delayed sleep phase syndrome.

Antidepressants for insomnia

- Some TCAs very sedating, eg amitriptyline
- TCAs problematic in elderly: anticholinergic, orthostatic hypotension
- Trazodone:
  - sedating, increases slow wave sleep
  - Start with 25 mg qhs in elderly
- SSRIs and others:many are stimulating
  - Sedating:
    - Mirtazapine (Remeron)
    - Paroxetine (Paxil): in some pts
    - Nefazodone (Serzone)
    - Venlafaxine (Effexor): can cause both somnolence & insomnia

Antipsychotics for insomnia

- Older phenothiazines:
    - anticholinergic, low BP, TD risk
- Olanzapine:
    - Low risk of EPS
    - Suppresses REM sleep: antidepressant
    - Increases slow wave sleep: pts feel rested
    - Useful in delirium, dementia, agitated or psychotic depressions
    - Mood stabilizer in bipolar disorder (eg mixed phase, dysphoric mania)

Antihistamines for insomnia

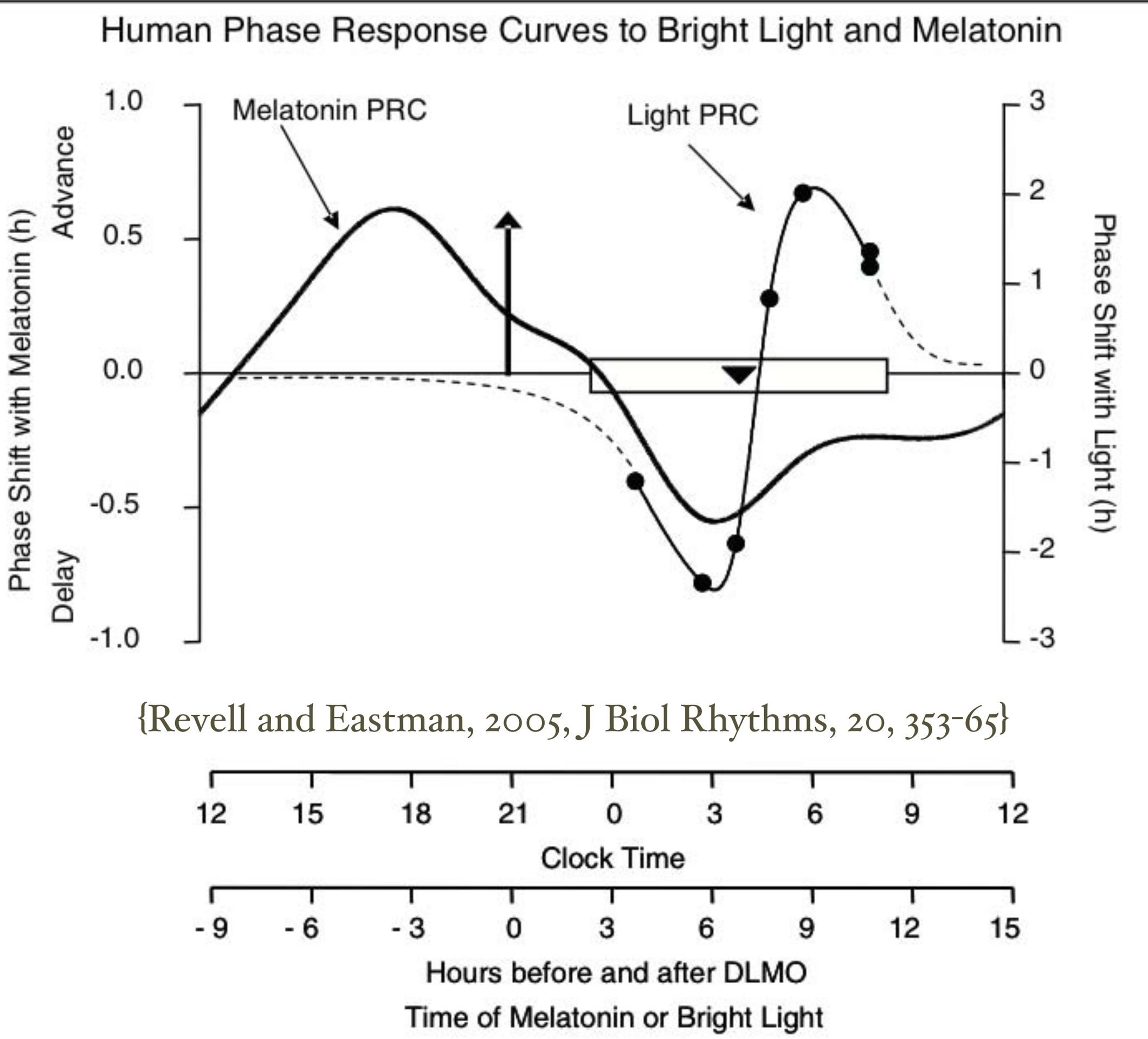
- eg, diphenhydramine (Benadryl) or hydroxyzine (Atarax)
- Also present in many OTC preparations with the suffix PM such as Tylenol® PM
- Rapid development of tolerance
- Often highly anticholinergic

Disorders of sleep timing

- Advanced sleep phase syndrome
- Delayed sleep phase syndrome
- "human rhythms advance more slowly than they delay, and reentrainment is often incomplete after advances"
  {Revell and Eastman, 2005, J Biol Rhythms, 20, 353-65}

Advanced Sleep Phase Disorder Advanced sleep phase disorder (ASPD) is the converse of the delayed sleep phase syndrome. Most commonly, this syndrome occurs in older people, 15% of whom report that they cannot sleep past 5 A.M., with twice that number complaining that they wake up too early at least several times per week. Patients with ASPD experience excessive daytime sleepiness during the evening hours, when they have great difficulty remaining awake, even in social settings. Typically, patients awaken from 3-5 A.M. each day, often several hours before their desired wake times. In addition to age-related ASPD, an early-onset familial variant of this condition has also been reported. In one such family, autosomal dominant ASPD was due to a missense mutation in a circadian clock component (PER2, as shown in Fig. 28-2) that altered the circadian period. Patients with ASPD may benefit from bright-light phototherapy during the evening hours, designed to reset the circadian pacemaker to a later hour.

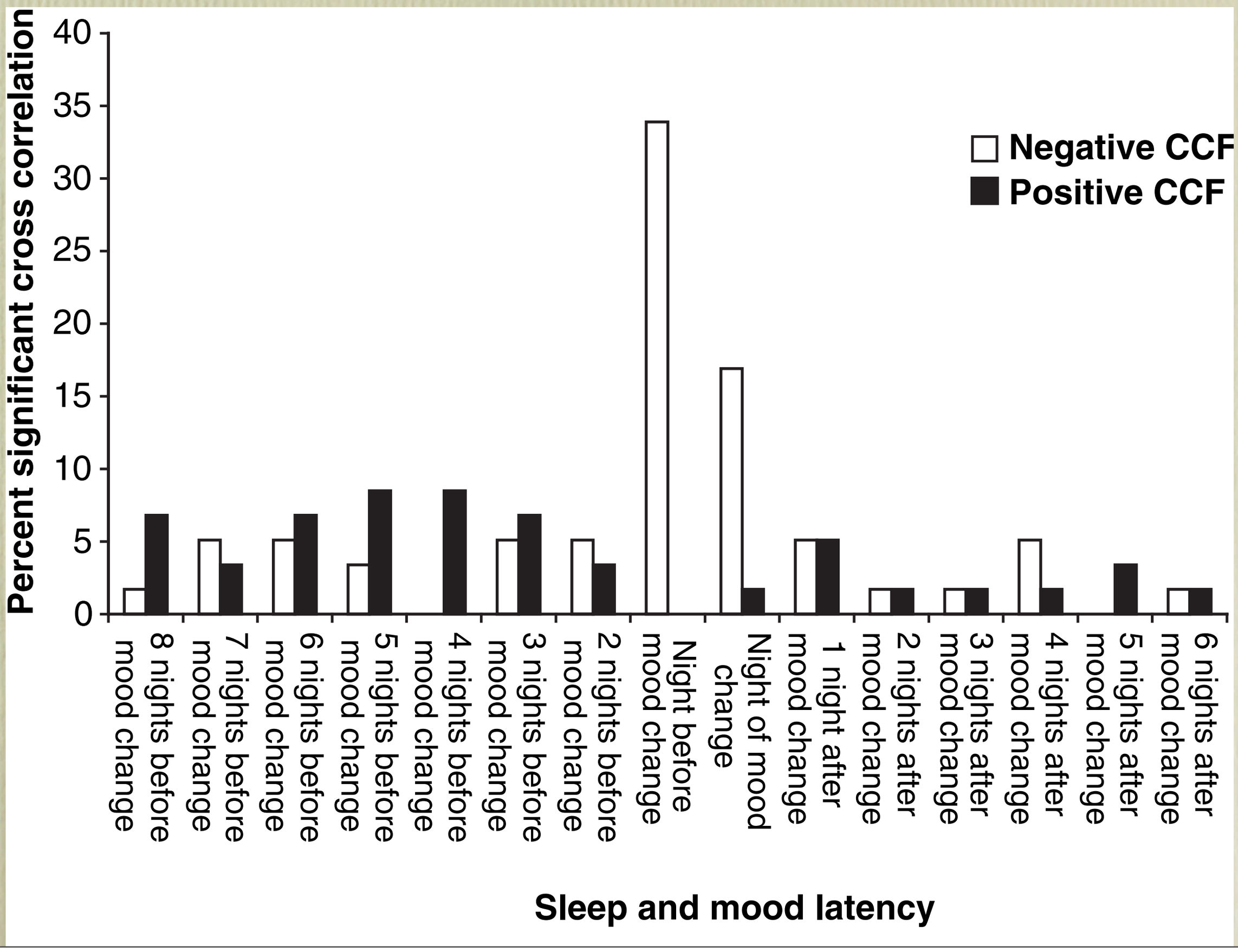
Delayed Sleep Phase Disorder Delayed sleep phase disorder is characterized by: (1) reported sleep onset and wake times intractably later than desired, (2) actual sleep times at nearly the same clock hours daily, and (3) essentially normal all-night polysomnography except for delayed sleep onset. Patients exhibit an abnormally delayed endogenous circadian phase, with the temperature minimum during the constant routine occurring later than normal. This delayed phase could be due to: (1) an abnormally long, genetically determined intrinsic period of the endogenous circadian pacemaker; (2) an abnormally reduced phase-advancing capacity of the pacemaker; or (3) an irregular prior sleep-wake schedule, characterized by frequent nights when the patient chooses to remain awake well past midnight (for social, school, or work reasons). In most cases, it is difficult to distinguish among these factors, since patients with an abnormally long intrinsic period are more likely to "choose" such late-night activities because they are unable to sleep at that time. Patients tend to be young adults. This self-perpetuating condition can persist for years and does not usually respond to attempts to reestablish normal bedtime hours. Treatment methods involving bright-light phototherapy during the morning hours or melatonin administration in the evening hours show promise in these patients, although the relapse rate is high.



{Revell and Eastman, 2005, J Biol Rhythms, 20, 353-65}

Figure 1. The light PRC was generated from 7 subjects who free-ran through about 3 days (73.5 h) of an ultradian LD cycle (2.5 h wake in dim light < 100 lux alternating with 1.5 h sleep in dark) (Eastman and Burgess, unpublished data). Subjects lived on the ultradian schedule on 2 different occasions, once with bright light pulses, about 3500 lux, for 2 h at the same time each day, and once without bright light pulses, counterbalanced. Phase shifts of the midpoint of the melatonin rhythm collected in dim light (<5 lux) before and after the 3 days were plotted against the time of the light pulse relative to each subject's baseline dim light melatonin onset (DLMO) and corrected for the free run when the bright light was not applied. Upward arrow: average baseline DLMO, rectangle: average baseline sleep schedule, triangle: estimated time of body temperature minimum (DLMO + 7 h). The solid line is a smoothed curve fit to the 7 points. The melatonin PRC was calculated from the data of Lewy et al. (1998). Subjects (n = 6), living at home, took 0.5 mg melatonin at the same time each day for 4 days. Phase shifts of the DLMO were plotted against the time of melatonin administration relative to each subject's baseline DLMO. A smoothed curve was fit to the data after averaging the 70 data points into 3-h bins.

Bauer M, Grof P, Rasgon N, Bschor T, Glenn T, Whybrow PC. Temporal relation between sleep and mood in patients with bipolar disorder. Bipolar Disord. 2006;8:160-167.



Finally, I want to talk about bipolar disorder as a type of sleep disorder. This graph is from a recent article describing a study of bipolar disorder patients who were each asked to document their daily mood as well as the number of hours of sleep. 59 patients provided at least 100 days' worth of data that were included in the analysis. The sleep durations and the mood for each patient represent time series, to which a first-order filter was applied so that only changes in sleep duration and changes in mood were looked at, and then a cross-correlation function was applied. The significant cross correlations were then totaled for the 59 patients to produce this graph.
The white bars represents a negative cross correlation, ie a change to more sleep correlates with a decrease in mood (ie becoming more depressed) and a decrease in sleep correlates with becoming more manic. They found that in 34% of patients there was a significant negative correlation the night before a mood change, and for 17% of the patients there was a significant negative correlation the same night as the mood change. No patients had a significantly positive correlation the night before the mood change, although for other time intervals, there were more positive than negative correlations.

What I think is important

- short naps
- avoid night-time light
- dawn light
- stimulants, eg caffeine
- regular sleep pattern
- nozinan for sleep, manic symptoms
- antidepressants, CHEIs may cause agitation
- deal with attitudes about poor sleep

Links:

article on insomnia: http://tinyurl.com/2p9axc

pdf of today's slides:

That covers what I wanted to cover today. Just a reminder that you can access the sleep disorder stuff on a wiki, here:

If there is interest, I can go into a little more depth on benzodiapine pharmacology.

Should you prescribe BDZ?

- Problems with BDZs:
  - Increased risk of depression

    Patten SB, Williams JV, Love EJ. Self-reported depressive symptoms following treatment with corticosteroids and sedative-hypnotics. Int J Psychiatry Med. 1996;26:15-24.
  - Behavioural disinhibition

    Gardner DL, Cowdry RW. Alprazolam-induced dyscontrol in borderline personality disorder. Am J Psychiatry. 1985;142:98-100.
    - The Mouse Defense Test Battery

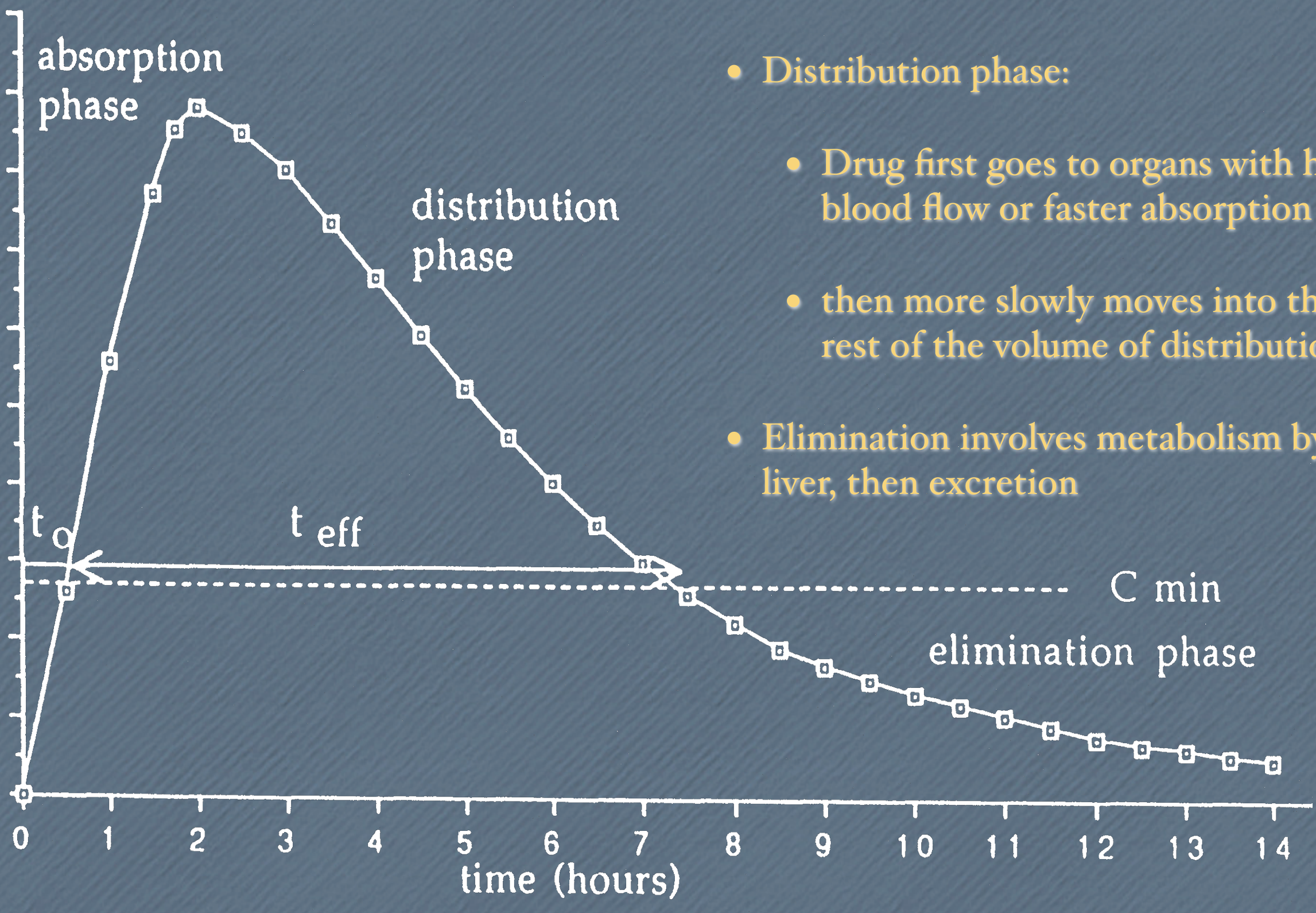
      Griebel G, Blanchard DC, Blanchard RJ. Predator-elicited flight responses in Swiss-Webster mice: an experimental model of panic attacks. Prog Neuropsychopharmacol Biol Psychiatry. 1996;20:185-205.
  - Risk of dependence and abuse
  - Rebound insomnia/anxiety/disturbed sleep
  - In elderly:
    - Risk of falling
    - Cognitive impairment
- If you do use, consider pharmacokinetics...

Pharmacokinetics of sedative/ hypnotics

- Rate of absorption
- Alpha & Beta Half-lives
- Volume of Distribution
- Elimination Half-life
- Effects of aging

Medication Phases

Plasma concentration curve after a single dose of medication



- Distribution phase:
  - Drug first goes to organs with high blood flow or faster absorption
  - then more slowly moves into the rest of the volume of distribution
- Elimination involves metabolism by liver, then excretion

Let's discuss what happens in the brain with benzodiazepines. This slide shows a typical plasma concentration curve after a single dose of medication.

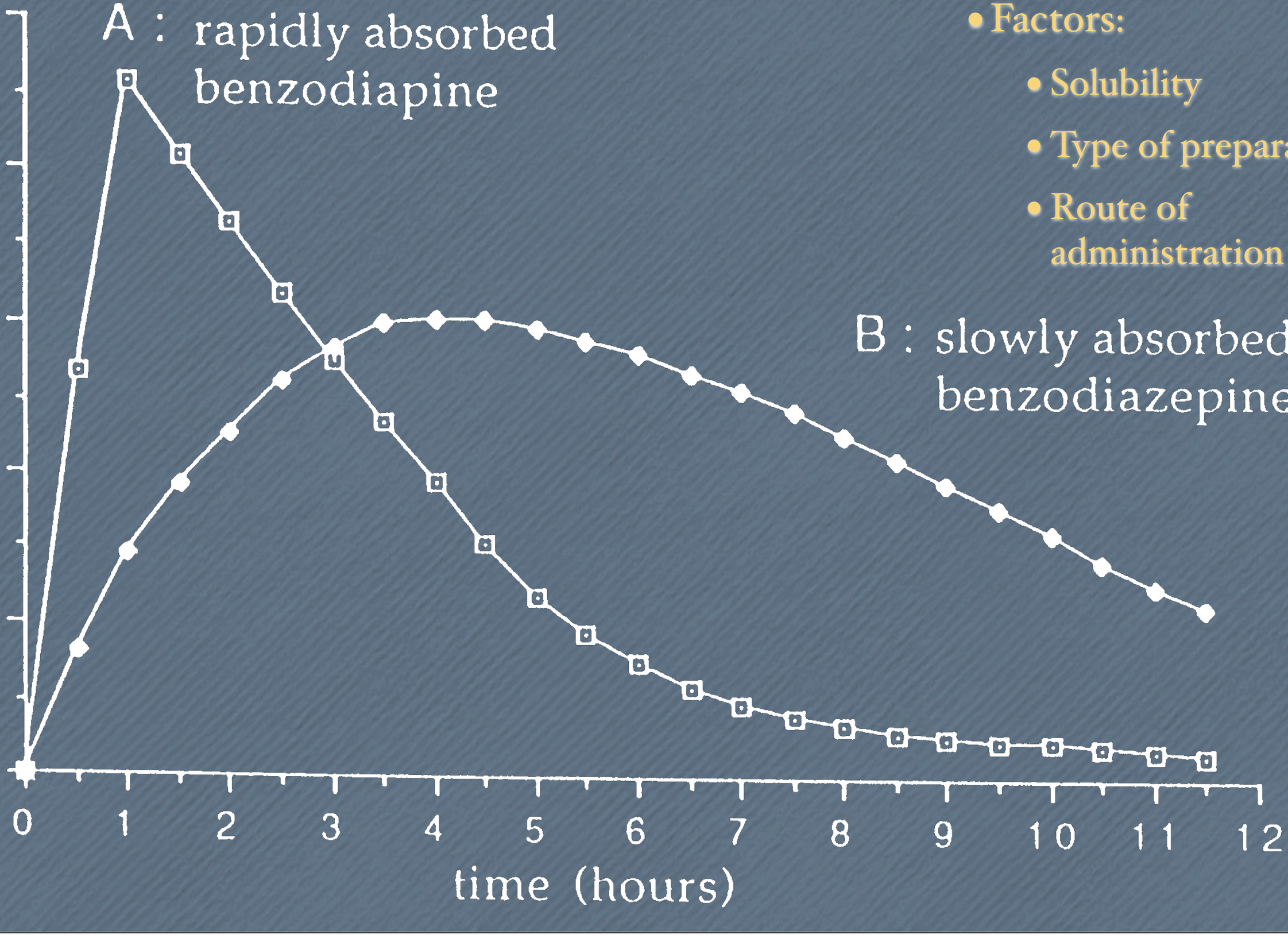
After the medication is absorbed, it first gets redistributed into its volume of distribution, and then gets eliminated from the body.

Benzodiazepines, as well as most psychotropics, are lipophilic. Thus, after an oral dose, a benzo will initially go to the part of the lipid compartment which has the highest blood circulation, the brain. Next, it will redistribute into the rest of the lipid compartment, the body fat stores, which has comparatively poor blood circulation.

Finally, the drug is taken up by the liver, turned into water-soluble compounds, which can then be flushed from the body by the kidneys.

Rate of Absorption

- Affects speed of action
  - Abuse potential
- Factors:
  - Solubility
  - Type of preparation
  - Route of administration



Obviously, a drug which is rapidly absorbed will have a shorter time to onset of clinical action. Factors which affect absorption of benzodiazepines have to do with solubility and the type of preparation, but most of all, the route of administration. The fastest route is inhalation, and the slowest is the oral route. Intravenous, sublingual, and intramuscular routes are intermediate.

Comparison of Absorption Speed for Lorazepam

Route of Administration	IV	S/L	IM	PO
Time to Peak Blood Level (minutes)	8-15	60	60-90	120

Teboul, 1989

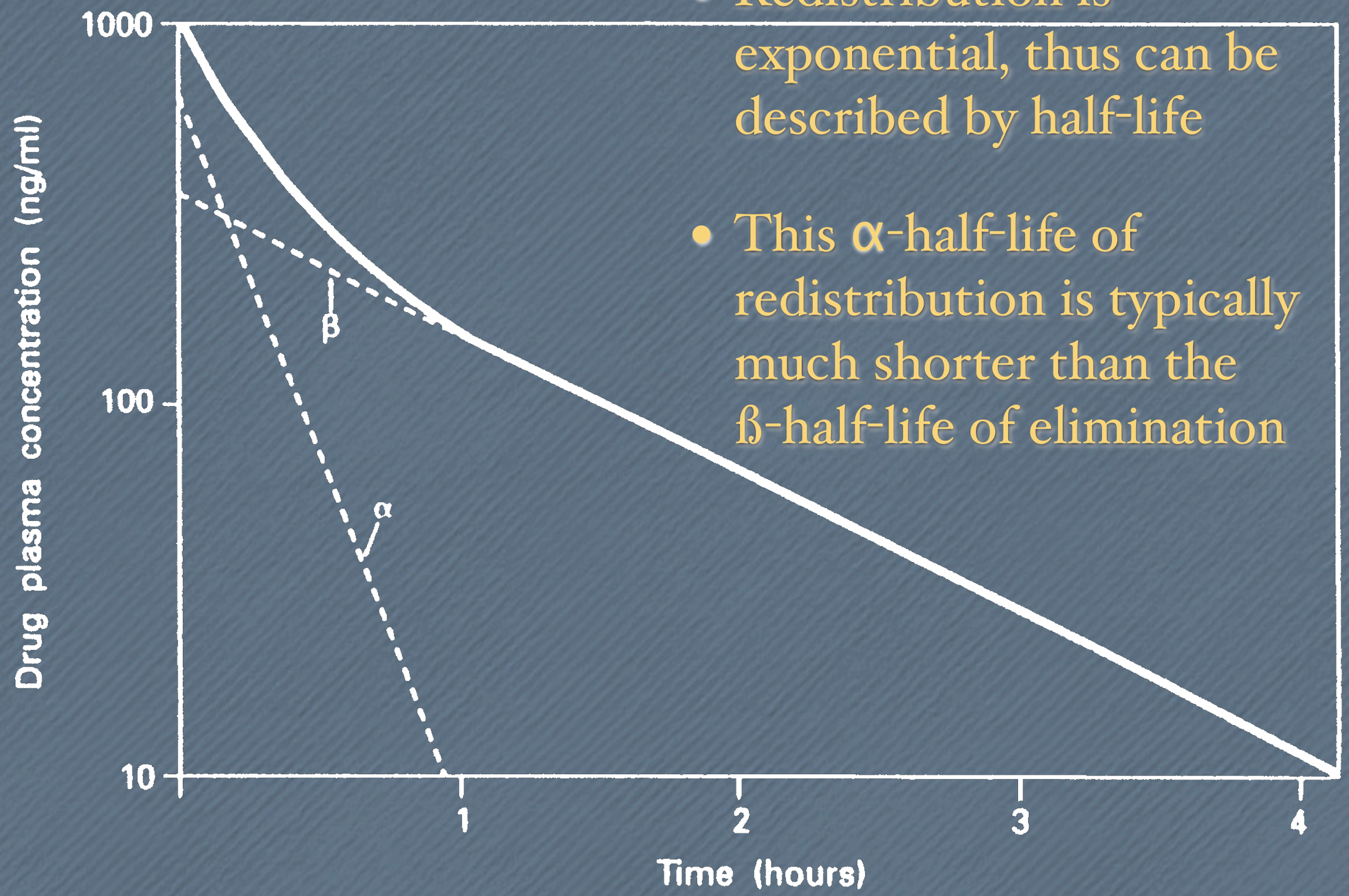
This slide compares times to peak blood level for different routes of administration of lorazepam.

What influences how rapidly a drug has its onset of effect? Clearly, rate of absorption is important, but so is the degree of lipid solubility, which determines how quickly the drug gets into the brain.

Medications which have a rapid onset of effect are most likely to be abused. This is why diazepam, which has fast absorption as well as the highest lipid solubility of the commonly used benzos, is widely available as a street drug. Others which are rapidly acting include flurazepam, lorazepam, alprazolam, and triazolam.

Note that all of these rapidly acting medications are frequently prescribed as hypnotics. On the other hand, oxazepam, which takes about 3 to 4 hours to reach peak blood levels, is less likely to be found on the street. Moreover, patients complain that it doesn't work when given to help sleep. What they mean is that they don't experience the knockout punch of the rapid-acting benzos.

Alpha & Beta Half-lives

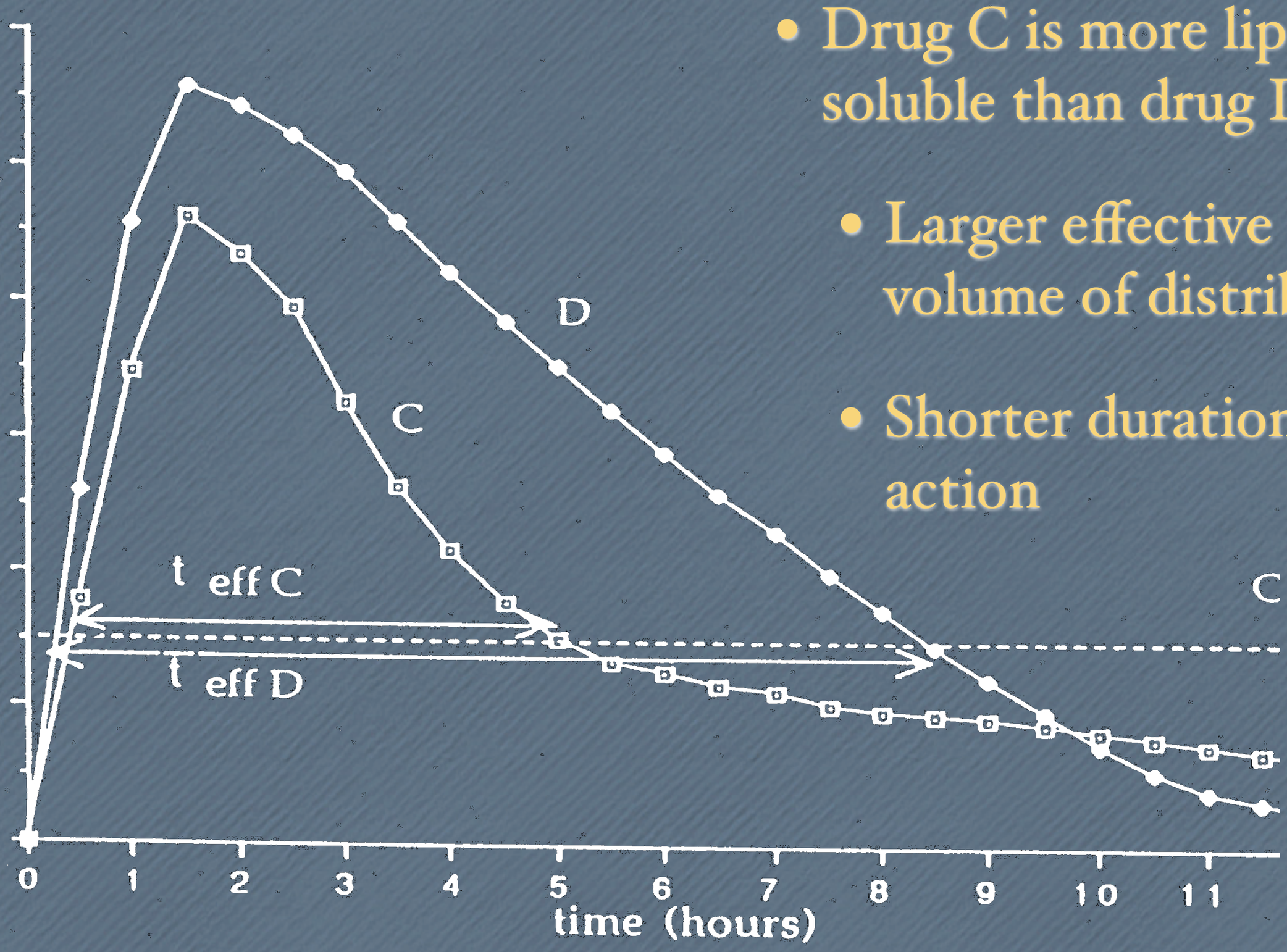


- Redistribution is exponential, thus can be described by half-life
- This α-half-life of redistribution is typically much shorter than the ß-half-life of elimination

For lipid-soluble medications, the distribution phase, when the drug is finding its way into the fat compartment, leads to an exponential decrease in blood concentrations. Thus, the rate of redistribution can be described in terms of its half-life.

This graph shows how the half-life of redistribution, also known as the alpha half-life, is typically much shorter than the half-life of elimination, called the beta half-life.

Effects of Volume of Distribution

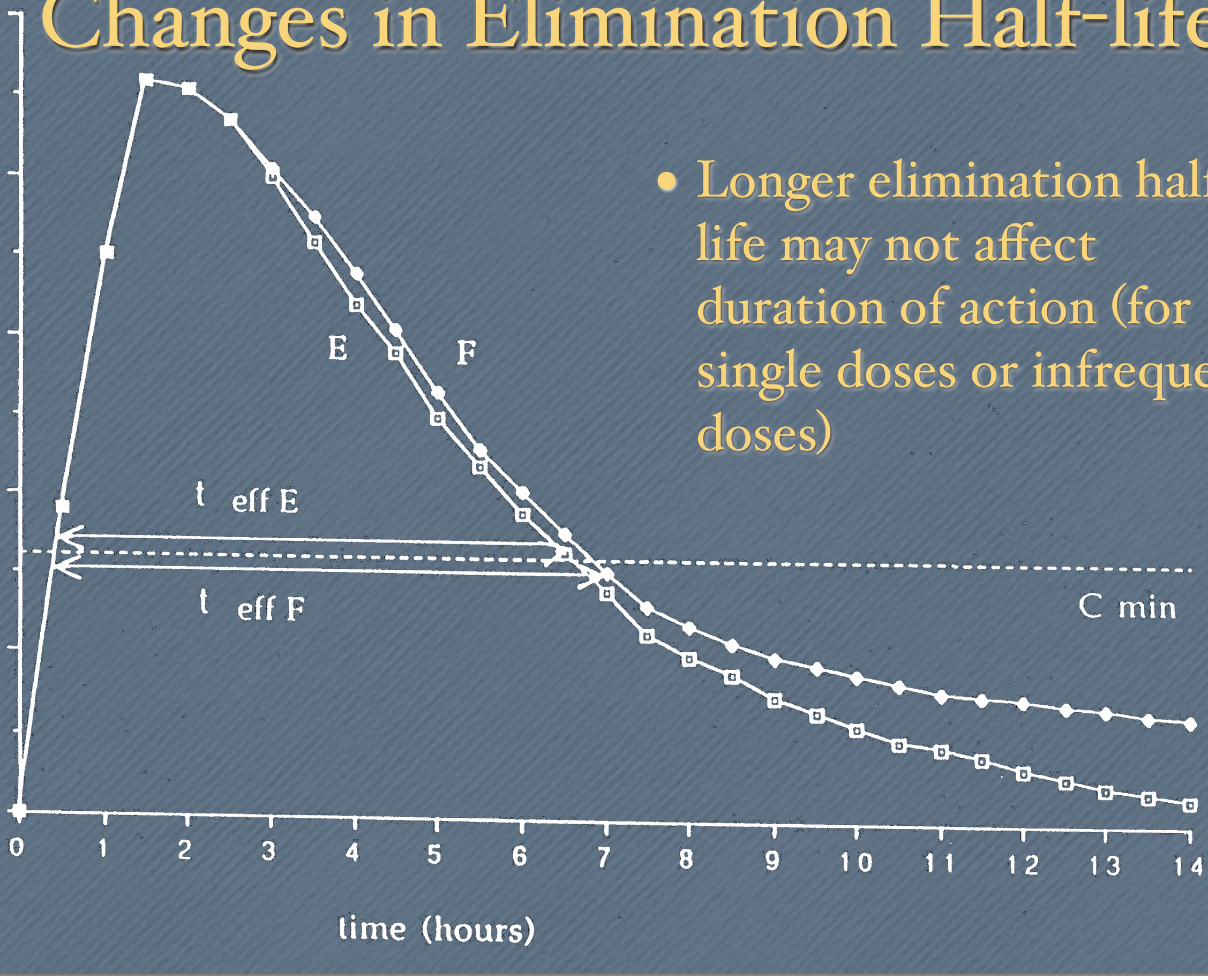


- Drug C is more lipid-soluble than drug D:
  - Larger effective volume of distribution
- Shorter duration of action

The effect of a higher lipid solubility is to make to volume of distribution effectively larger. For example, a typical person's water compartment is only 10 litres, compared to 40 litres for the lipid compartment. So the more that a drug prefers fats to water, the bigger its volume of distribution.

This graph shows that drug C with a higher volume of distribution because of greater lipid solubility, will have a shorter duration of action than drug D.

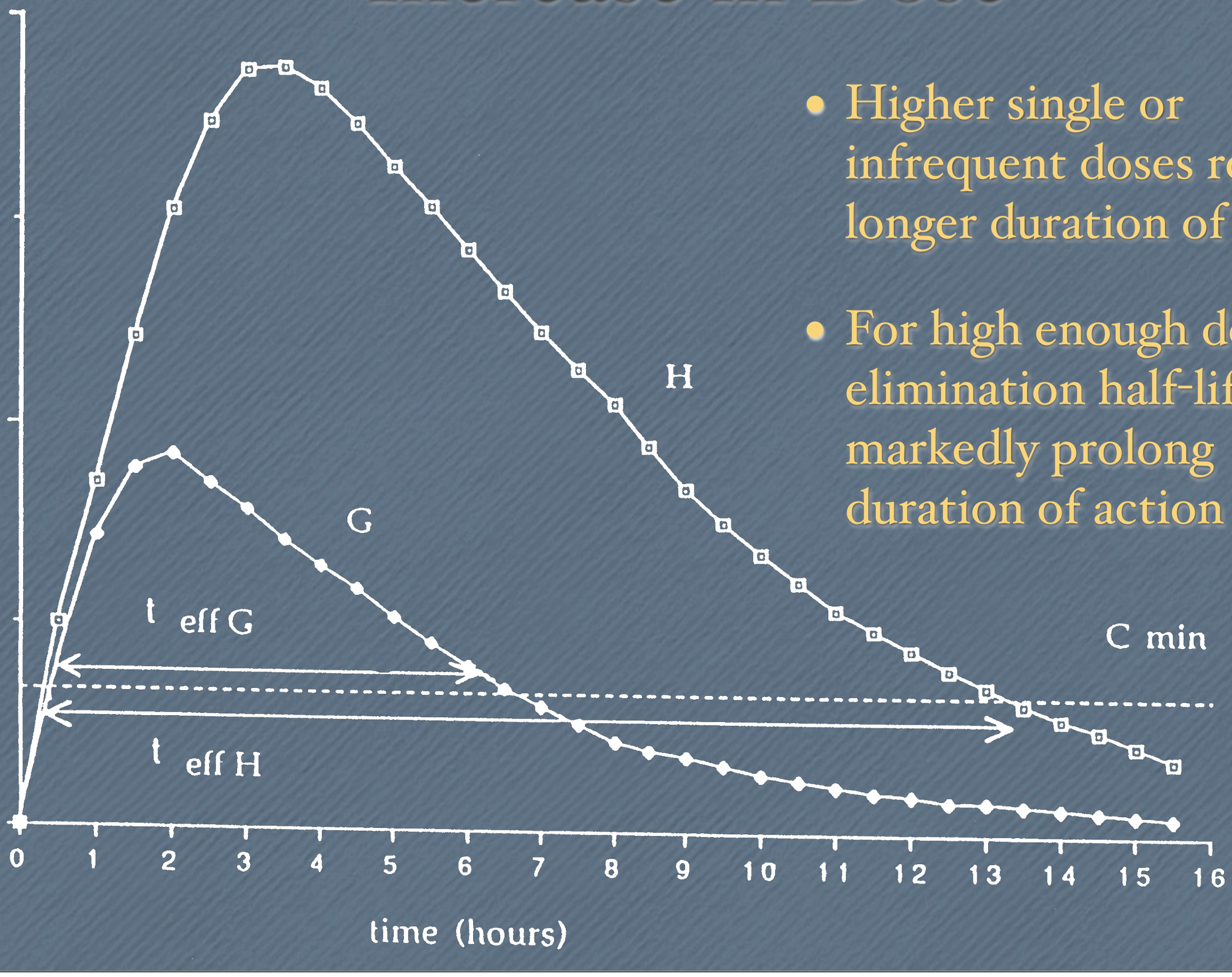
Changes in Elimination Half-life



- Longer elimination half-life may not affect duration of action (for single doses or infrequent doses)

This contrasts with the elimination half-life, which does not affect duration of action when the drug is given in single doses, or doses which are far enough apart.

Increase in Dose

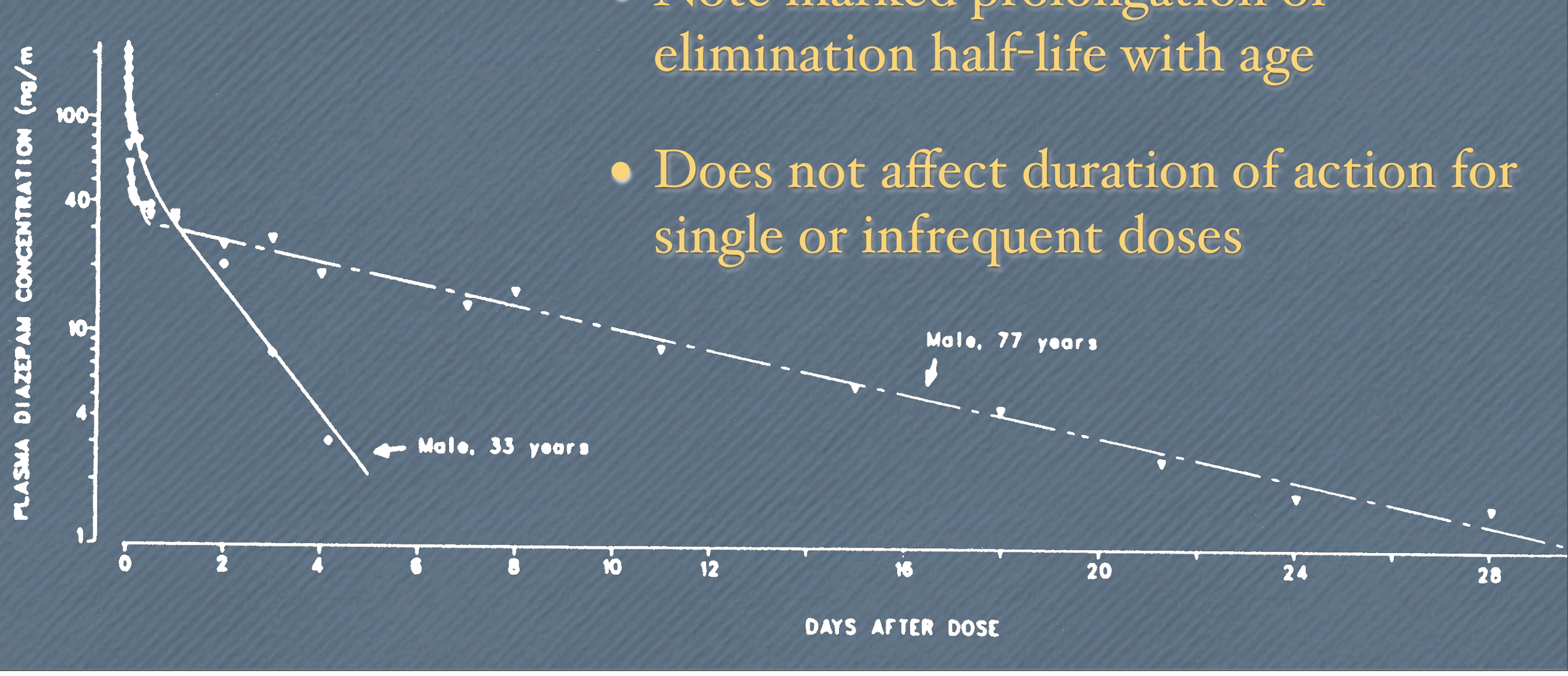


- Higher single or infrequent doses result in longer duration of action
- For high enough doses, elimination half-life may markedly prolong duration of action

If the dose is larger, of course, duration of action will increase. If the dose is sufficiently high, then the elimination phase will start to play a role in markedly increasing the duration of action.

Effects of Age

- plasma concentrations of diazepam after a single intravenous dose of 5 mg in volunteers of approximately the same weight
- Note marked prolongation of elimination half-life with age
- Does not affect duration of action for single or infrequent doses

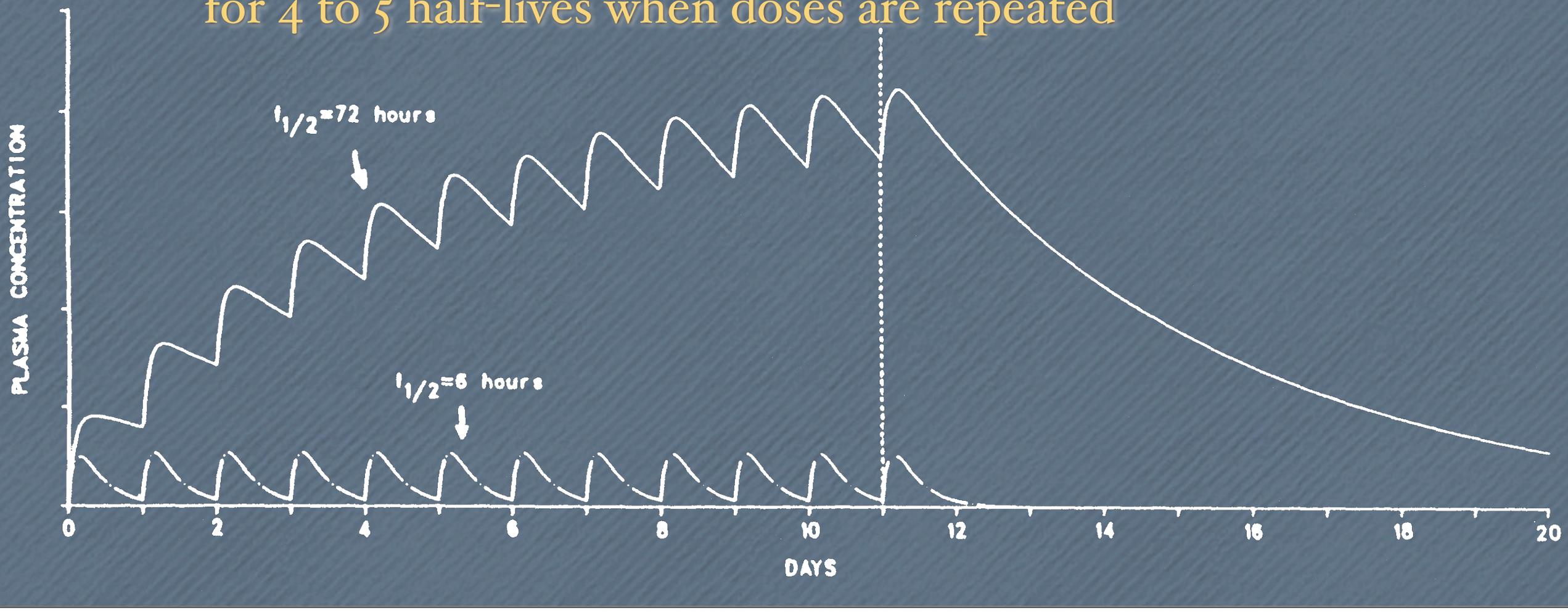


This graph represents plasma concentrations of diazepam after a single intravenous dose of 5 mg in volunteers of approximately the same weight. Note the extensive prolongation of the elimination half-life in the elderly subject.

So why is half-life of elimination important? We've already seen that it has little influence on speed of onset of action or on duration of action. But keep in mind that those graphs were for single doses. Here's what happens when medication is given repeatedly.

Long vs Short Half-life

- plasma concentrations for a BDZ given once daily for 11 days
  - top curve is for a half-life of 72 hrs
  - bottom curve is for a half-life of 6 hrs
- for long half-life drugs, blood levels will continue to increase for 4 to 5 half-lives when doses are repeated



This is a graph of plasma concentrations for a benzodiazepine given once daily for 11 days. The top curve is for a half-life of 72 hours, and the bottom curve is for a half-life of 6 hours.

The important point is that for long half-life drugs, blood levels will continue to increase for 4 to 5 half-lives when doses are repeated.

A scenario

- Diazepam has active metabolites with a half-life of up to 100 hrs in healthy people
- May increase to 400 hrs in elderly or in liver disease (> 2 weeks)
- peak blood levels reached in 8 to 10 weeks
- Scenario: elderly gentleman, just lost his spouse
  - Complains to family doctor of insomnia
  - Rx valium qhs x 2 wks
  - After 2 wks, still can't sleep without meds. Another Rx
  - Several wks later: falls, brought to ER, agitated, delirious. Valium not implicated (started 2 mos earlier)
  - Even if valium d/c'd, may take weeks before delirium clears

Consider diazepam, whose active metabolites can have a half-life of up to 100 hours in healthy people. This might go up to, say, 400 hours, in someone who's elderly or who has liver disease. 400 hours is more than 2 weeks. Thus, it might take 8 to 10 weeks to reach peak blood levels.

A typical scenario might be an elderly gentleman who has just lost his spouse. He goes to his family doctor complaining of insomnia, and is prescribed two weeks' worth of valium. After the two weeks, he tells his doctor that he couldn't sleep without the medication, and he receives another prescription.

Several weeks later, the patient ends up in the ER, having fallen. Seen by psychiatry for agitated behaviour. The diagnosis is delirium. No one thinks to implicate the valium; after all, he's been on it for 2 months already without problems. Even if someone does clue in, and decides to stop the valium, it may be weeks before it washes out of the patient's system.

Other considerations

- Oxazepam, lorazepam, alprazolam are less affected by liver disease
- BDZ decrease slow wave sleep:
  - Decreased feeling of having had a “restful” sleep
- BDZ decrease REM sleep:
  - Because of REM rebound & longer total sleep, total REM sleep may increase
  - May contribute to depression and fatigue