

Sleep and Anxiety Disorders in the Elderly

Henry Olders, MD, FRCPC

Saint Anne's Hospital

henry.olders@mcgill.ca

<http://henry.olders.ca/psychiatry>









A Proverb

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

—John Clarke (1596-1658):
proverb collection Paroemiologia 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
 - Narcolepsy
 - OSA
- REM sleep behaviour disorder
- Insomnia
 - Manifestations, causes, treatments

Outline - 3

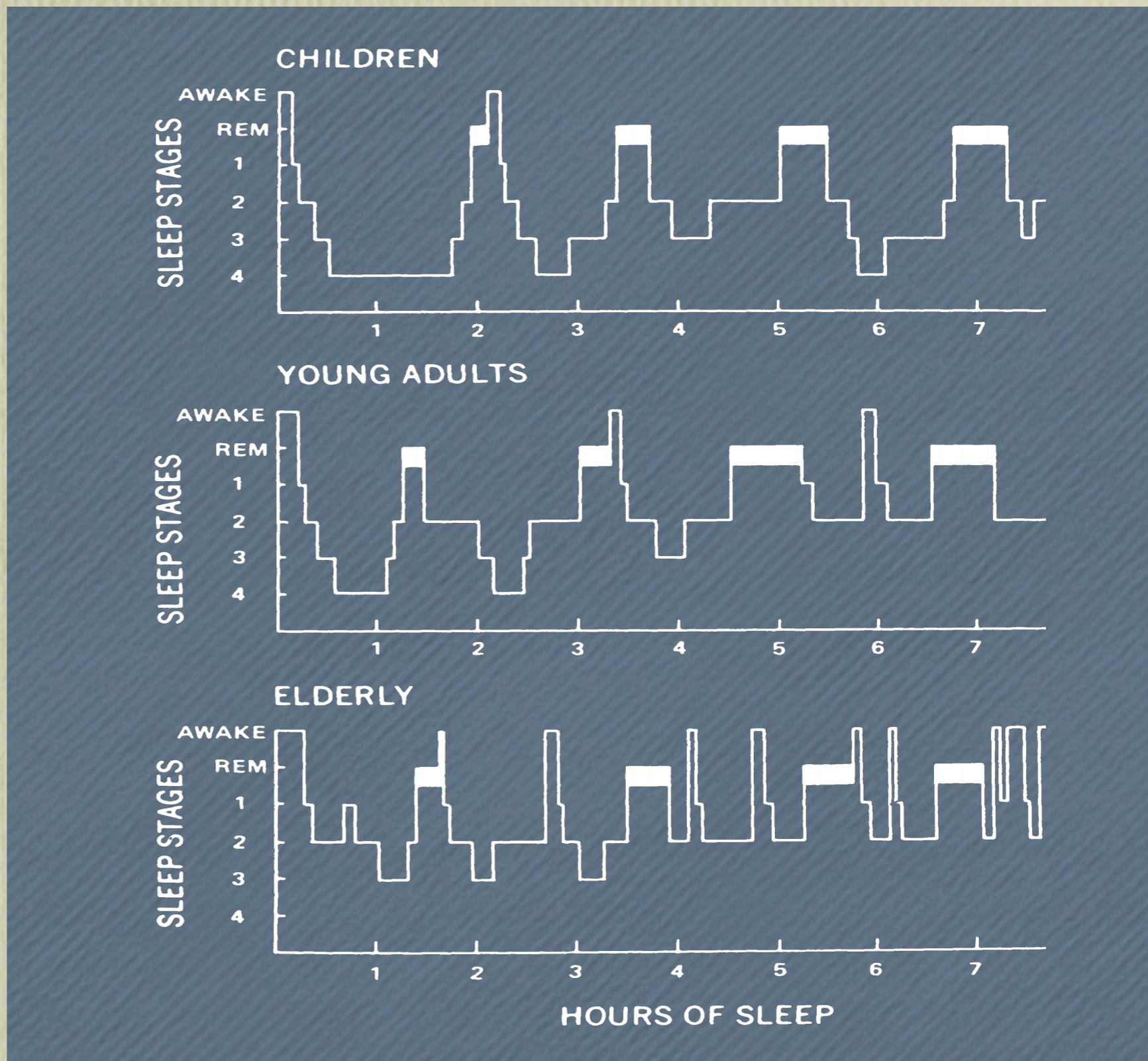
- Anxiety
 - What is anxiety?
 - Epidemiology of Anxiety Disorders
- What do sleep disorders & anxiety disorders have in common?
- Treatment of anxiety

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

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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;

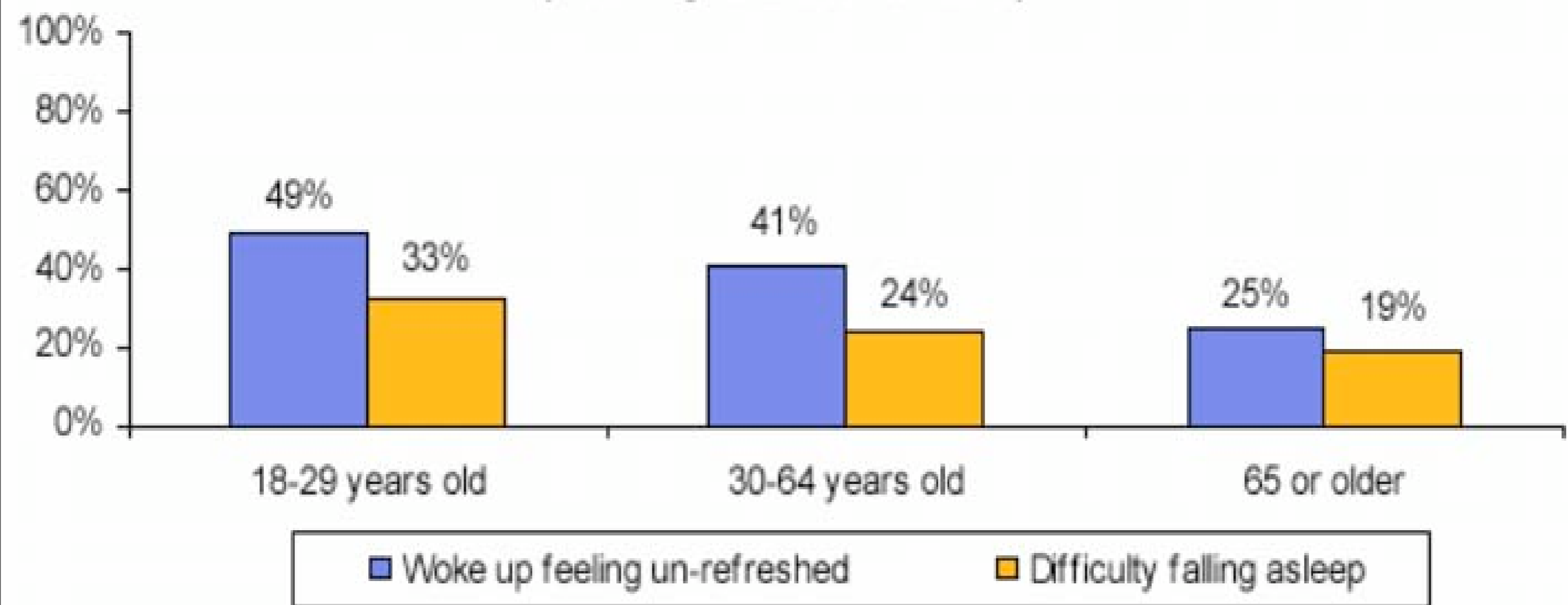
They reported fewer symptoms of insomnia and sleep disorders in general, and more of the elderly reported their mood as “very positive”.

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

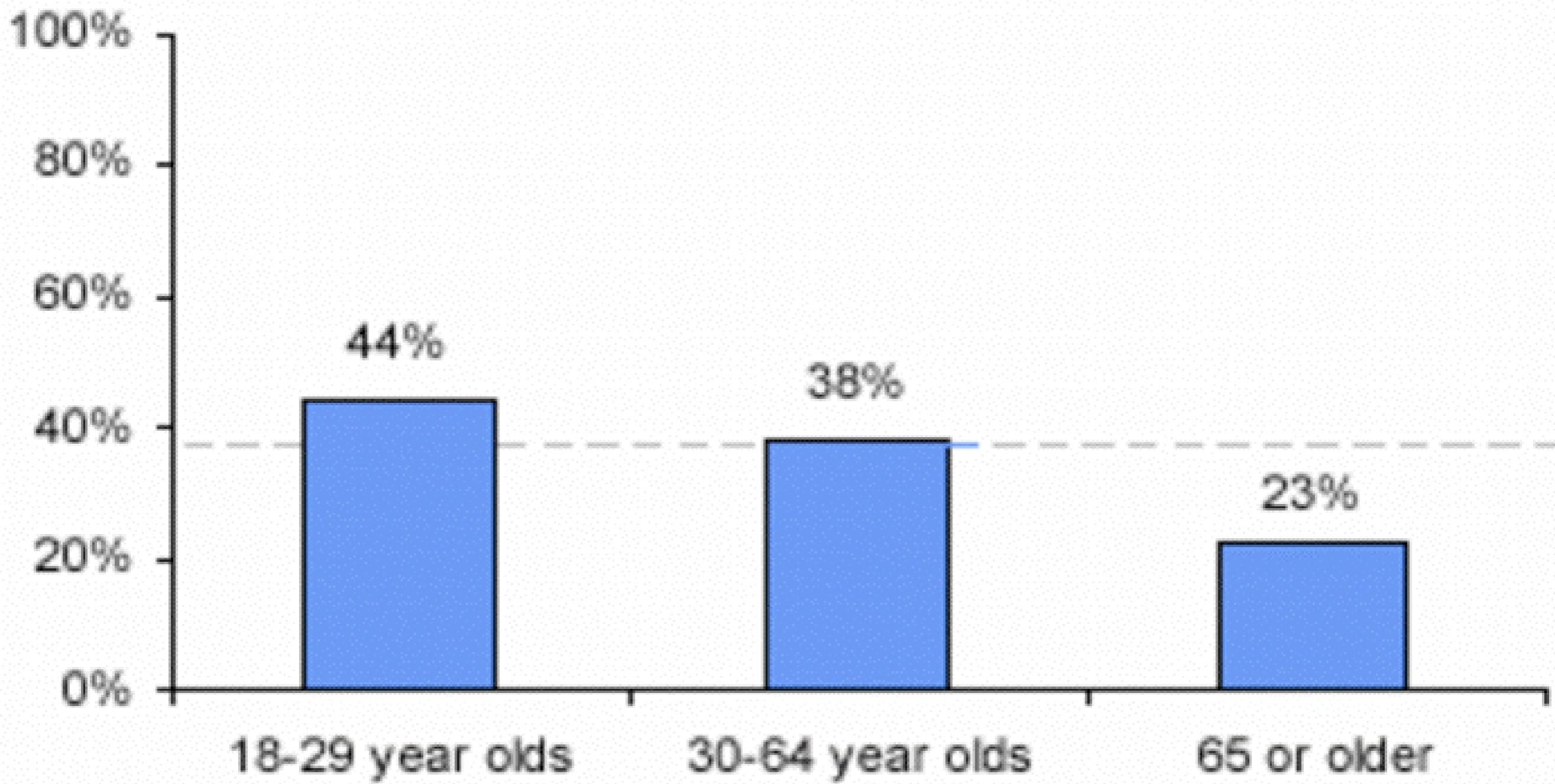
Feeling unrefreshed, difficulty falling asleep, by age

Percent Reporting Two Insomnia Symptoms by Age
(a few nights a week or more)



Daytime sleepiness, by age

Percent Reporting Daytime Sleepiness Interfering with Daily Activities (at least a few days a month) by Age



Sleep problems: Approach to the patient

- GSAQ: Global Sleep Assessment Questionnaire © Pharmacia Corporation 2001
- 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

<i>Disorder</i>	<i>Sensitivity</i>	<i>Specificity</i>
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

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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

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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

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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.

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

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%

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.

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; 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)
 - Start with 5 mg bid-tid
 - Go up to 50 mg or higher per day if necessary
 - Dextroamphetamine (Dexedrine)
 - Methamphetamine (Desoxyn - not available in Canada)
 - Pemoline (Cylert)
 - Modafinil (Alertec)

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

Breathing-Related Sleep Disorder (BRSD)

- Lifetime prevalence: 9% men, 4% women
- Diagnostic criterion: cessation of breathing for at least 10 sec, at least 5 x per hour
- 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. The diagnostic criterion shown here represents very mild illness, as it is not uncommon to see people who stop breathing for 60 to 120 seconds, hundreds of times per night.

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

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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.

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

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

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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

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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.

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

Insomnia: treatment

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

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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 promote 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
- Caffeine
- Exercise
- Deal with resistance
 - Address myths
 - Involve family or caregivers
- Antidepressants
- thyronine, B12

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)

<i>Generic name</i>	<i>Trade name</i>	<i>Dose (mg)</i>	<i>Absorption</i>	<i>Active metabolite</i>	<i>Half-life</i>
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
<u>clonazepam</u>	Rivotril	0.5 - 1.0	intermediate	yes	2 - 3 d
<u>oxazepam</u>	Serax	10 - 15	slow	no	8 - 12 h
<u>lorazepam</u>	Ativan	0.5 - 4	intermediate	no	10 - 20 h

<i>Generic name</i>	<i>Trade name</i>	<i>Dose (mg)</i>	<i>Absorption</i>	<i>Active metabolite</i>	<i>Half-life</i>
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
<u>zolpidem</u>	Ambien	5 - 10	intermediate	no	2 - 5 h
<u>zopiclone</u>	Imovane	7.5 - 15	rapid	weak	4 - 7 h
<u>zaleplon</u>	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

<i>Generic name</i>	<i>Trade name</i>	<i>Dose (mg)</i>	<i>Absorption</i>	<i>Active metabolite</i>	<i>Half-life</i>
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			

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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)

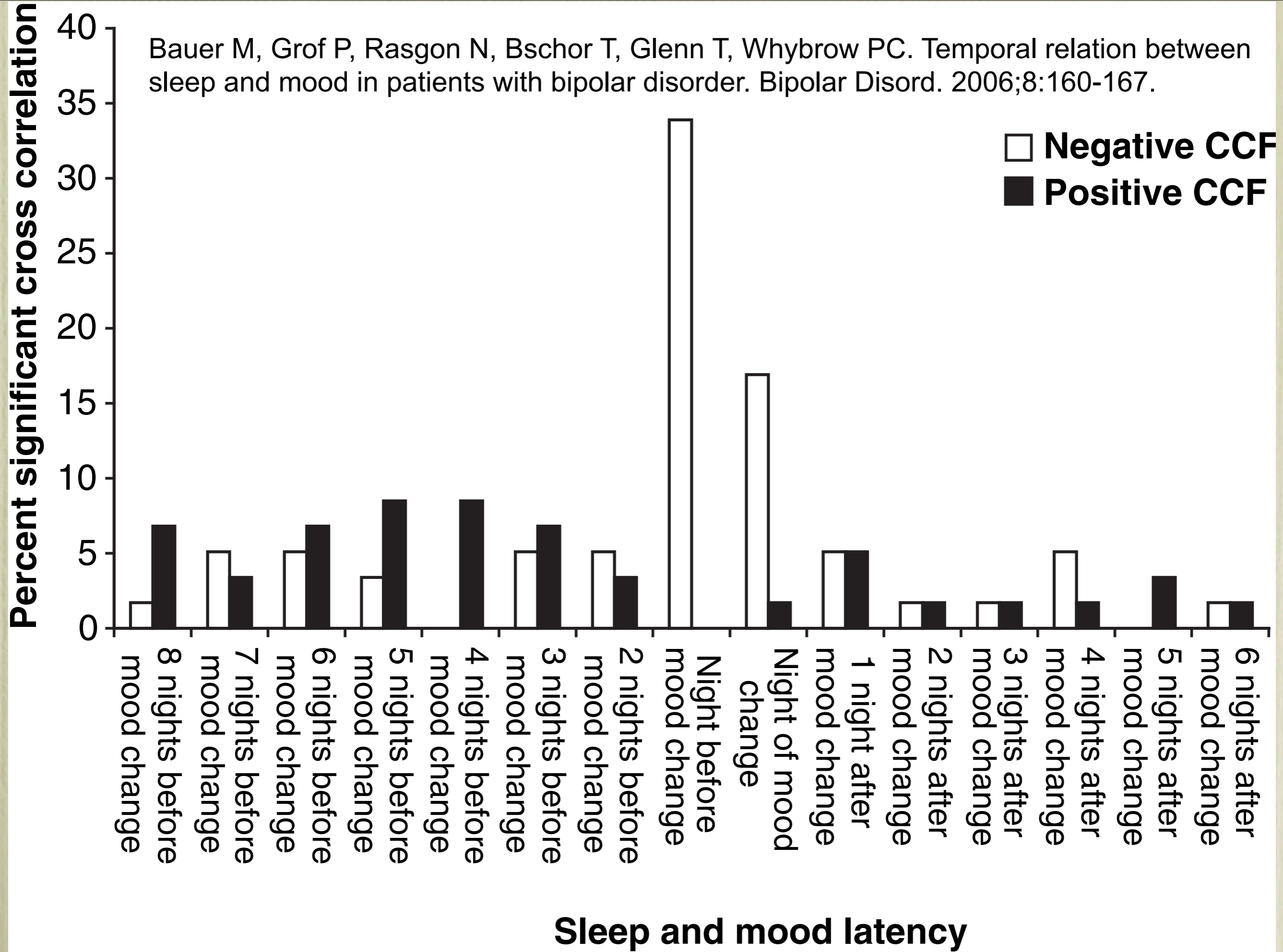
Antihistamines for insomnia

- 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

Pharmacodynamics: effects of age

- ↓ drug absorption 2°:
 - decreased blood flow to GI tract
 - Increased gastric pH
 - Altered transport across gastric mucosa
- ↑ body fat prolongs half-life of BDZ
- ↓ plasma proteins increases level of free drug
- ↓ hepatic oxidative metabolism increases plasma drug levels
- ↓ glomerular filtration rate decreases renal clearance (probably not important for BDZ) [Blazer, 1997]
- Bottom line: start low, go slow!

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.



Sleep and mood latency

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's the connection between sleep disorders and anxiety?

- Common treatments (eg, BDZ, antidepressants)
- Often seen together, eg in depression, dementia
- Both disorders are often treatment resistant
- People with insomnia are more anxious/aroused than good sleepers
- Specifically, they have fear of cognitive dyscontrol:
 - “When I cannot keep my mind on a task, I worry that I might be going crazy”
 - “When I am nervous, I worry that I am mentally ill”

What is anxiety?

- A biological warning system
- Preparation to react mentally and physically to potentially dangerous situations (fight or flight response)

Physiology of anxiety/fear

- Increased muscle tension
- Activation of sympathetic nervous system:
 - Increased heart rate, blood pressure, sweating, breathing
- Some activation of parasympathetic nervous system:
 - Increased gastro-intestinal, bladder activity
- Neuroendocrine: increases in:
 - Epinephrine
 - Norepinephrine
 - Cortisol
 - Growth hormone
 - Prolactin

Physiology in anxiety disorders

- **Diminished physiological flexibility in anxiety disorder patients** Hoehn–Saric R, McLeod DR. Anxiety and arousal: physiological changes and their perception. *J Affect Disord.* 2000;61:217–224.
 - decreased response to stressors
 - take longer to return to baseline
- **Abnormally sensitive CNS fear mechanism in panic disorder patients** Sinha S, Papp LA, Gorman JM. How study of respiratory physiology aided our understanding of abnormal brain function in panic disorder. *J Affect Disord.* 2000;61:191–200.
 - Stress causes patient to hyperventilate
 - Exaggerated levels of cerebral vasoconstriction with hyperventilation
- **Cocaine use may trigger panic attacks** Louie AK, Lannon RA, Rutzick EA, Browne D, Lewis TB, Jones R. Clinical features of cocaine-induced panic. *Biol Psychiatry.* 1996;40:938–940.

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There is some evidence that anxiety disorder patients have a physiology that differs from normals. For example, a decreased response to stressors has been found, along with a slower return to baseline after the stressor.

Panic disorder patients may have an abnormally sensitive fear mechanism; stress leads to hyperventilation which then causes vasoconstriction of blood vessels in the brain.

The connection between cocaine use and subsequent onset of panic attacks, even if no longer using cocaine, is fascinating. This is thought to be some sort of kindling mechanism. But do elderly people use cocaine? Clearly some do, especially now that the baby boomers are arriving at that age.

Anxiety physiology in elderly

- Elderly have reduced heart rate reactivity to stressor tasks, but return to baseline more rapidly, compared to young adults

Lau AW, Edelstein BA, Larkin KT. Psychophysiological arousal in older adults: a critical review. Clin Psychol Rev. 2001;21:609–630.

- Norepinephrine levels and responses to stressors are higher in elderly, may take longer to return to baseline

Kogan JN, Edelstein BA, McKee DR. Assessment of anxiety in older adults: current status. J Anxiety Disord. 2000;14:109–132.

- This may explain why elderly experience more fear symptoms and less negative affect factors (depression, anxiety-guilt, hostility)

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The physiologic differences are never consistent, unfortunately. We saw on the previous slide that the elderly take longer to return to baseline for physiologic responses to anxiety, but for heart rate reactivity, it seems they return to baseline more rapidly than young adults. But for norepinephrine, again, there's a longer return to baseline.

Symptoms of anxiety

- Feeling tense and flushed
- Palpitations
- Shortness of breath
- Increased respiration
- Need to defecate or urinate
- “Butterflies” in stomach
- Sweaty

Anxiety symptoms: differential Dx

- GAD
- Panic disorder
- Major depression (with agitation)
- Dementia (with agitation)
- Hyperthyroidism
- Caffeinism
- Bipolar disorder (hypomania)
- hypoglycemia

Anxiety symptoms: differential Dx - 2

- Mitral valve prolapse
- Cardiac arrhythmia
- Substance-induced anxiety disorder:
 - EtOH, stimulants, withdrawal from sedatives/hypnotics, thyroid preparations, SSRIs, akathisia
2° neuroleptics, BDZ toxicity
- Parkinson's disease
- Sleep disorders

Epidemiology of anxiety in elderly

- Anxiety feelings in very old (> 78)

Forsell Y, Winblad B. Feelings of anxiety and associated variables in a very elderly population. *Int J Geriatr Psychiatry*. 1998;13:454–458

- 20% of group of 966; increase with age
- Associated with psychiatric disorder, esp. depression; dementia; being female; being unsatisfied with social network

- Hospitalized geriatric patients

Kvaal K, Macijauskiene J, Engedal K, Laake K. High prevalence of anxiety symptoms in hospitalized geriatric patients. *Int J Geriatr Psychiatry*. 2001;16:690–693.

- 41% females, 47% males had significant anxiety symptoms;
- worse in COPD

Epidemiology of anxiety in elderly - 2

- Anxiety & functional status

Upadhyaya AK, Lyness JM, Cox C, Seidlitz L, Caine ED. Anxiety and functional status in older primary care patients. *Int J Psychiatry Med.* 2000;30:221-228.

- Poorer social functioning with higher anxiety
- Better functioning on instrumental & physical self-maintenance tasks

- Berlin Aging Study: anxiety Sx in >50% of subjects

Schaub RT, Linden M. Anxiety and anxiety disorders in the old and very old-- results from the Berlin Aging Study (BASE). *Compr Psychiatry.* 2000;41:48-54.

Anxious patients had better functioning on instrumental and self-maintenance tasks than low-anxiety patients, when controlled for depressive symptoms.

Prevalence of anxiety disorders in elderly

- Review of studies of over-65s, published in English

Krasucki C, Howard R, Mann A. The relationship between anxiety disorders and age. *Int J Geriatr Psychiatry*. 1998;13:79-99.

- Social phobia: 1%
 - Simple phobia: 4%
 - Agoraphobia: 1.4 - 7.9%
 - OCD: 0.1% - 0.8%
 - Panic disorder: 0.1%
 - GAD: 4%
- Prevalences decrease with age, except for GAD
 - However, studies in elderly have yielded an extremely wide range of results, eg phobic disorders 0.01% - 10%

Fuentes K, Cox BJ. Prevalence of anxiety disorders in elderly adults: a critical analysis. *J Behav Ther Exp Psychiatry*. 1997;28:269-279.

Prevalence of anxiety disorders in elderly - 2

Lower prevalences in elderly than under-65s

Fuentes K, Cox BJ. Prevalence of anxiety disorders in elderly adults: a critical analysis. *J Behav Ther Exp Psychiatry*. 1997;28:269–279.

- May be an artifact caused by diagnostic criteria unsuitable for over-65s
- Older adults may underreport symptoms because they
 - Experience physical symptoms with less intensity
 - May attribute anxiety symptoms to a medical problem (eg a concurrent illness such as hyperthyroidism, diabetes) or to medication side effects
 - Consider mental disorders socially unacceptable, thus explain their symptoms in medical terms
 - Are more familiar with medical than with psychiatric terminology
- New onset anxiety disorders infrequent in elderly
 - Gallo JJ, Lebowitz BD. The epidemiology of common late-life mental disorders in the community: themes for the new century. *Psychiatr Serv*. 1999;50:1158–1166.

Why is it that anxiety disorders are less common in over-65s compared to younger adults? This slide gives several possible explanations.

First, the diagnostic criteria may need to be modified somewhat for elderly. Some of this may have to do with vocabulary. For example, what does someone mean when they say they're "nervous"? In Romania, it means that you're angry!

Prevalence of anxiety disorders in elderly - 3

- Longitudinal Aging Study Amsterdam (LASA)
Beekman AT, Bremmer MA, Deeg DJ, et al. Anxiety disorders in later life: a report from the Longitudinal Aging Study Amsterdam. *Int J Geriatr Psychiatry*. 1998;13:717-726.
 - Overall prevalence of anxiety disorders: 10.2%
 - GAD: 7.3%
 - Phobic disorders: 3.1%
 - Panic disorder: 1.0%
 - OCD: 0.6%
 - Risk factors: female gender, less education, extreme WWII experiences, external locus of control, stresses (recent family losses, chronic physical illness), smaller networks

Comorbidity of Anxiety disorders in elderly

- LASA

van Balkom AJ, Beekman AT, de Beurs E, Deeg DJ, van Dyck R, van Tilburg W. Comorbidity of the anxiety disorders in a community-based older population in The Netherlands. *Acta Psychiatr Scand.* 2000;101:37-45.

- 10% of those with an anxiety disorder had two or more anxiety disorders

Anxiety disorder	Present	Absent
Major depression	13%	3%
BDZ use	24%	11%
Chronic somatic illness	12%	7%

☒ Alcohol abuse, cognitive impairment not associated with anxiety disorder

The same study found that 10% of anxiety disorder patients had more than one anxiety disorder. In addition, 13% of anxiety disorder patients in this study also had major depression, compared to only 3% of the group without an anxiety disorder. The percentage of anxiety patients using BDZ was more than double that of non-anxious patients. Anxiety was also associated with chronic illness, but there were no significant differences between anxiety and non-anxiety groups for alcohol abuse (around 5%) or cognitive impairment (around 12%).

Co-occurrence of anxiety & depression

- LASA

Beekman AT, de Beurs E, van Balkom AJ, Deeg DJ, van Dyck R, van Tilburg W. Anxiety and depression in later life: Co-occurrence and communality of risk factors. *Am J Psychiatry*. 2000;157:89-95.

- 47.5% of major depression cases also had anxiety disorder
- 26.1% of anxiety disorder cases had major depression

- Comorbid anxiety & depression, compared to either condition alone, has

Lenze EJ, Mulsant BH, Shear MK, Alexopoulos GS, Frank E, Reynolds CF, 3rd. Comorbidity of depression and anxiety disorders in later life. *Depress Anxiety*. 2001;14:86-93.

- greater severity (more severe somatic Sx; may predispose to more medication side effects & worse compliance);
- poorer social function
- Greater suicidal ideation
- Poorer treatment response

This slide points out that depression and anxiety disorder often go together, and when they do, patients are worse off in terms of symptoms, social functioning, suicidality, and response to treatment.

Diagnosis of unipolar depression

- 41% of pts hospitalized for unipolar depression developed mania/hypomania during 15 yr followup
Goldberg JF, Harrow M, Whiteside JE. Risk for bipolar illness in patients initially hospitalized for unipolar depression. *Am J Psychiatry*. 2001;158:1265–1270.
- Manic symptoms in unipolar depressed outpatients
Benazzi F. Major depressive episodes with hypomanic symptoms are common among depressed outpatients. *Compr Psychiatry*. 2001;42:139–143.
 - Irritable mood: 35.4%
 - More talkative: 9.6%
 - Racing thoughts: 58.0%
 - Distractibility: 22.5%
 - One symptom: 38.7%
 - Two symptoms: 38.7%
 - Three or more symptoms: 3.2%
 - At least one symptom: 80.6%

I want to take a little side trip at this point, to talk about anxiety in depression. First, to say that many cases of depression are really bipolar or bipolar spectrum disorders. These two studies make the point.

Agitated depression

Koukopoulos A, Sani G, Koukopoulos AE, Manfredi G, Pacchiarotti I, Girardi P. Melancholia agitata and mixed depression. Acta Psychiatr Scand Suppl. 2007;50-57.

- depressed, anxious mood
- inner psychic agitation:
 - anxiety and fearfulness
 - intense inner tension
 - muscular aches and pains
 - increased diastolic blood pressure
 - irritability or feelings of unprovoked rage
 - verbal, rarely physical violence
 - rage + hopelessness: violent suicidality, suicide-homicide
 - crowded or racing thoughts
- may have psychomotor agitation

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How do you distinguish between a straightforward retarded or inhibited depression, which may include anxiety symptoms, and an agitated depression? This slide lists some of the symptoms and signs of agitated depression, which many consider a type of mixed state. Clearly, some of the symptoms, such as irritability and racing thoughts, are manic symptoms.

Relate my differentiating these on 4East.

Back in the days when the usual treatment for depression was ECT, it really didn't matter much whether it was a retarded depression or an agitated depression; ECT was equally effective for both. Unfortunately, this thinking persists - we tend to lump both kinds of depression into just "depression" and to treat with antidepressants. What has become increasingly clear, though, is that many patients with agitated depression get worse with antidepressants, especially SSRIs. The agitation gets worse and so does the patient's suffering. In the study by Koukopoulos et al, the great majority of agitated depressions actually emerged during treatment with antidepressants.

However, ECT, antipsychotics, and mood stabilizers are effective first-line treatments.

All that to say that, when there is depression, it pays to evaluate symptoms of anxiety carefully, and to ensure that we are not dealing with an agitated depression if we contemplate using an antidepressant medication.

Treatment of anxiety

- BDZ
- Antidepressants
- Beta-blockers
- Antipsychotic agents
- Buspirone
- Cholinesterase inhibitors
- Pregabalin (Lyrica): comparable to lorazepam, alprazolam, venlafaxine; efficacious in elders
Bandelow B, Wedekind D, Leon T. Pregabalin for the treatment of generalized anxiety disorder: a novel pharmacologic intervention. *Expert Rev Neurother.* 2007;7:769–781.
- Psychosocial interventions

Treatment of anxiety: BDZ

- BDZ prescribed for 17% of elderly outpatients, 50% of nursing home patients

Stanley MA, Beck JG. Anxiety disorders. Clin Psychol Rev. 2000;20:731-754.

- Studies of BDZ in elderly are usually institutionalized patients, & look for effects on agitation, depression, insomnia, restlessness, pacing, & irritability

- Very little research on effects of BDZ on specific anxiety disorders in elderly; mostly we extrapolate from younger

Lenze EJ, Pollock BG, Shear MK, Mulsant BH, Bharucha A, Reynolds CF. Treatment considerations for anxiety in the elderly. CNS Spectr. 2003;8:6-13.

- Bottom line: avoid BDZ in elderly because of risks

Treatment of anxiety: Antidepressants

- In young adults:
 - TCAs effective in panic disorder, agoraphobia
 - SSRIs effective in panic disorder
 - Clomipramine, SSRIs effective in OCD
- SSRIs are better tolerated in the elderly than TCAs
- citalopram effective in open-label study in over-60s
Blank S, Lenze EJ, Mulsant BH, et al. Outcomes of late-life anxiety disorders during 32 weeks of citalopram treatment. J Clin Psychiatry. 2006;67:468-472.

Treatment of anxiety: Beta-blockers

- Propranolol used to treat stage fright, eg professional musicians
- Open-label trial of betaxolol:
Swartz CM. Betaxolol in anxiety disorders. *Ann Clin Psychiatry*. 1998;10:9-14.
 - Long-acting beta-blocker
 - Enters the CNS
 - Effective against panic attacks and anxiety
 - Kerlone - not available in Canada
- propranolol vs placebo in disruptive nursing home residents with AD led to improvements, including in anxiety and aggression
Peskind ER, Tsuang DW, Bonner LT, et al. Propranolol for disruptive behaviors in nursing home residents with probable or possible Alzheimer disease: a placebo-controlled study. *Alzheimer Dis Assoc Disord*. 2005;19:23-28.

Treatment of anxiety: Antipsychotics

- Avoid older antipsychotics (as for insomnia)
- Antipsychotics are not recommended for treating GAD or panic disorder
Alexopoulos GS, Streim J, Carpenter D, Docherty JP. Using antipsychotic agents in older patients. *J Clin Psychiatry*. 2004;65 Suppl 2:5-99; discussion 100-102; quiz 103-4.
- Olanzapine was better than bromazepam in decreasing anxiety, in a study to treat agitation/aggression in vascular dementia outpatients
Moretti R, Torre P, Antonello RM, Cattaruzza T, Cazzato G, Bava A. Olanzapine as a possible treatment for anxiety due to vascular dementia: an open study. *Am J Alzheimers Dis Other Demen*. 2004;19:81-88.
- Olanzapine is useful for anxiety & agitation in delirium, dementia, agitated depression, & dysphoric manic states

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Antipsychotics are not recommended for treating uncomplicated anxiety disorders. That being said, however, they are effective at reducing anxiety, as demonstrated by this study in which olanzapine was compared to a BDZ in vascular dementia patients.

The last point, about using this medication in delirium and dementia: there are a couple of important caveats. First, the increased mortality observed with atypicals compared to placebo when treating behaviour problems in dementia.

Second, my own clinical experience with olanzapine in delirium is that in some patients, the delirium worsens. Studies show that low-dose haloperidol is equally efficacious and does not have a greater incidence of side effects in these patients, so it still has an important role to play.

Treatment of anxiety: Buspirone

- Most studies are open trials
- Does not have BDZ side effects of sedation, cerebellar impairment, cognitive impairment
- 20-30% of elderly anxious pts have side effects (GI symptoms, dizziness, headache, sleep disturbance, nausea/vomiting, uneasiness, fatigue, diarrhea)

Palmer BW, Jeste DV, Sheikh JI. Anxiety disorders in the elderly: DSM-IV and other barriers to diagnosis and treatment. *J Affect Disord.* 1997;46:183-190.

- Inconsistent therapeutic response - probably unsuitable for pts with prior BDZ exposure
- Slow onset of action
- Less useful than antidepressants

Flint AJ. Generalised anxiety disorder in elderly patients : epidemiology, diagnosis and treatment options. *Drugs Aging.* 2005;22:101-114.

Treatment of anxiety: Cholinesterase inhibitors

- Improves cognition and behaviour, including agitation, in patients with Alzheimer's, Lewy Body dementia, and vascular dementia

Herrmann N. ChEIs: Good for whatever ails ya? Bull Can Acad Ger Psychiatry. 2001;9:5-7.

- Herrmann N, Rabheru K, Wang J, Binder C. Galantamine treatment of problematic behavior in Alzheimer disease: post-hoc analysis of pooled data from three large trials. Am J Geriatr Psychiatry. 2005;13:527-534.

Cholinesterase inhibitors may improve anxiety in patients with dementia. It isn't clear if this is a specific effect against anxiety.

Treatment of anxiety: Pregabalin (Lyrica)

Bandelow B, Wedekind D, Leon T. Pregabalin for the treatment of generalized anxiety disorder: a novel pharmacologic intervention. *Expert Rev Neurother*. 2007;7:769–781.

- comparable to lorazepam, alprazolam, venlafaxine
- efficacious in elders

Treatment of anxiety: Psychosocial Interventions

- Meta-analysis of manualized therapies for depression, panic disorder, & GAD in adults

Westen D, Morrison K. A multidimensional meta-analysis of treatments for depression, panic, and generalized anxiety disorder: an empirical examination of the status of empirically supported therapies. *J Consult Clin Psychol.* 2001;69:875-899.

- Many panic pts improve & remain improved
- Impressive short-term effects for treatment of GAD, but improvement is not maintained

Treatment of anxiety: Psychosocial Interventions

Ayers CR, Sorrell JT, Thorp SR, Wetherell JL. Evidence-based psychological treatments for late-life anxiety. *Psychol Aging*. 2007;22:8-17.

- Review of 17 evidence-based studies
- CBT for late-life GAD has the most consistent support
- relaxation training is efficacious and low in cost
- less support for supportive therapy and cognitive therapy for treating subjective anxiety symptoms

Links:

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

article on sleep disorders in the elderly:
<http://tinyurl.com/yrboqy>

pdf of today's slides: <http://tinyurl.com/2ftvwd>



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 benzodiazepine pharmacology.

Should you prescribe BDZ?

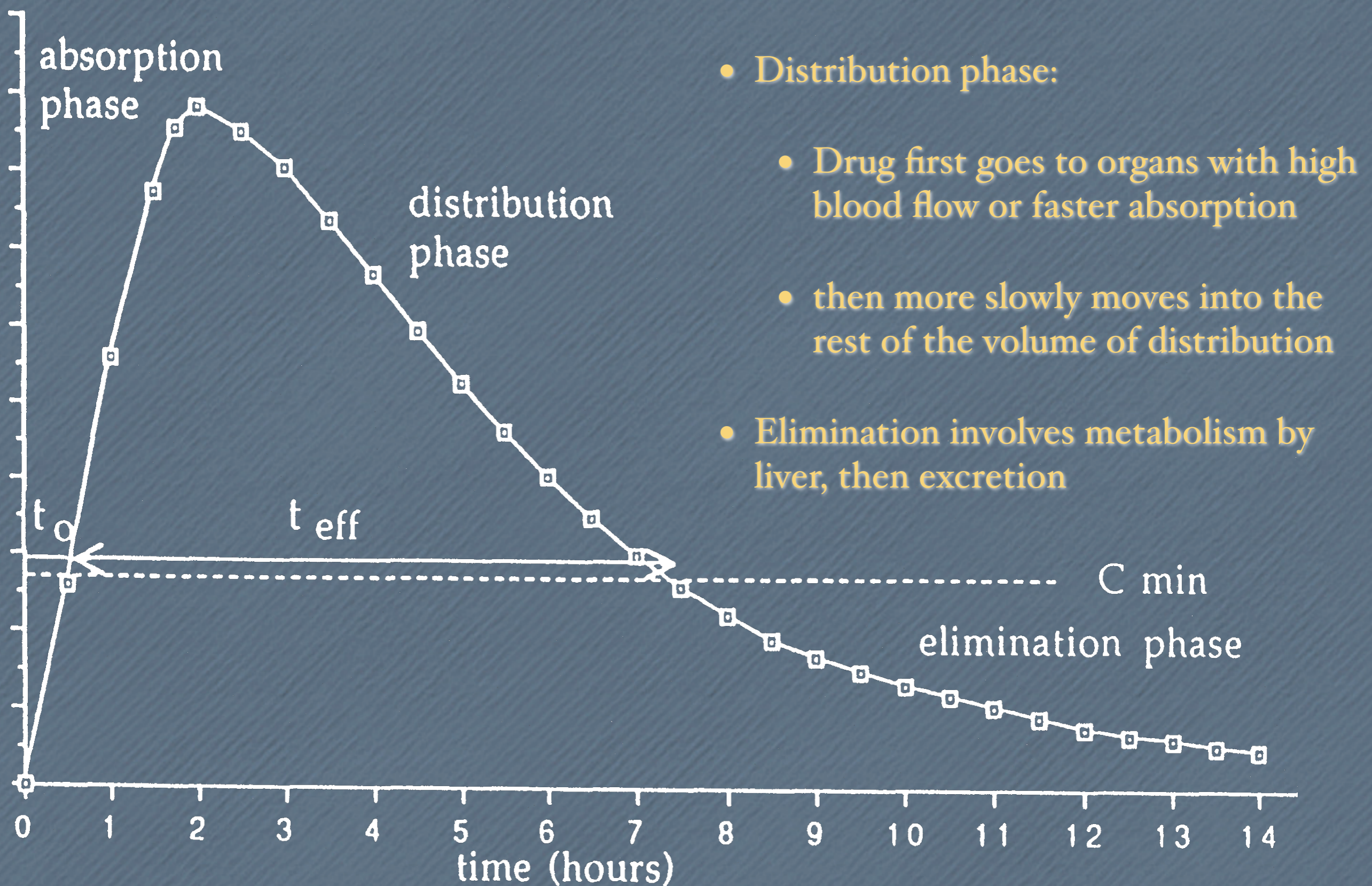
- Problems with BDZs:
 - Increased risk of depression
Patten SB, Williams JV, Love EJ. Self-reported depressive symptoms following treatment with corticosteroids and sedative-hypnotics. *Int J Psychiatry Med.* 1996;26:15-24.
 - Behavioural disinhibition
Gardner DL, Cowdry RW. Alprazolam-induced dyscontrol 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



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

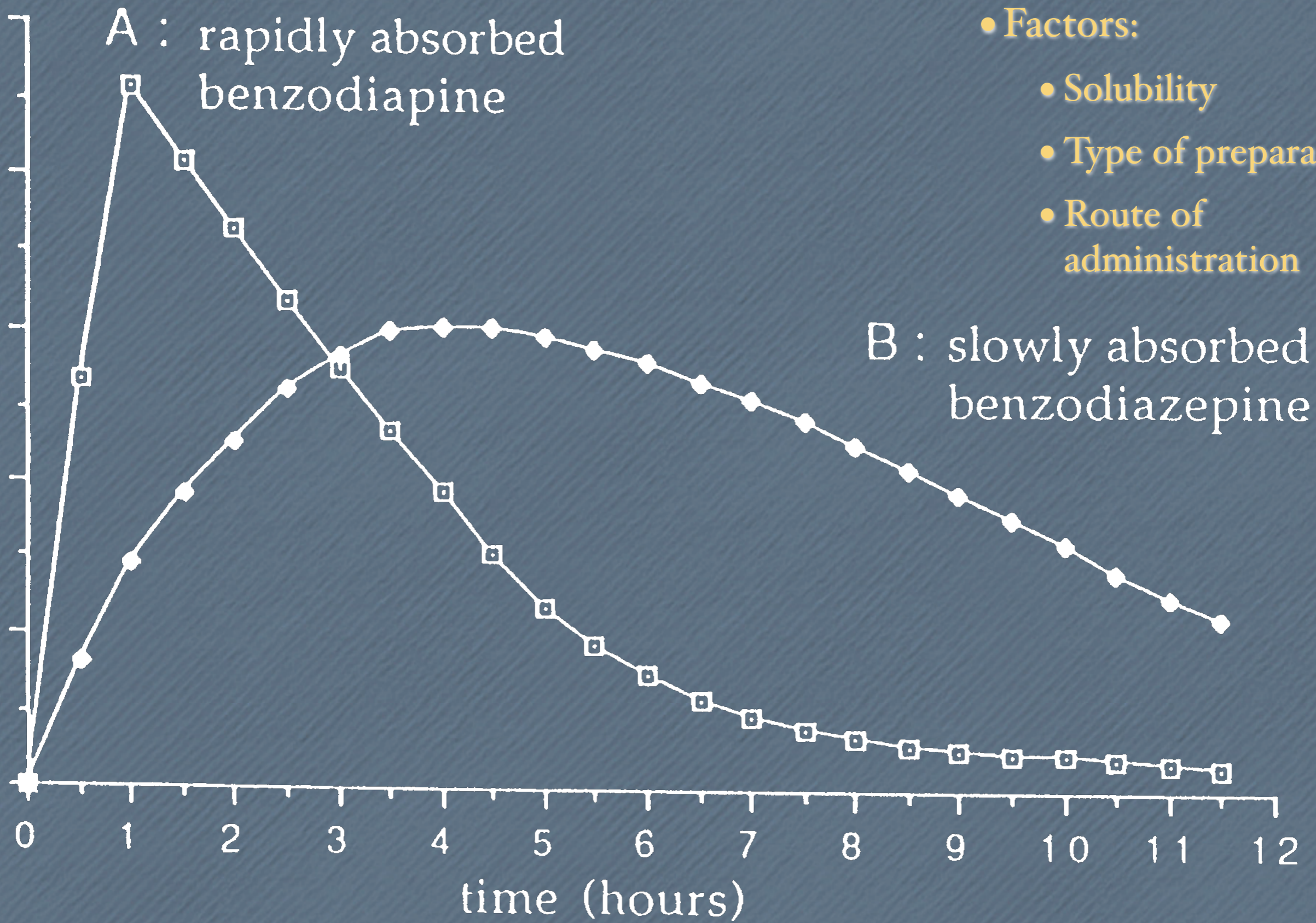
After the medication is absorbed, it first gets redistributed into its volume of distribution, and then gets eliminated from the body.

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

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

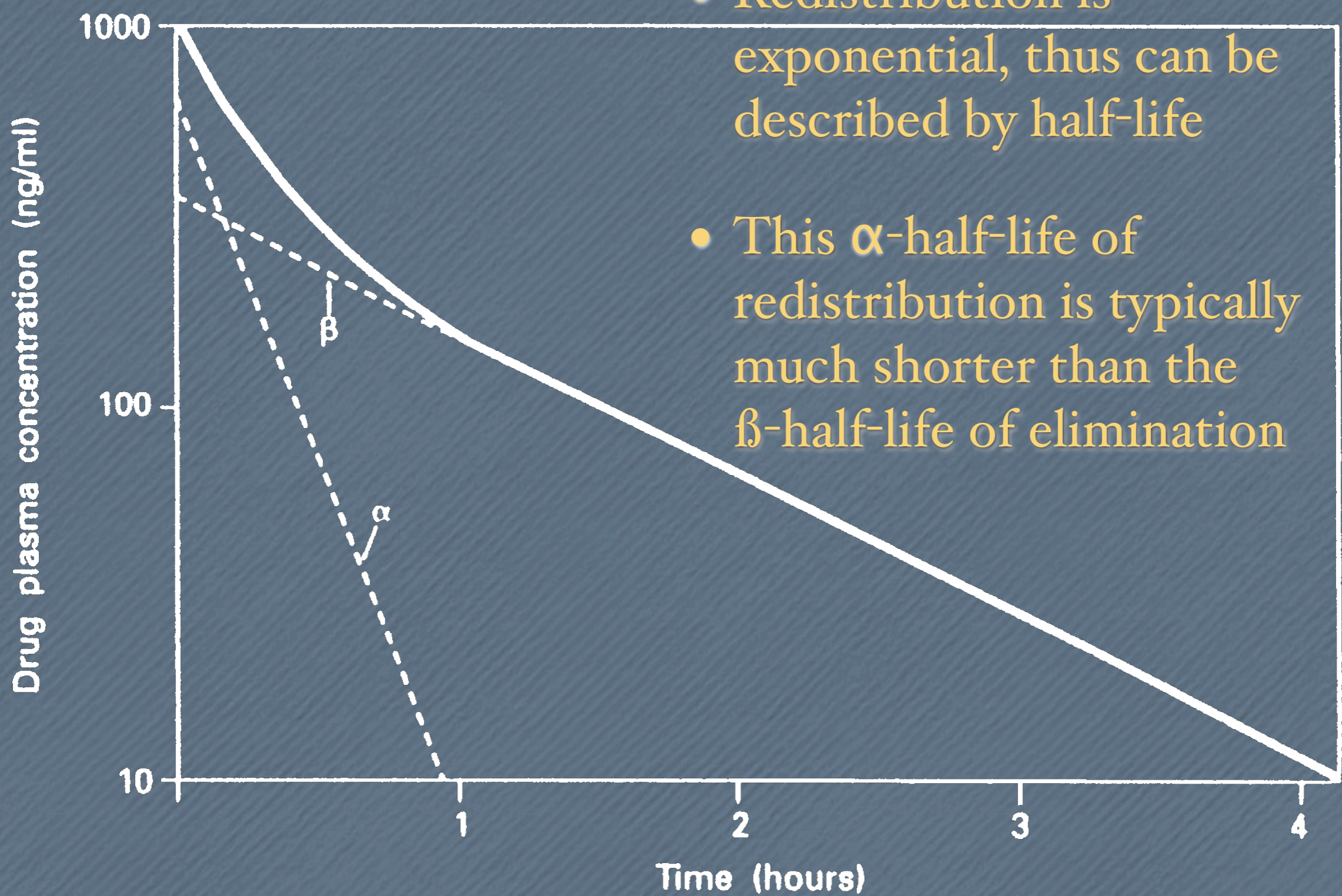
What influences how rapidly a drug has its onset of effect? Clearly, rate of absorption is important, but so is the degree of lipid solubility, which determines how quickly the drug gets into the brain.

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 β -half-life of elimination



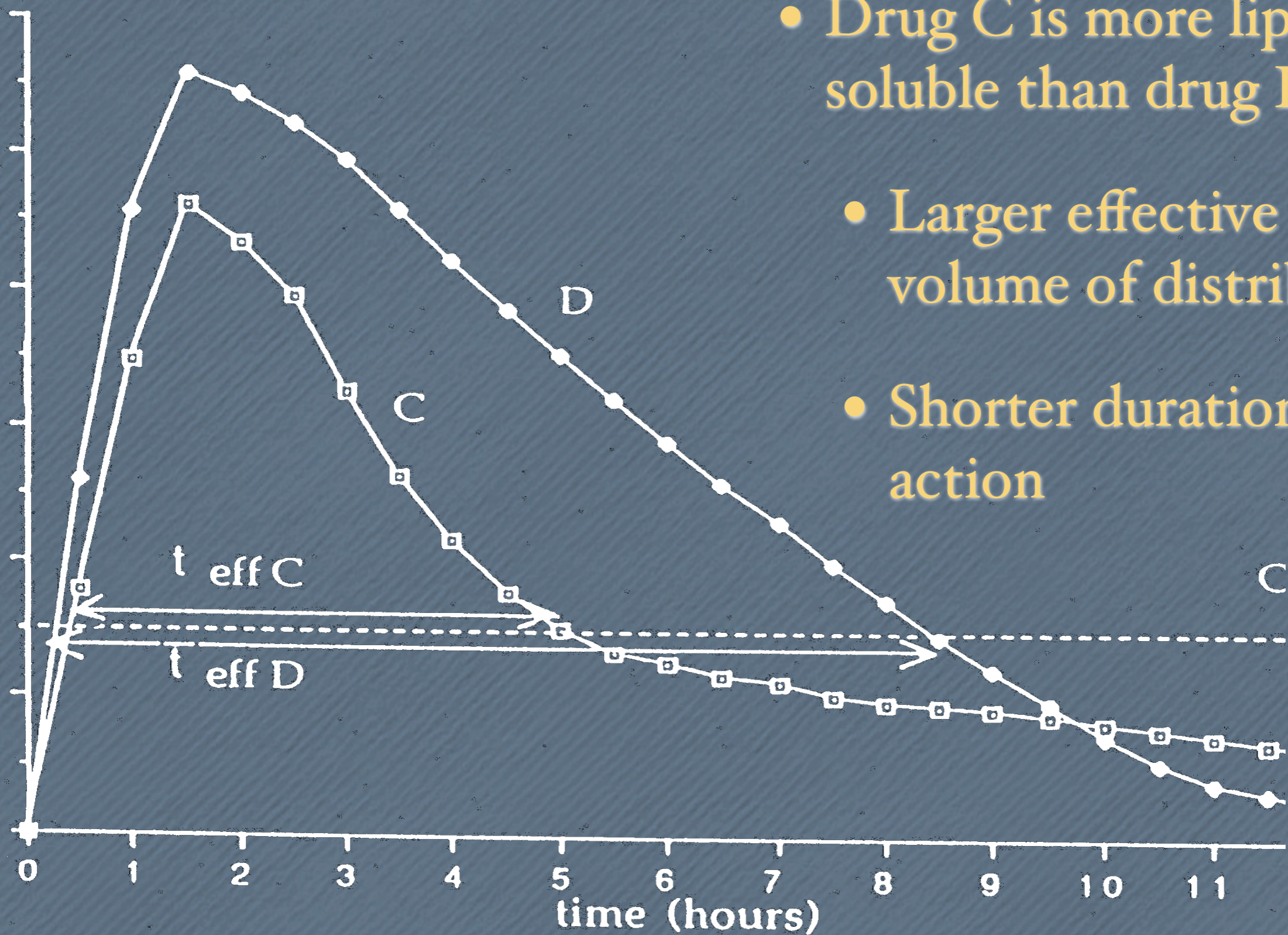
86

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

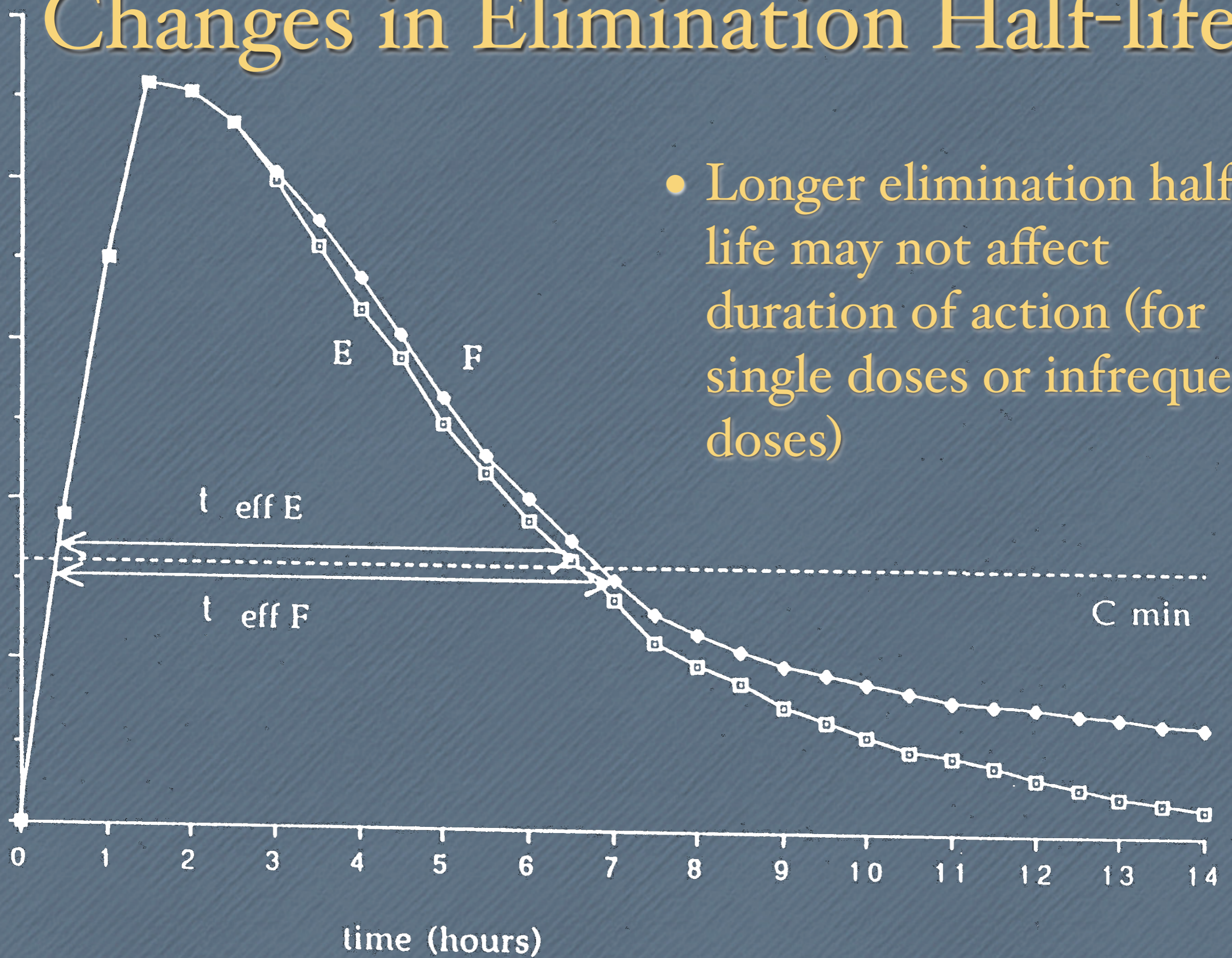


87

The effect of a higher lipid solubility is to make the 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.

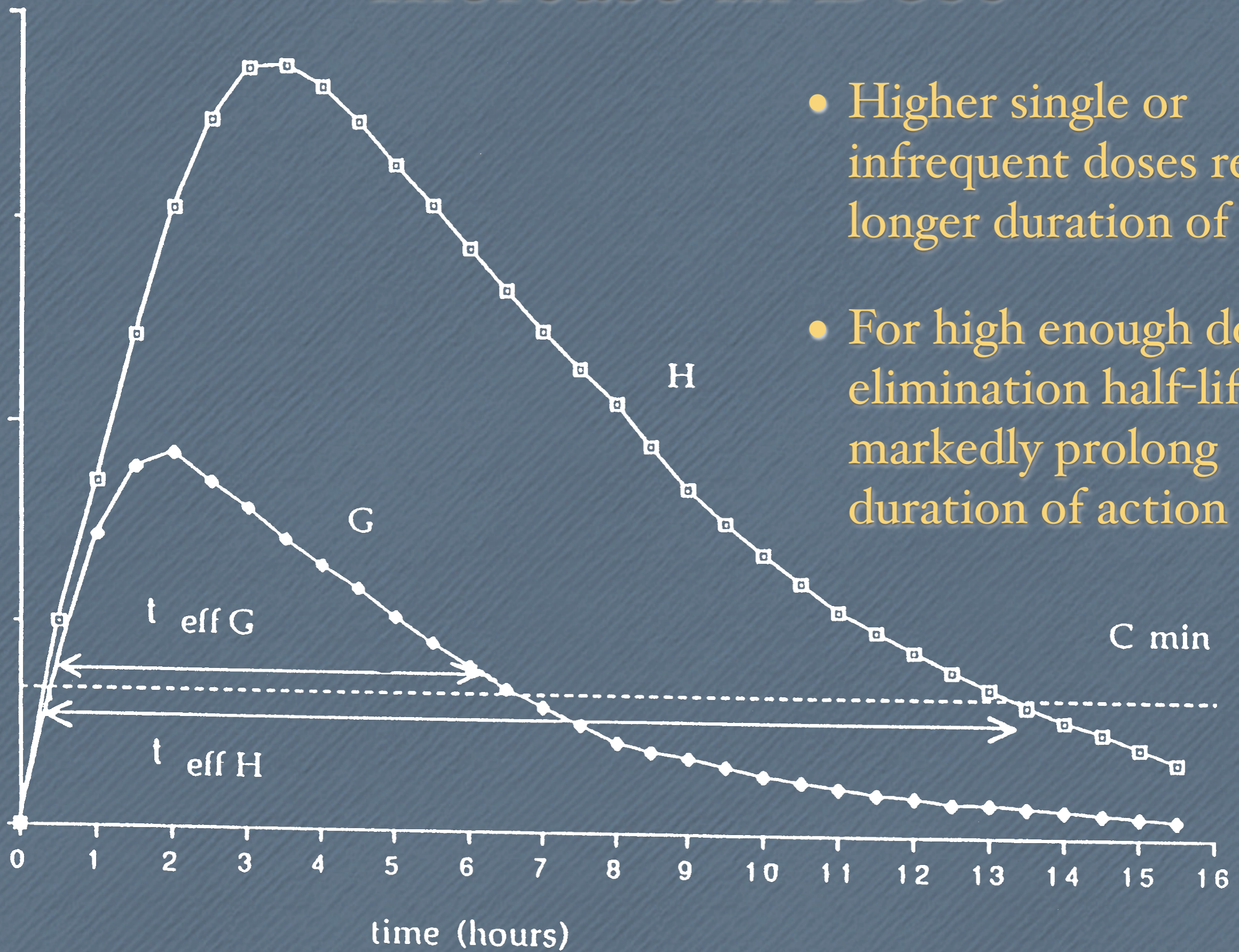
This graph shows that drug C with a higher volume of distribution because of greater lipid solubility, will have a shorter duration of action than drug D.

Changes in Elimination Half-life



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.

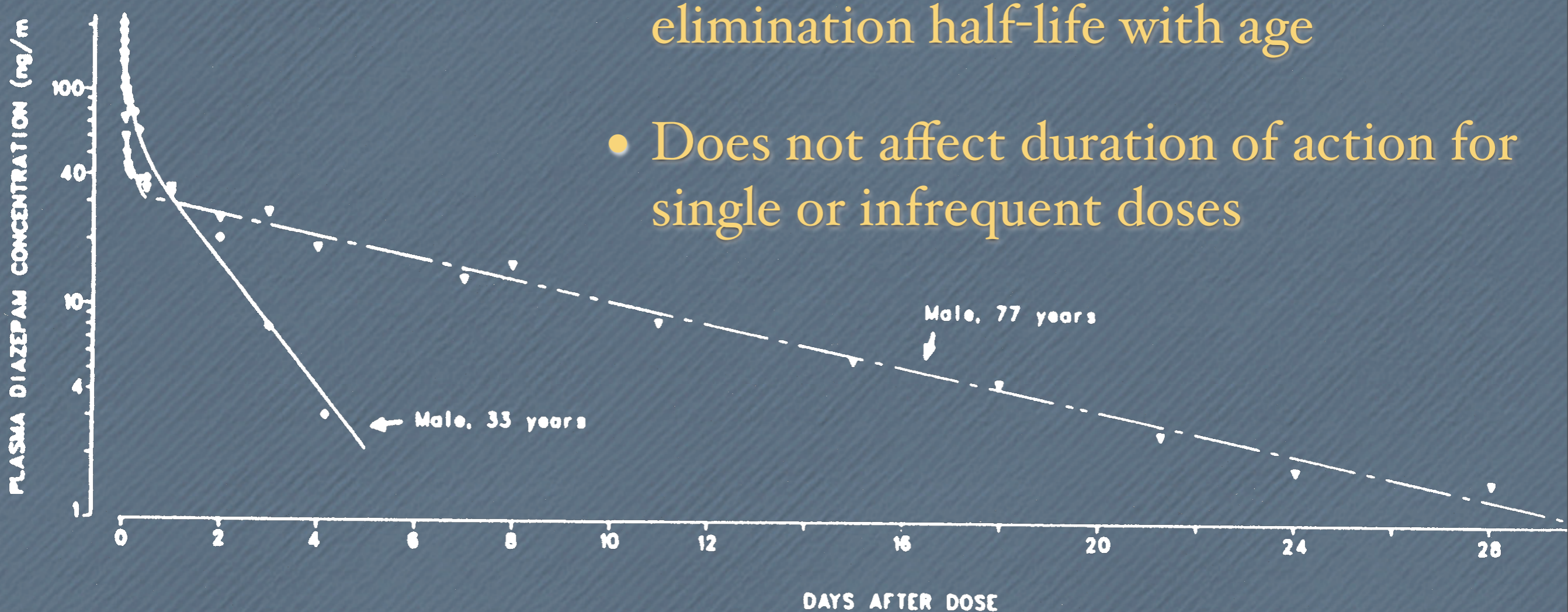
Increase in Dose



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



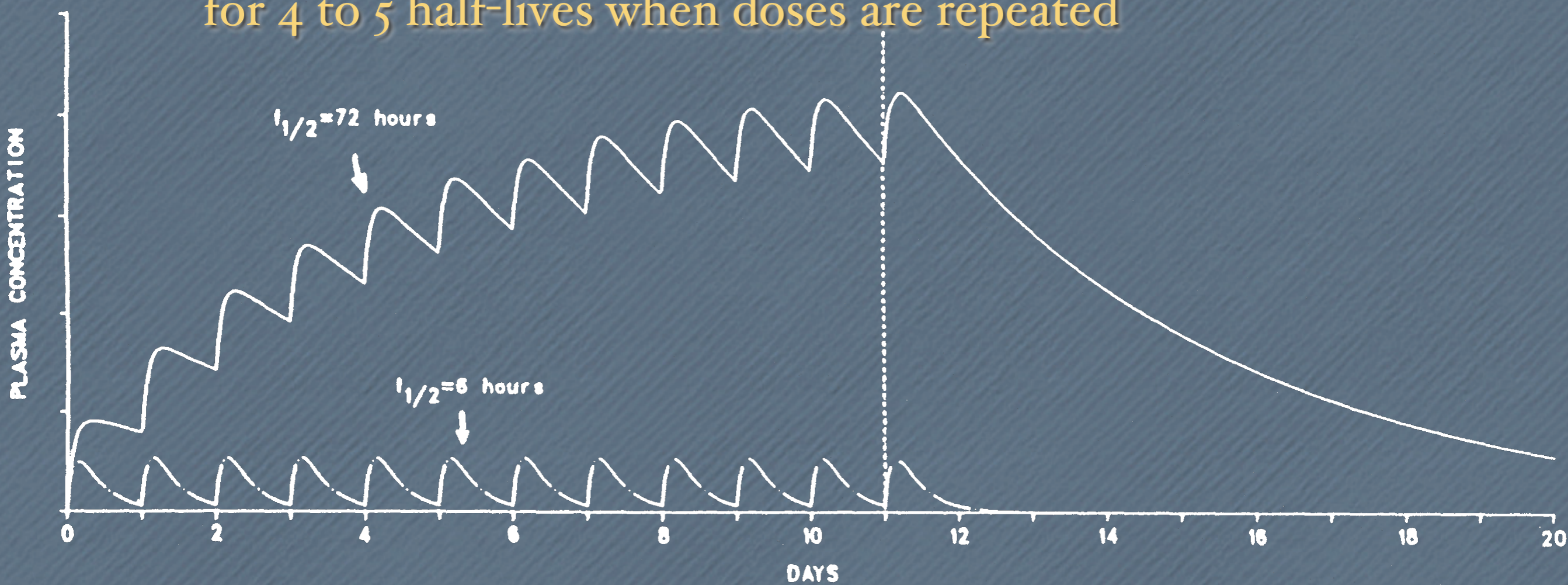
90

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



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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

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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