Pharmacology of Sleep Disorders

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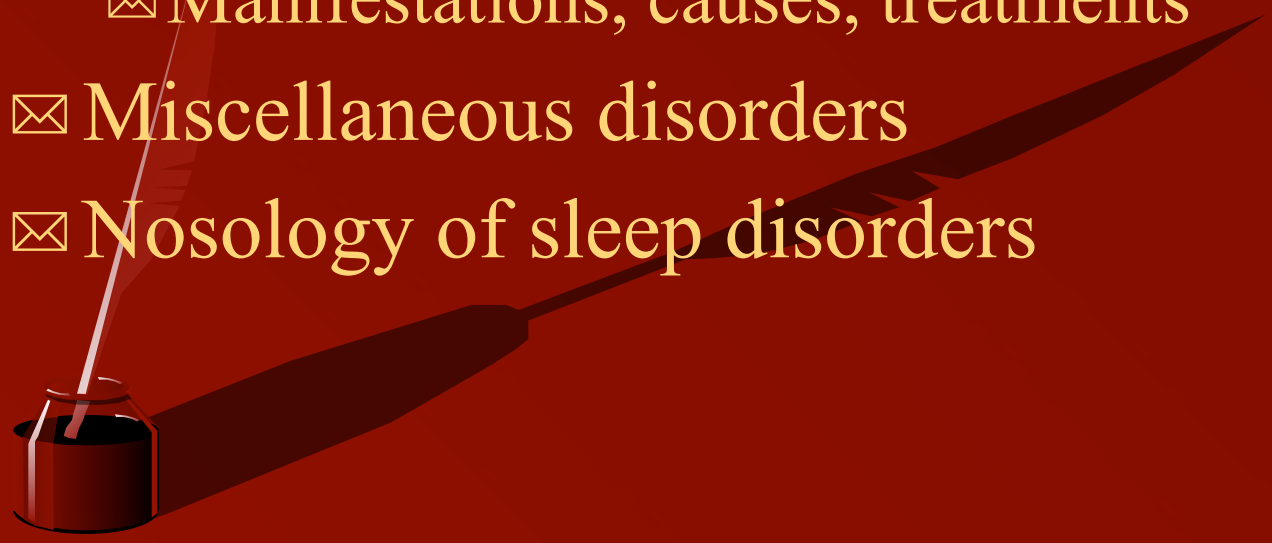
Outline

- Characteristics of sleep
- Sleep complaints
- Epidemiology
- Approach to the patient

Outline - 2

- Insomnia
  - Manifestations, causes, treatments
- Hypersomnia
  - Manifestations, causes, treatments
- Miscellaneous disorders
- Nosology of sleep disorders

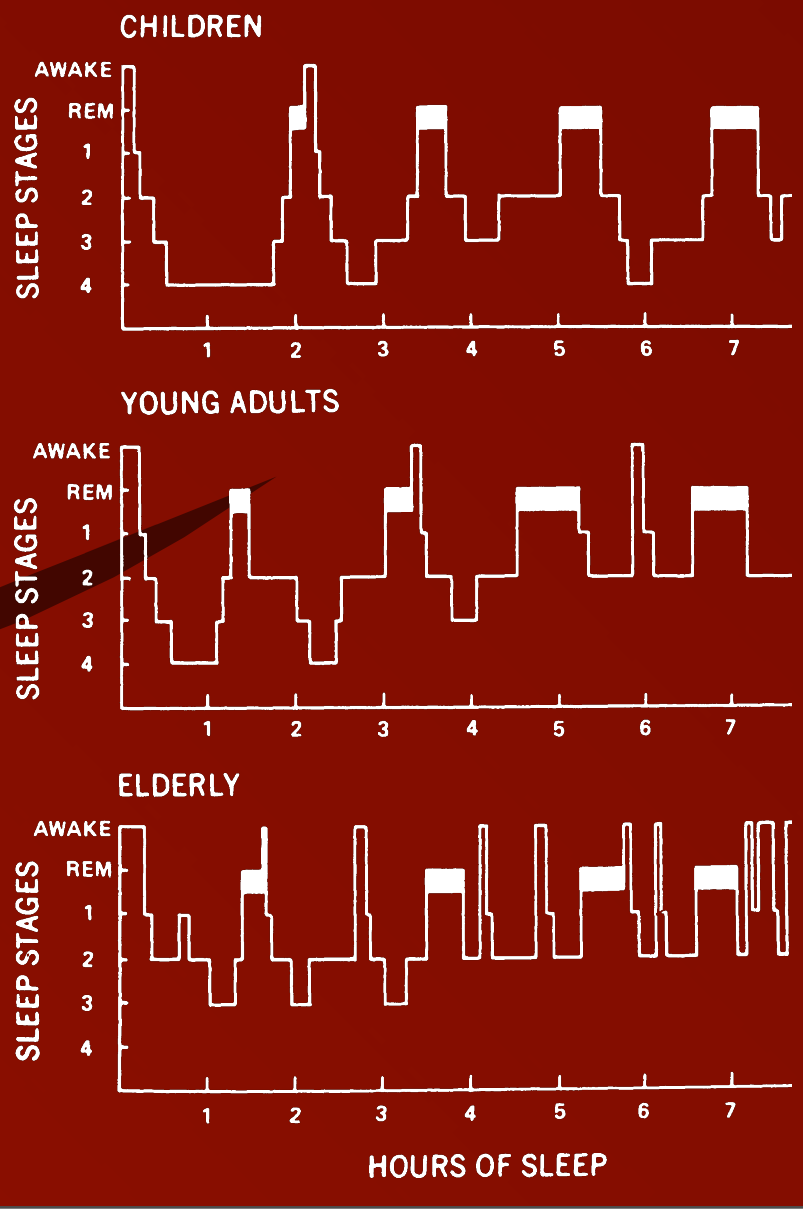


Characteristics of Sleep

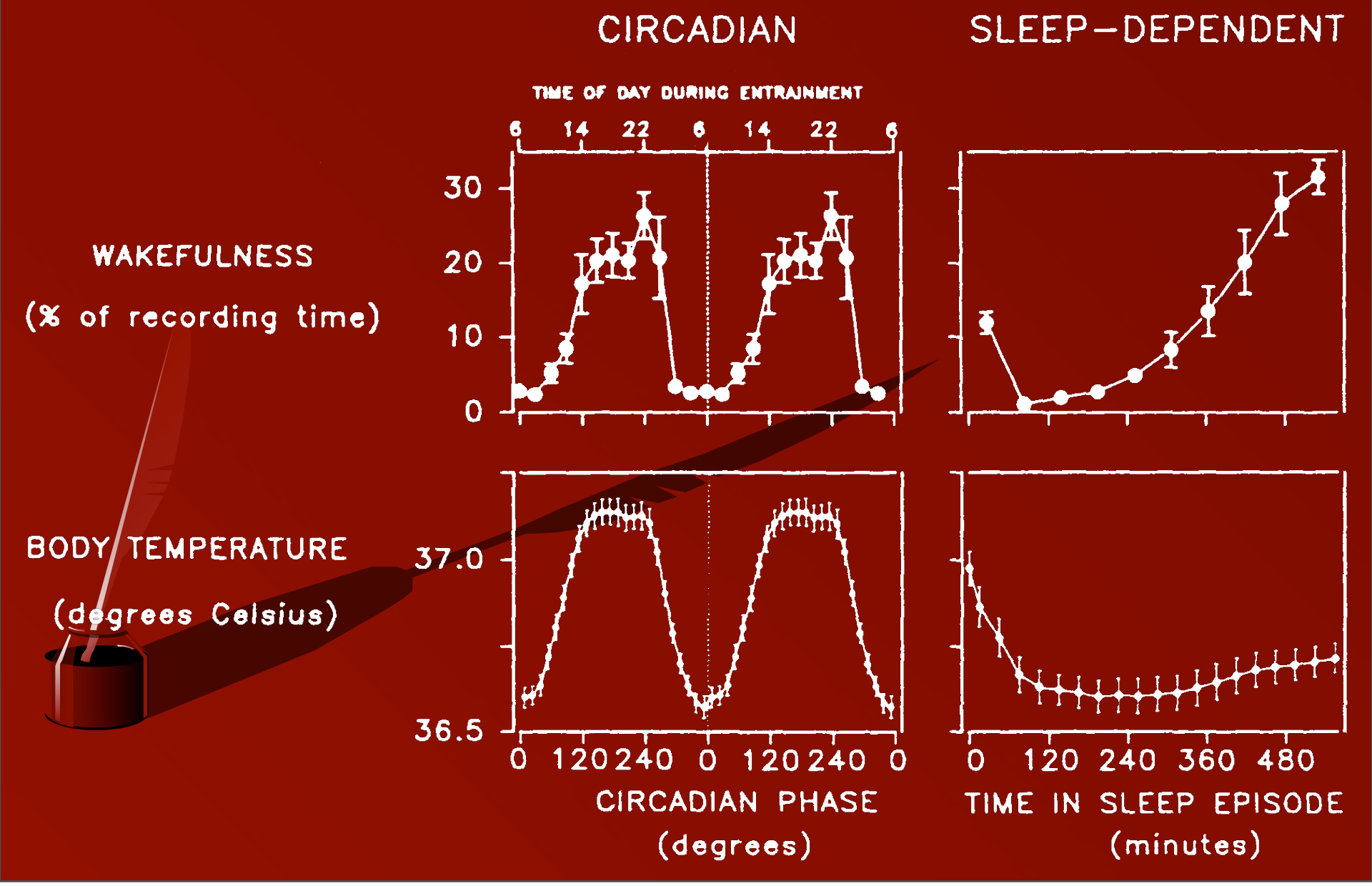
- 2 independent states: NREM and REM sleep
- REM sleep: 20-25%
  - First cycle: 60-90 min after sleep onset
  - Recurs every ~90 min
  - Successive stages generally get longer
- NREM sleep: 4 stages (based on EEG)
  - Stage 1: 3-8%
  - Stage 2: 45-55%
  - Stage 3 & 4 (Slow wave sleep, delta sleep): 15-20%

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



Wakefulness



This slide shows how sleep characteristics are multiply determined. The bottom two graphs are of core body temperature, which is frequently used as a marker for an individual's circadian rhythms. You can see the scale on the bottom where circadian phase in degrees is given, with 360 degrees representing a full cycle, normally about 24 hours. At the top left, the scale is hours of the day. Body temperature is at its lowest typically about an hour or so before awakening.

The point of this experiment was to attempt to separate out the influence of time of day from the effects of sleep itself. What they did was to have normal young males live in an environment free of any time clues for several weeks, and keeping to a 28-hour sleep-wake cycle. Thus, over the course of the experiment, their sleep periods would occur at all points of their baseline circadian rhythm.

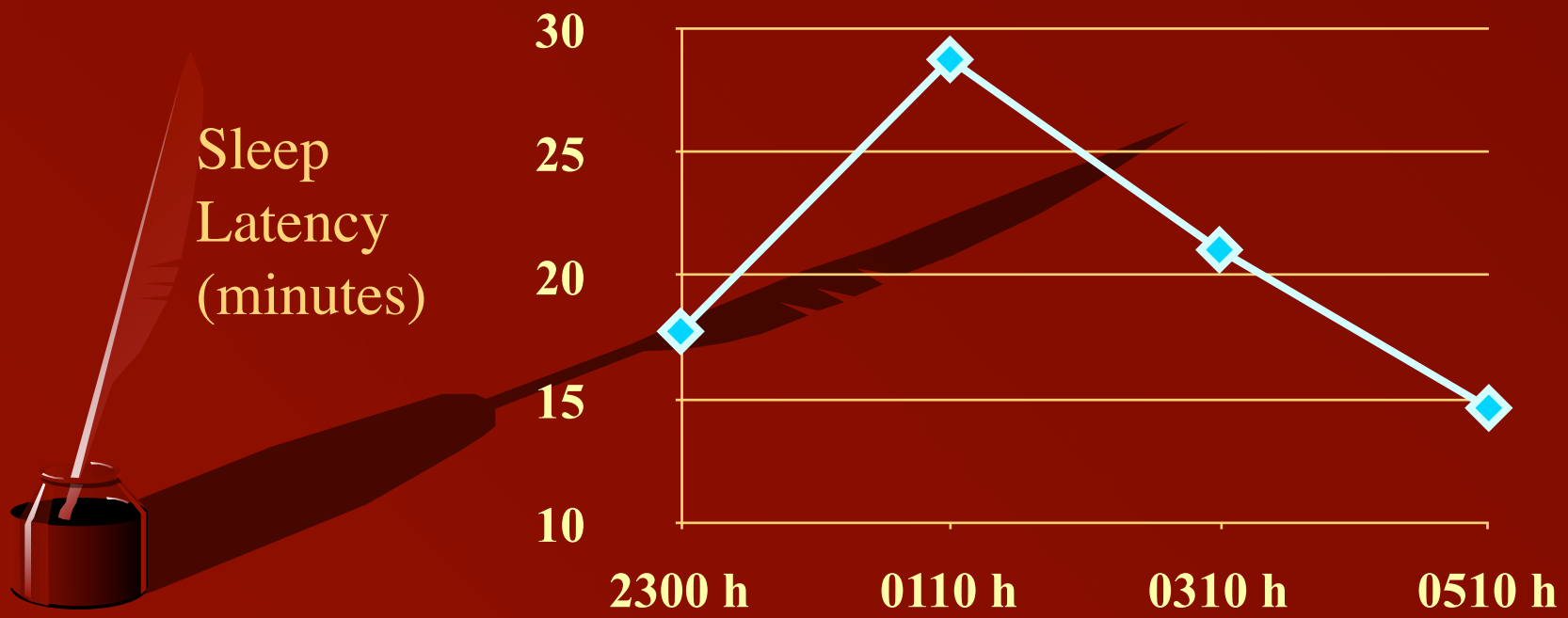
You can see that core body temperature is mostly determined by circadian rhythm, with little influence from sleep except for the first hour of sleep when temperature drops.

Wakefulness, shown in the upper two graphs, behaves very interestingly. It is lowest when our core body temperature is lowest, that is, around 6 in the morning. As you would expect, wakefulness increases the longer we are asleep, and at about the 7-hour mark it matches the amount of wakefulness due to circadian rhythm.

[ref: Dijk & Czeisler, 1995, #1413]

Nocturnal Sleep Propensity

Helmus et al 1996

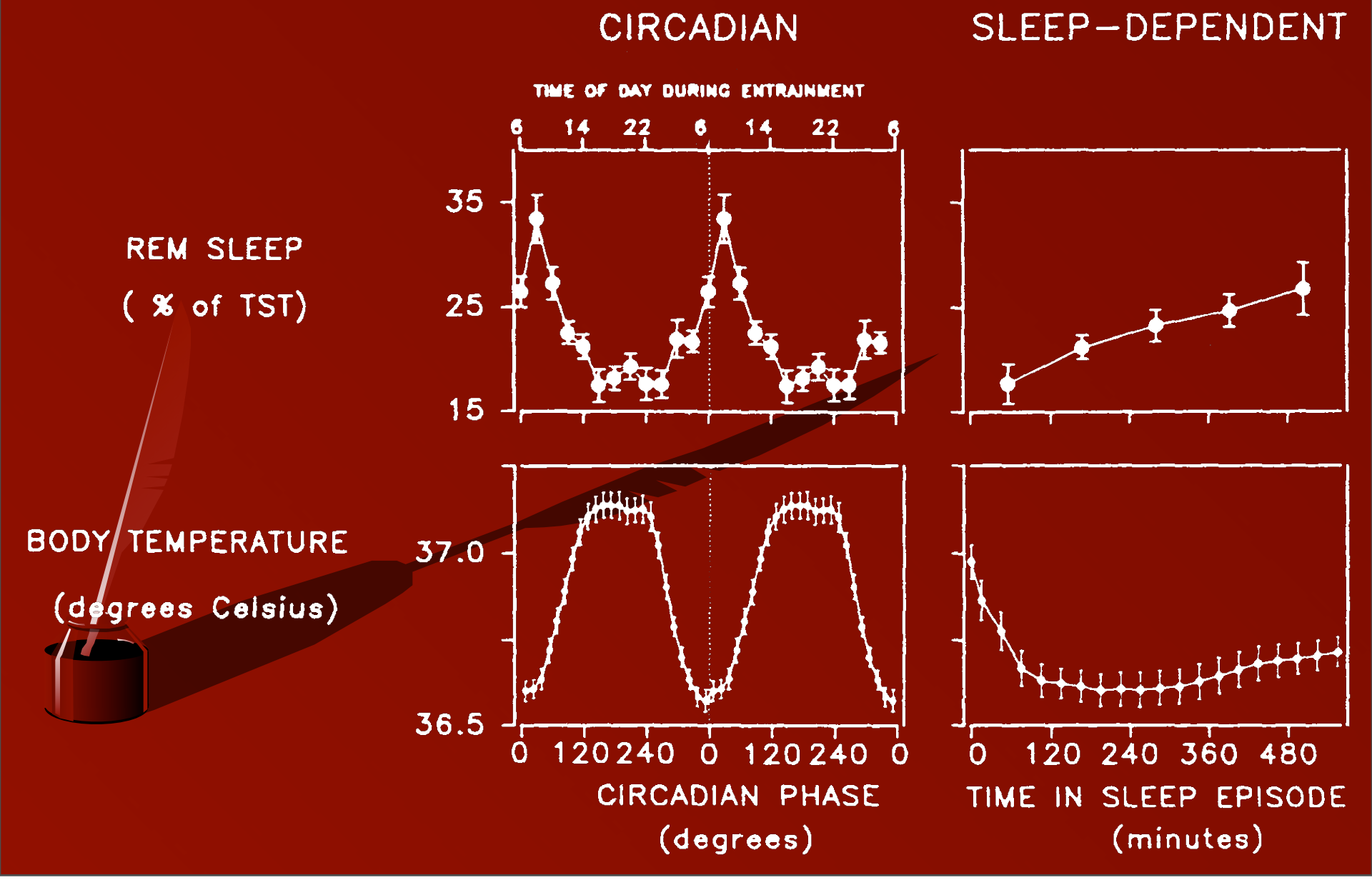


Time of night

Suppose you took people who were sleeping normally, put them in the sleep lab, and then woke them up at different times during the night. Keep them awake for 10 minutes, then let them go back to sleep and time how long it takes for them to fall back to sleep. What time of the night do you think they would be sleepiest?

It turns out that people fall asleep quickest at 5 am, after having slept for 6 hours. This was true for normal people, normal people who were sleep-deprived for a whole night prior to the study night, and individuals who tended to be sleepy during the day. This finding suggests that, the more you sleep, the more sleepy you will be! Sounds paradoxical, doesn't it? I don't have any explanation for why this might be so. But it helps to explain why it's so easy to sleep in, if you have the opportunity and the inclination to do so.

REM sleep propensity

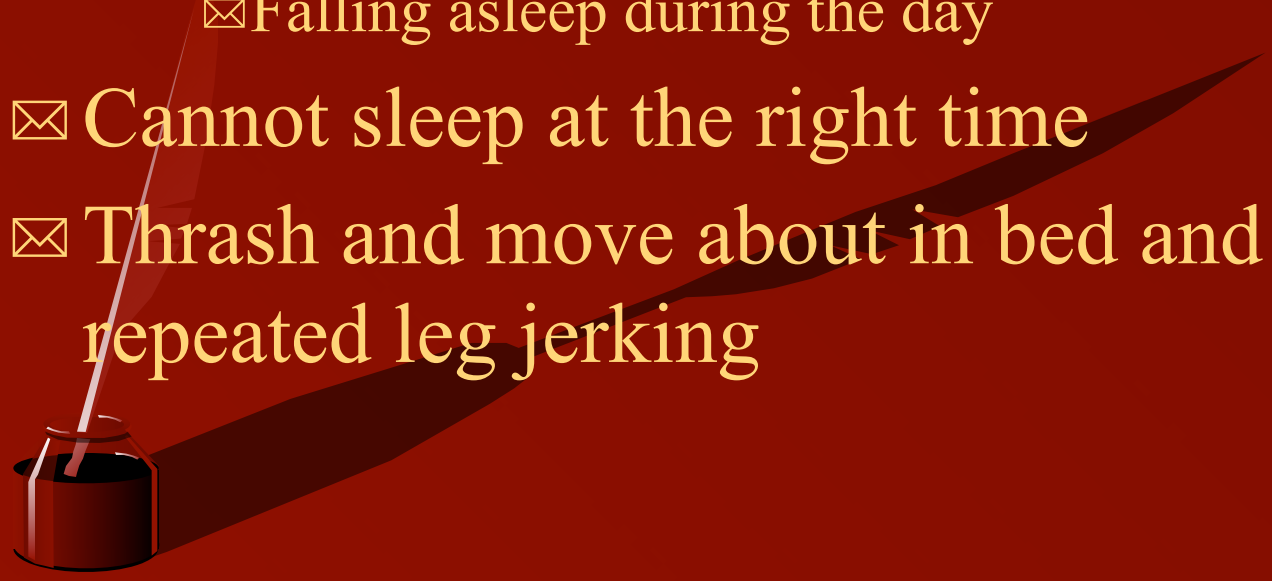


Here we have a slide showing REM sleep propensity. The important point to note is that we are most likely to have REM sleep if we are sleeping at around 8 am. Moreover, the more we sleep, the more REM sleep we will have. Thus, getting up late and spending a long time in bed will bring about lots of REM sleep.

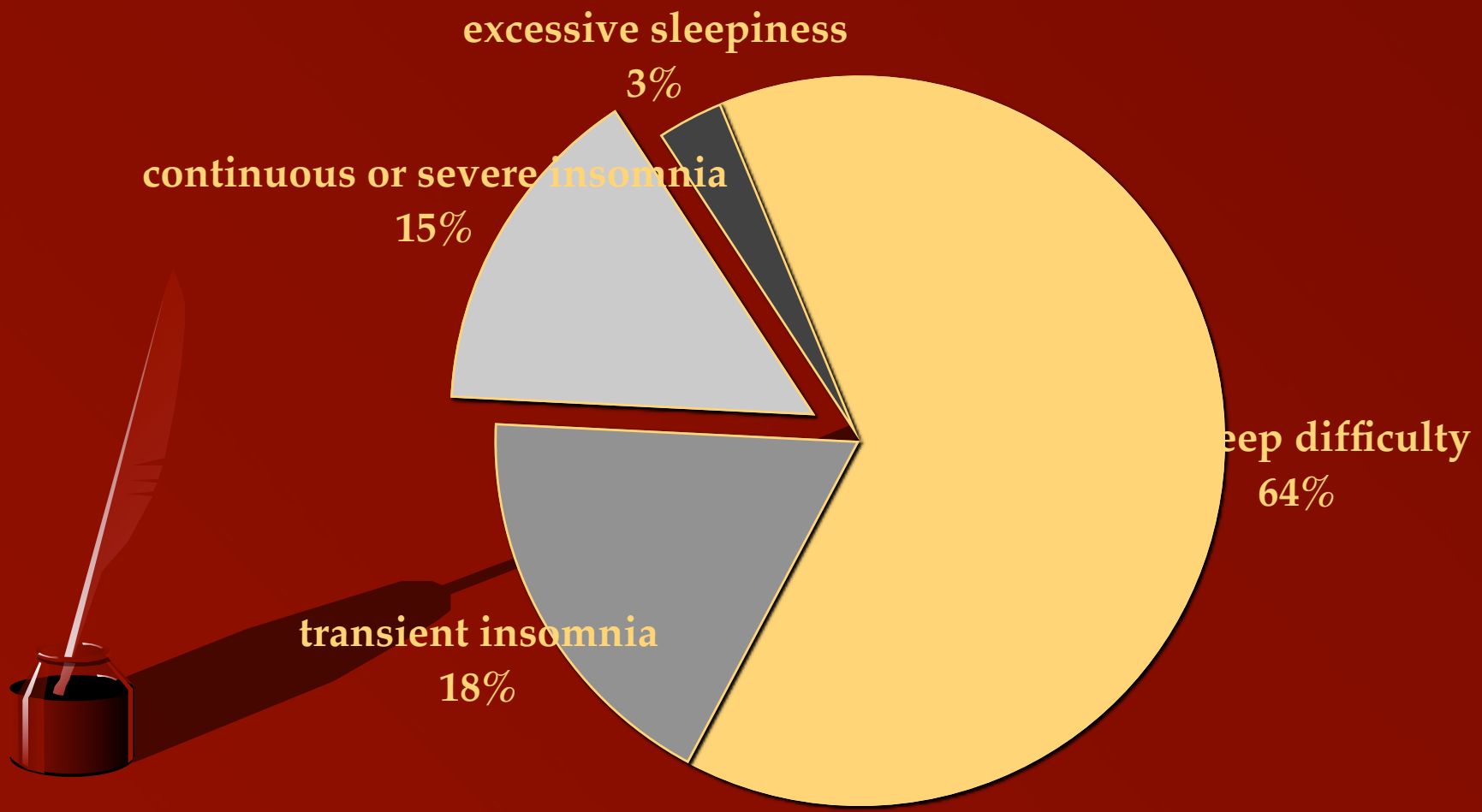
[ref: Dijk & Czeisler, 1995, #1413]

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 Difficulty: Epidemiology



This slide summarizes a number of large-scale epidemiologic studies. About 36% of adults and elderly complain of difficult sleep; this includes 3% with excessive sleepiness, 18% with transient insomnia, and 15% who complain of continuous or severe insomnia.

Analysis of Canadian data from the Statistics Canada General Social Survey in 1991 of about 12,000 people over age 16:

24%: difficulties in initiating or maintaining sleep

27%: unrefreshing sleep all or most of the time

5%: complain of always being sleepy

Sleep in America: the Gallup Poll

- Occasional insomnia: 27%
- Regular, chronic sleep problem: 9%
- Insomniacs:
  - Wake up feeling drowsy or tired: 72%
  - Wake in middle of night: 67%
  - Difficulty returning to sleep: 57%
  - Initial difficulty falling asleep: 56%
  - Self-medicate (alcohol or OTC drugs): 40%

National Sleep Foundation, 1991

The National Sleep Foundation asked the Gallup organization to conduct a poll. The results were published in 1991, with the imposing title "Sleep in America".

A random sample of 700 adults with sleep problems was compared to 300 adults with no sleep problem. They estimated that, based on the poll results, 27% of Americans suffer from occasional insomnia, and 9% have a regular, chronic sleep problem.

Here are some of the characteristics of the insomnia group.

Insomniacs reported impaired concentration and memory, decreased ability to accomplish daily tasks, and decreased enjoyment of interpersonal relationships.

Risk factors for insomnia:

•Low socio-economic status

•Female, elderly

•Low marital satisfaction

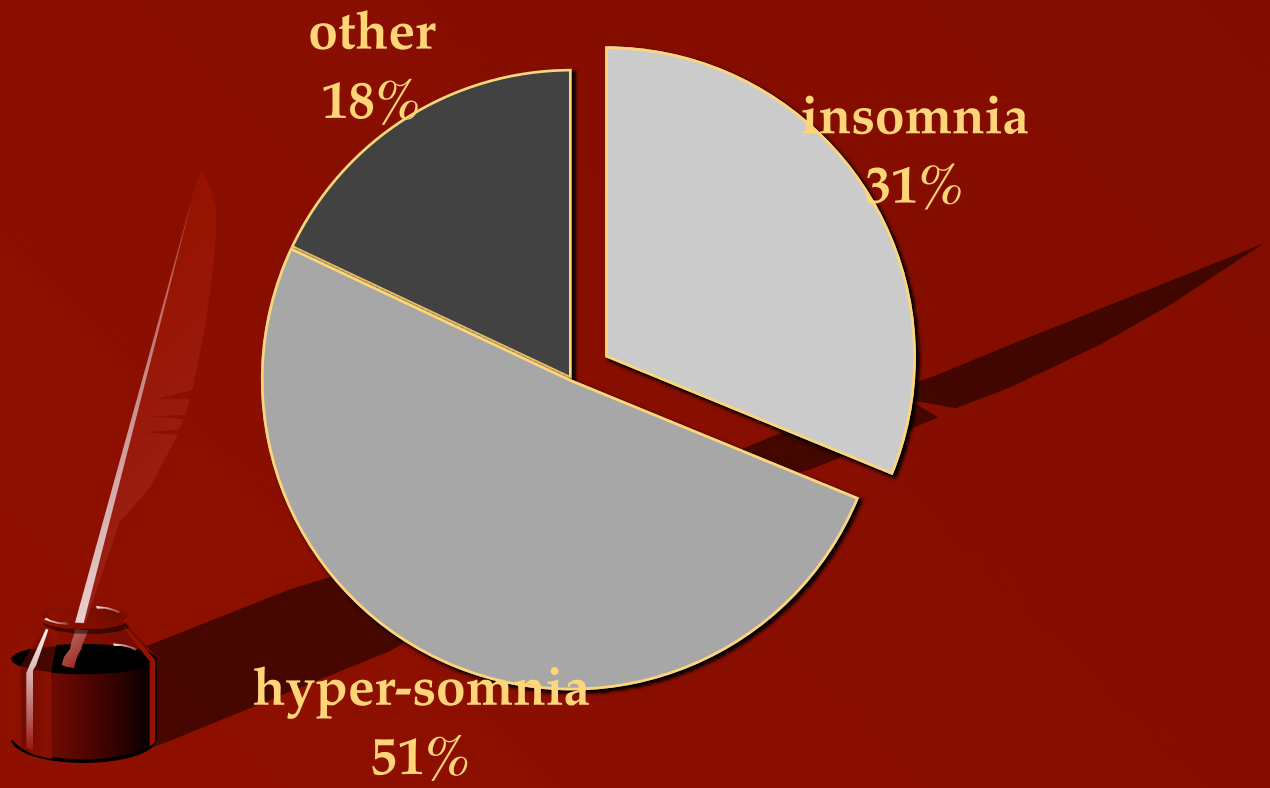
•Having children under age 18

•Sleeping with your children

•Medical or psychiatric illness

•Shift workers

Patients seen at Sleep Disorders Centers for Evaluation

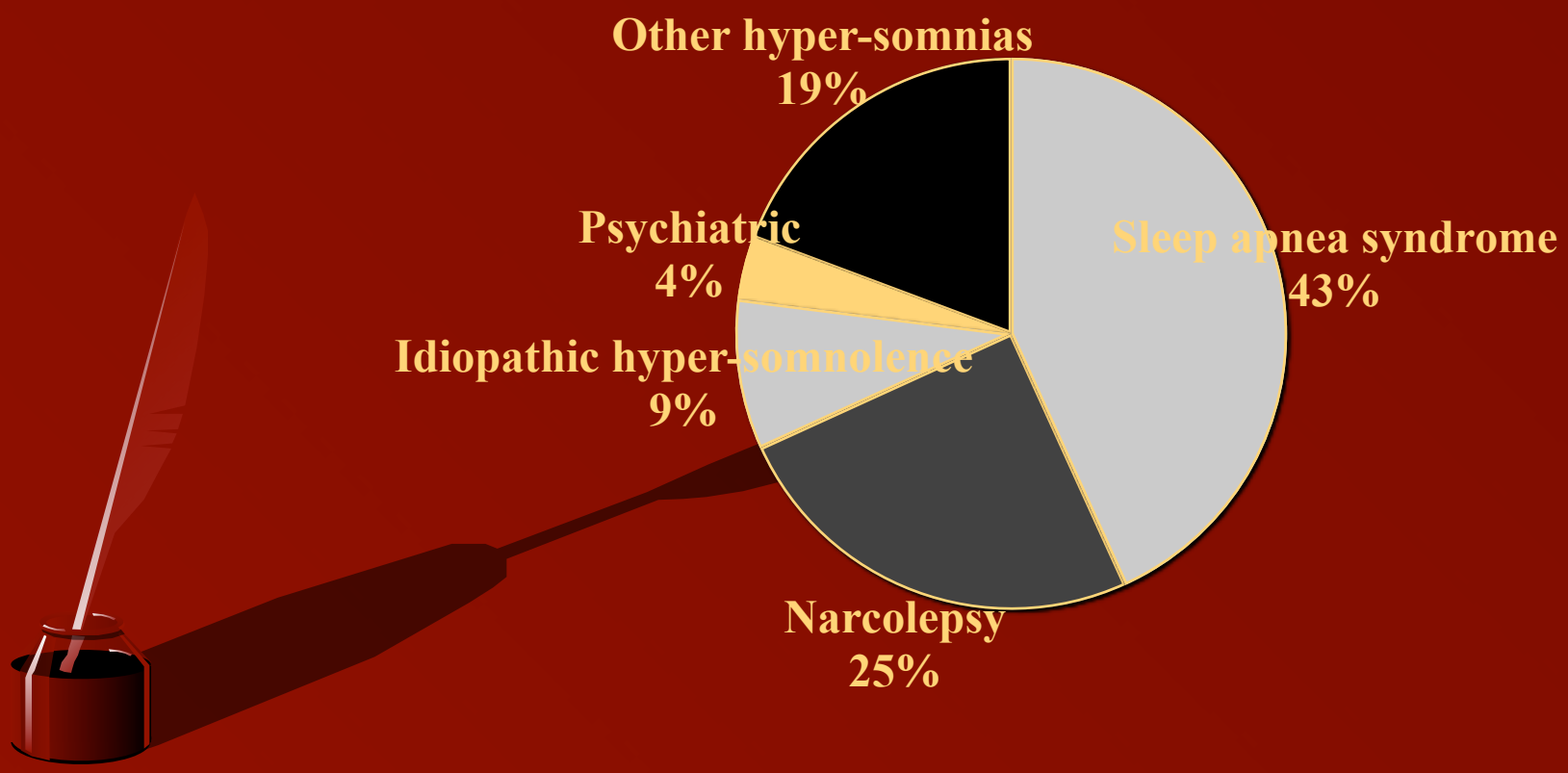


Cooperative study of 3900 patients evaluated in 11 centres

I haven't been able to find good data on the prevalence of specific types of sleep disorders in the general population. However, for those with problems severe enough or so difficult to diagnose that they were referred to a Sleep Disorders Centre, there is a cooperative study pooling data for 3900 such individuals from 11 centres.

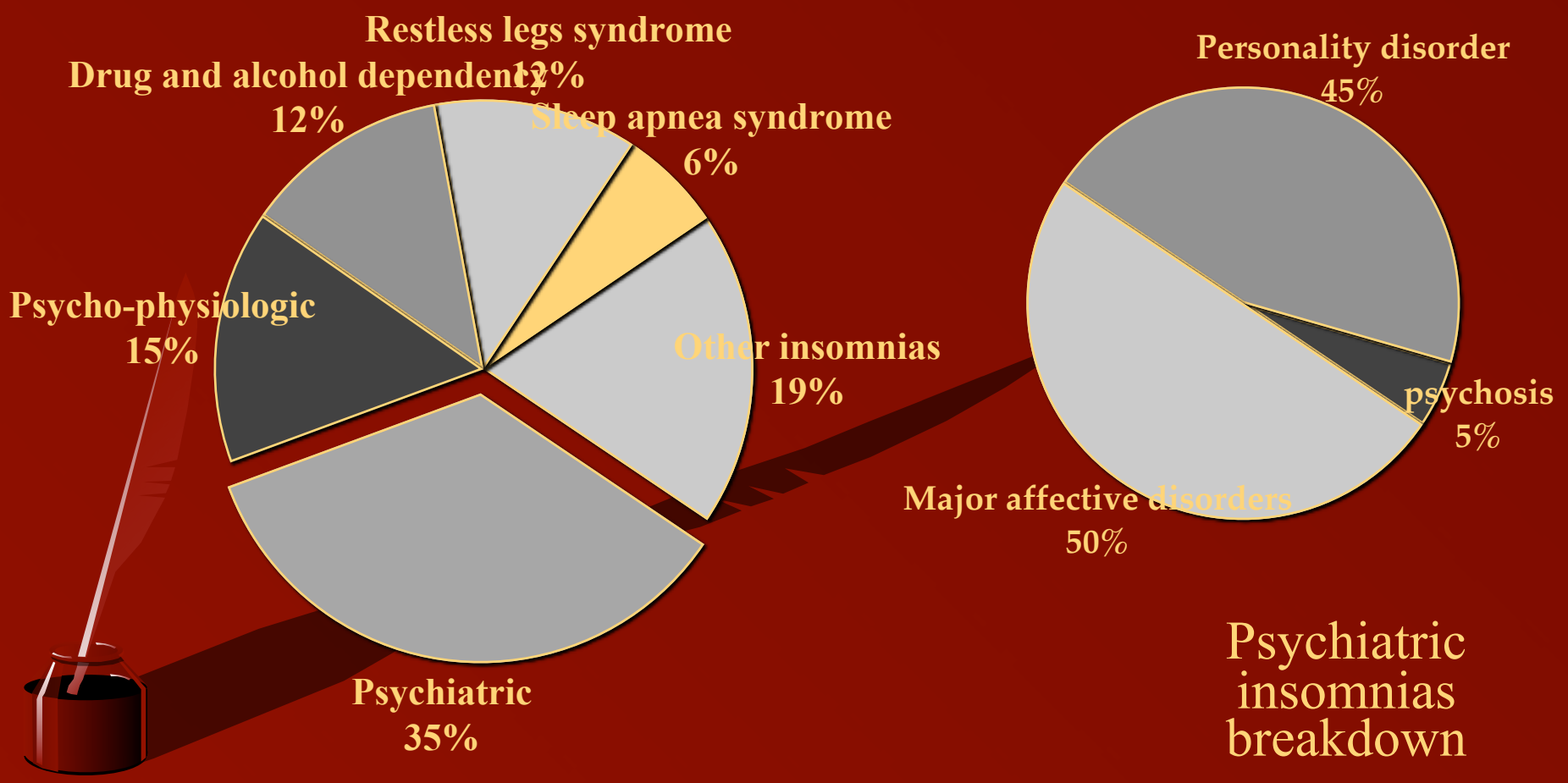
As you can see, hypersomnia is the presenting problem for half of these patients. Compare this to 3% hypersomnia in the general population. Since hypersomnia is the condition most likely to cause accidents or impair work performance, this high referral rate makes sense.

Hypersomnia Diagnoses



The hypersomnia group breakdown is shown here. Note especially the large group with sleep apnea, and also narcolepsy.

Insomnia Diagnoses



The 31% of sleep disorder centre patients who complained of insomnia, received the diagnoses shown here. Of note is that more than a third were felt to have insomnia related to a psychiatric condition; this group is further broken down in the pie chart on the right; here we see that affective disorders account for half of this group.

I found it interesting that only 15% of the sleep disorder centre insomniacs were felt to have psychophysiologic, also known as primary, insomnia. The percentage in a general practice is typically much higher.

Sleep Questionnaire

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

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.

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 assessment

- 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.

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: commonly used definitions

- "a nearly nightly complaint of an insufficient amount of sleep"
  - Becker et al 1993
- "... lack of sufficient sleep to maintain physical and mental health"
  - Lamb 1982

Most people, including sleep researchers, believe that insomnia means the person is not getting enough sleep. This slide quotes two typical definitions.

But is it really true that insomniacs are sleep deprived? Let's look at the research on insomnia.

Insomnia: the reality

- insomniacs have been found to sleep as much as normals
  - Carskadon et al 1976; Waters et al 1993; Pace-Schott et al 1994
- insomniacs sleep more during the day
  - Johns et al 1971

Most insomniacs sleep as much as normal people do; they also tend to sleep during the day more.

Hypothesis: Attempting to sleep too much causes insomnia

- Chambers & Keller 1993
- Insomnia patients tend to spend more time in bed than normals
  - Middelkoop et al 1996
- They underestimate the amount they actually sleep
  - Frankel et al 1976; McCall & Edinger 1992
- Have worse sleep efficiency with longer times in bed
  - Levine et al 1988

Chambers and Keller formulated the hypothesis that insomnia can be caused by attempting to sleep too much, that is, trying to get more sleep than one needs. We know that insomniacs spend more time in bed than normal people. They typically underestimate the amount they actually sleep, so they may believe that they need to get more sleep. But the more time they spend in bed, the poorer their sleep quality becomes.

Hypothesis: Attempting to sleep too much causes insomnia

- The amount of daytime sleep is directly related to sleeping problems
  - Rosa 1993; Bazargan 1996
- Voluntarily extending sleep causes insomnia
  - Aserinsky 1969
- Insomniacs have less daytime sleepiness than normals
  - Middelkoop et al 1996

Insomniacs sleep more during the day than normals, and the amount of daytime sleep correlates with their sleep difficulty.

If someone without insomnia starts sleeping longer than usual, it's been shown that insomnia will develop.

If it were true that insomniacs are not getting enough sleep, you would expect them to be sleepy during the day, right? What's been found is that daytime sleepiness occurs less in insomniacs.

Implications of Excessive Sleep in Insomniacs

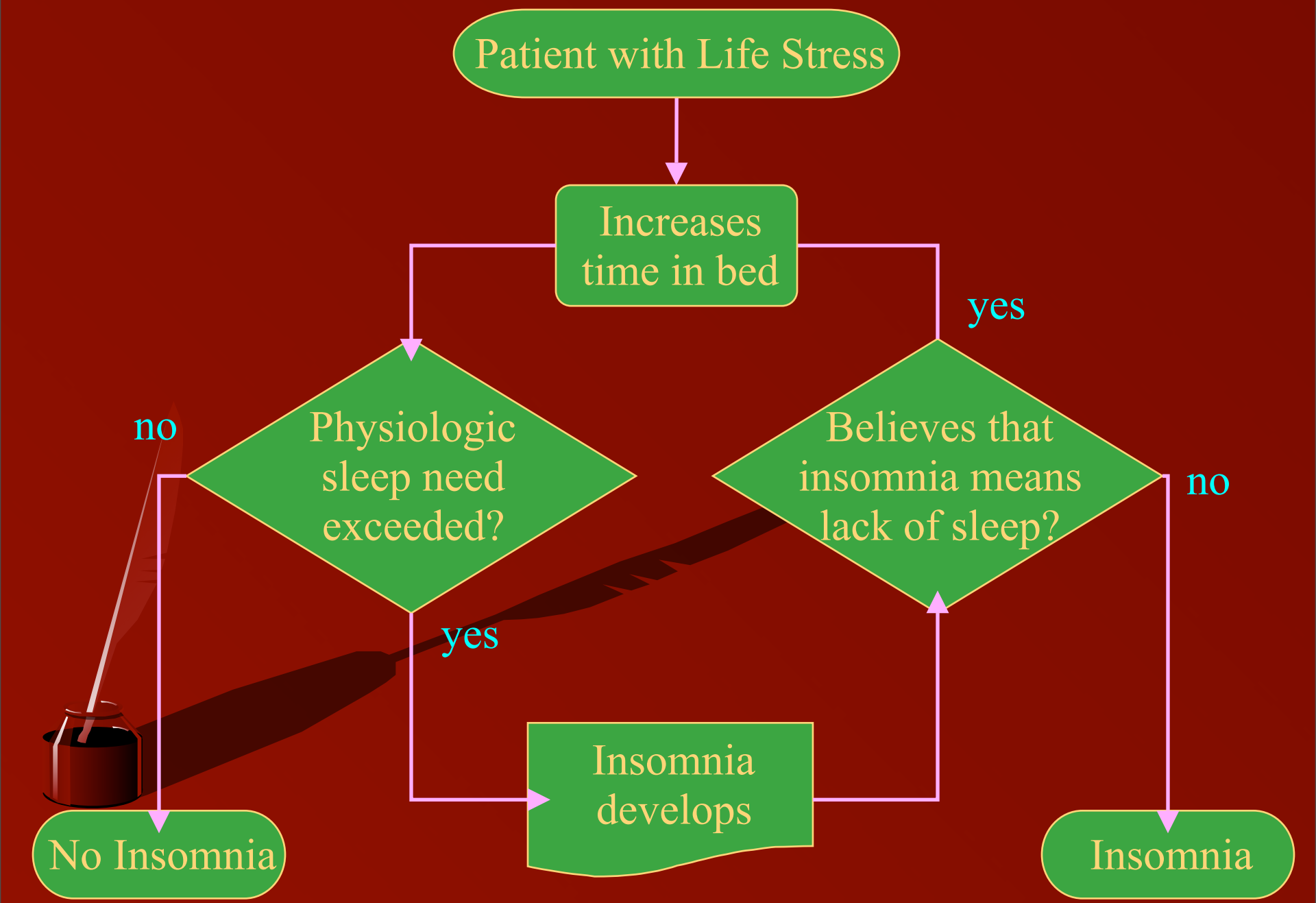
- Insomnia is a risk factor for depression
  - Ford & Kamerow 1989; Schramm et al 1995; McCurry & Terri 1995
- Fatigue and insomnia are closely linked in:
  - Cancer (Nail et al 1991; Sarna 1993; Graydon 1994)
  - Myocardial infarct (McCorkle & Quint-Benoliel 1983)
  - Hemodialysis (Brunier & Graydon 1993)
  - Rheumatoid arthritis (Mahowald et al 1989)
  - Chronic fatigue syndrome (Whelton 1988; Krupp et al 1993)
  - Myositis syndrome (Saskin et al 1987)

So if you accept this hypothesis, that symptoms of primary insomnia are caused by sleeping more than you need, then it is likely that these insomniacs are getting too much REM sleep, particularly since many insomniacs tend to sleep late, when REM sleep peaks. If they do get too much REM sleep, and too much REM sleep has been hypothesized to cause depression or fatigue, then you would expect insomniacs to be depressed or fatigued, right?

Ford and Kamerow carried out a large prospective study of almost 8000 people. Subjects were interviewed twice, with one year between interviews. They found that those who still had insomnia on the second interview were 40 times more likely to develop a new major depression than those without insomnia.

Another study found that insomniacs had 4 times the rate of affective disorder compared to the general population.

As for fatigue, I was unable to find direct evidence for the hypothesis that insomnia can cause fatigue, but there is lots of research demonstrating that fatigue and insomnia are closely linked in cancer and during cancer treatment. They are also Associated in people who have had heart attacks, who are receiving hemodialysis, who suffer from rheumatoid arthritis, and especially in chronic fatigue syndrome patients, of whom 81% had at least one sleep disorder.



As an engineer, I like to illustrate concepts with diagrams, so here's a flowchart to show what I think goes on. First of all, a person with life stress, such as a serious illness like cancer, increases time in bed, perhaps to escape painful feelings, acute phase inflammatory response hormones, or simply because of increased opportunity, for example, when a person with illness goes on sick leave.

Following the arrow to the left, suppose the person's physiologic sleep need is now exceeded because of their increased time in bed. If so, insomnia develops. If the individual further believes that insomnia means that he or she's not getting enough sleep, then they are likely to try to sleep even more, by increasing their time in bed, or by taking sleeping pills. Either way, their sleep need will be exceeded even more, and we have a vicious circle.

This vicious circle can be even more problematic if the excessive time in bed leads to increased REM sleep. Remember the hypothesis that too much REM sleep may cause fatigue? If the person ascribes their fatigue to lack of sleep, they are likely to try to sleep even more.

Treatment

- Early rising to reduce REM sleep
- Taper hypnotics
- Sleep hygiene
- Sleep restriction or compression
- Short naps
- Psychostimulants
- Light
- Caffeine
- Exercise
- Deal with resistance
  - Address myths
  - Involve family or caregivers
- Antidepressants
- thyronine, B_{12}

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.

Treatment

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- thyronine, B_{12}

I have found the psychostimulant methylphenidate, commonly known as Ritalin, very helpful in treating fatigue and depression. Retrospective studies show an effectiveness at least equal to other antidepressants, but with a peak response time of about 2 days instead of weeks. Ritalin suppresses REM sleep directly, and it also helps keep people awake. Thus, when given at 6 am, it makes it possible for people to benefit from the REM suppressing effects of early rising, even when they remain in bed.

The rest of these topics could each take up a whole hour, but I'll just say that morning light is effective against winter depressive symptoms, possibly in part because it gets people up earlier.

Caffeine acts as a mood elevator: women who drink no coffee commit suicide at 2.9 times the rate of those who drink 2 to 3 cups a day.

Vigorous cardiovascular exercise of at least 30 minutes duration stimulates endorphin production. Exercise has been shown to be a useful treatment for both depression and fatigue, perhaps by suppressing REM sleep.

An empathetic, non-challenging approach to help individuals modify erroneous beliefs about sleep and fatigue works best. In some cases, family members can be recruited to help the patient wake up early and get out of bed.

Antidepressants are always an option if ritalin fails to work.

Finally, remember to check TSH and B12 levels, and supplement when necessary.

Insomnia: Stimulus Control Therapy

- Curtail time spent awake while in bed. Go to bed only when sleepy. Do not remain in bed for more than 20-30 min while awake
- Get up at the same time each day
- Avoid the bedroom clock
- Avoid caffeine, alcohol, and tobacco near bedtime
- Exercise during the morning or afternoon
- Eat a light snack before bed
- Adjust sleeping environment for optimal temperature, sound, and light
- Do not worry right before and in bed. Use the bed for sleeping
- Do not nap during the day

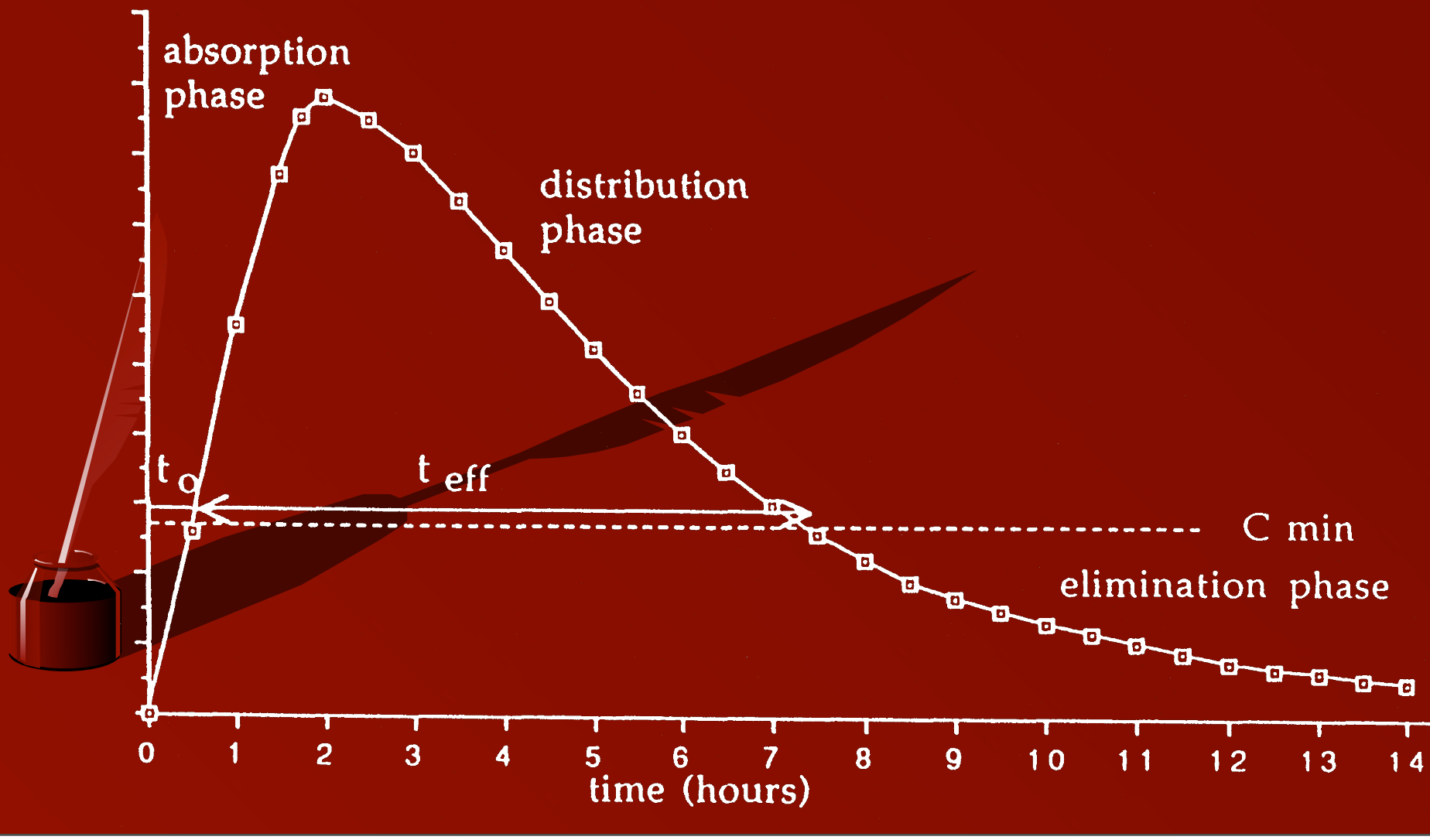
(Tasman, 1997)

Insomnia: Sleep restriction therapy

(Tasman, 1997)

- 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.

Medication Phases



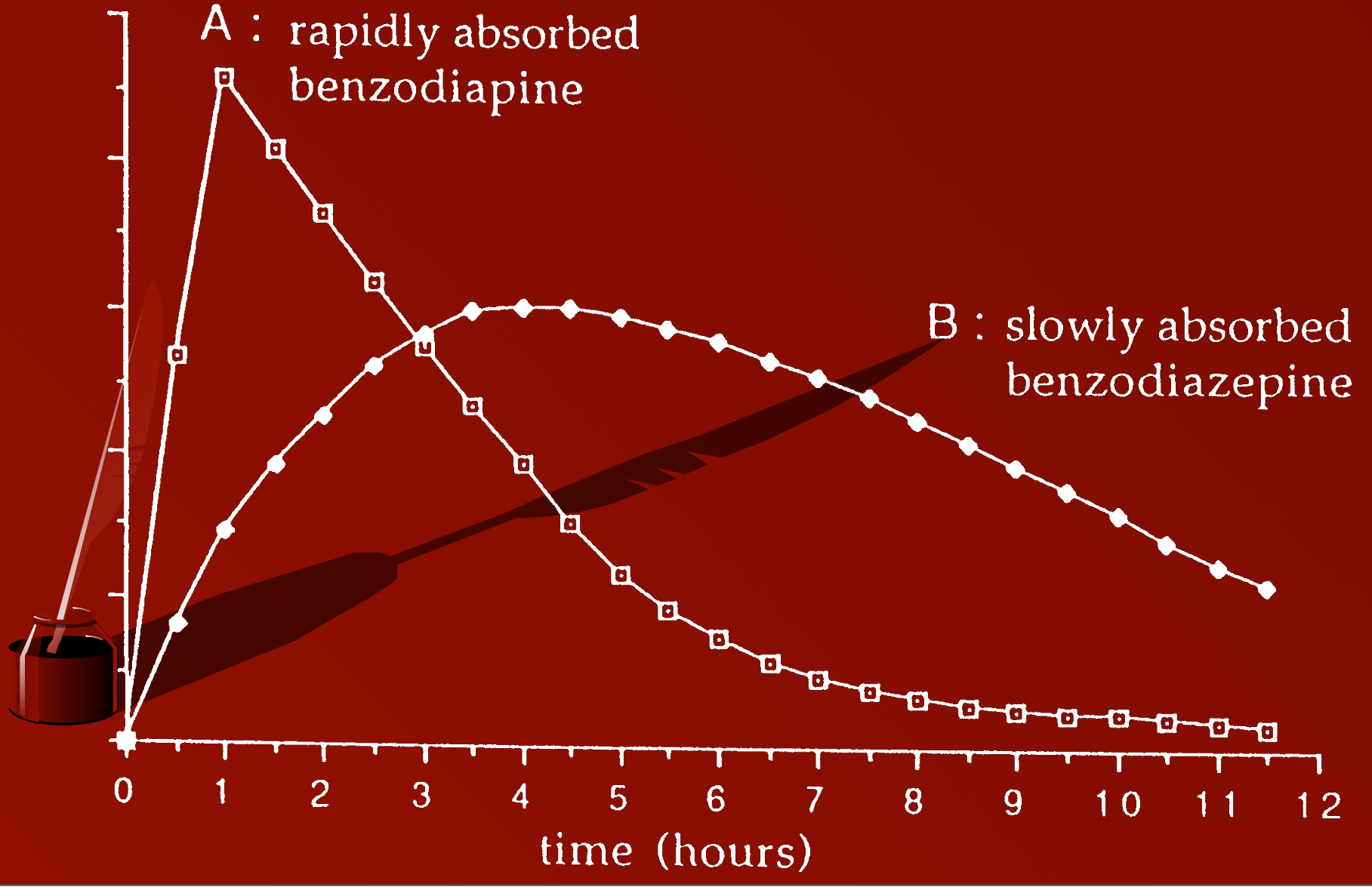
Let's discuss what happens in the brain with benzodiazepines. This slide shows a typical plasma concentration curve after a single dose of medication.

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



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

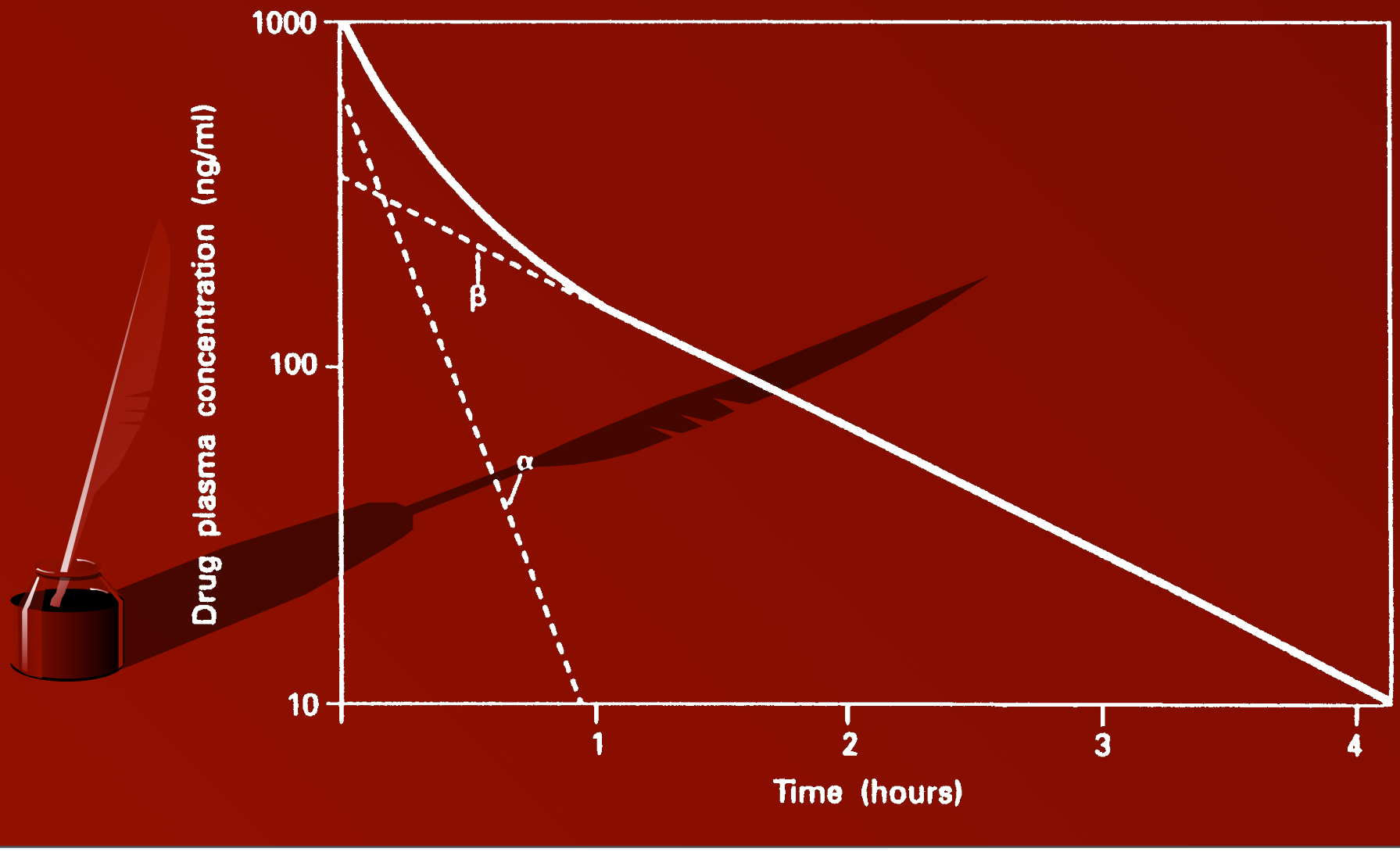
This slide compares times to peak blood level for different routes of administration of lorazepam.

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.

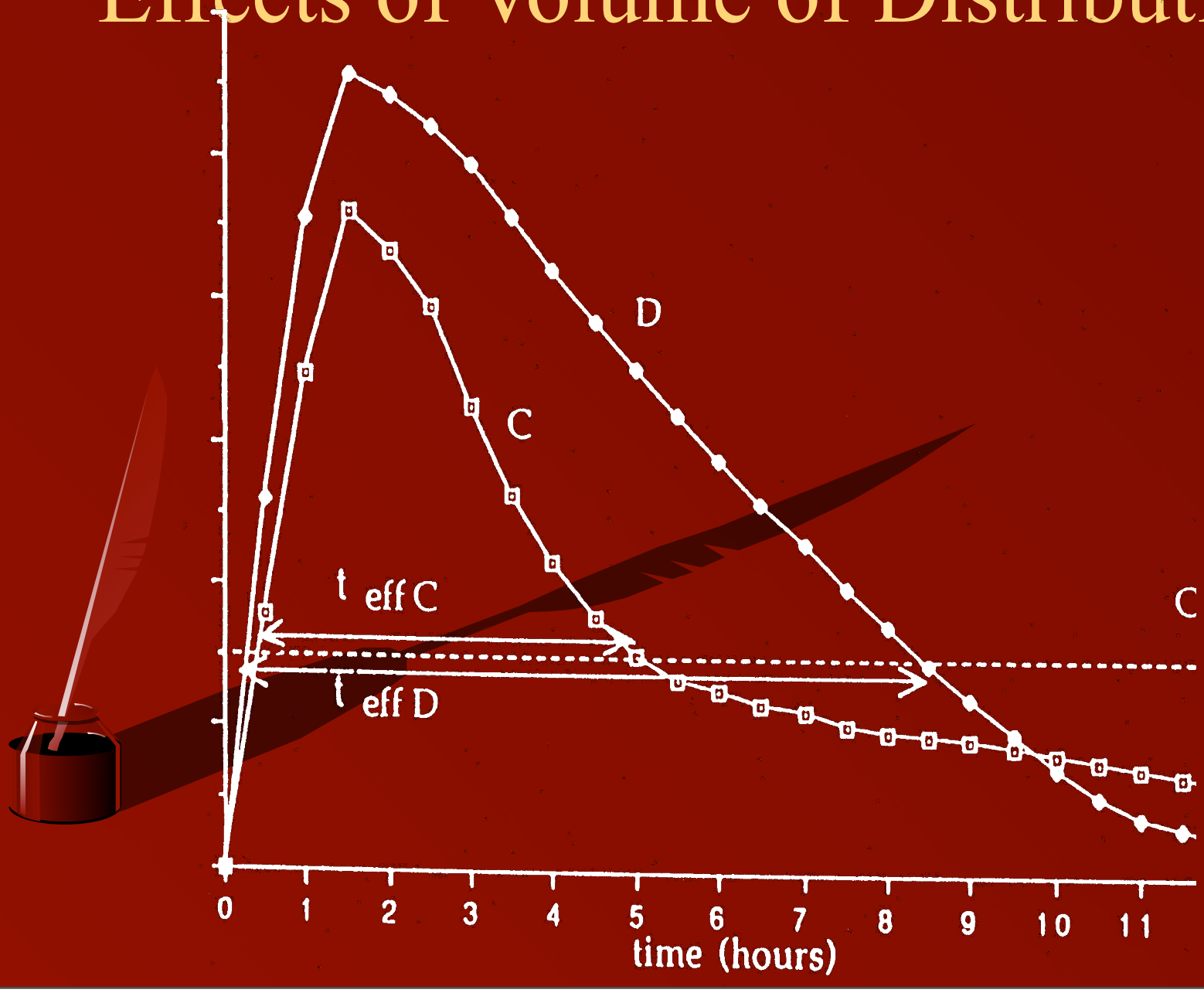
Alpha & Beta Half-lives



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.

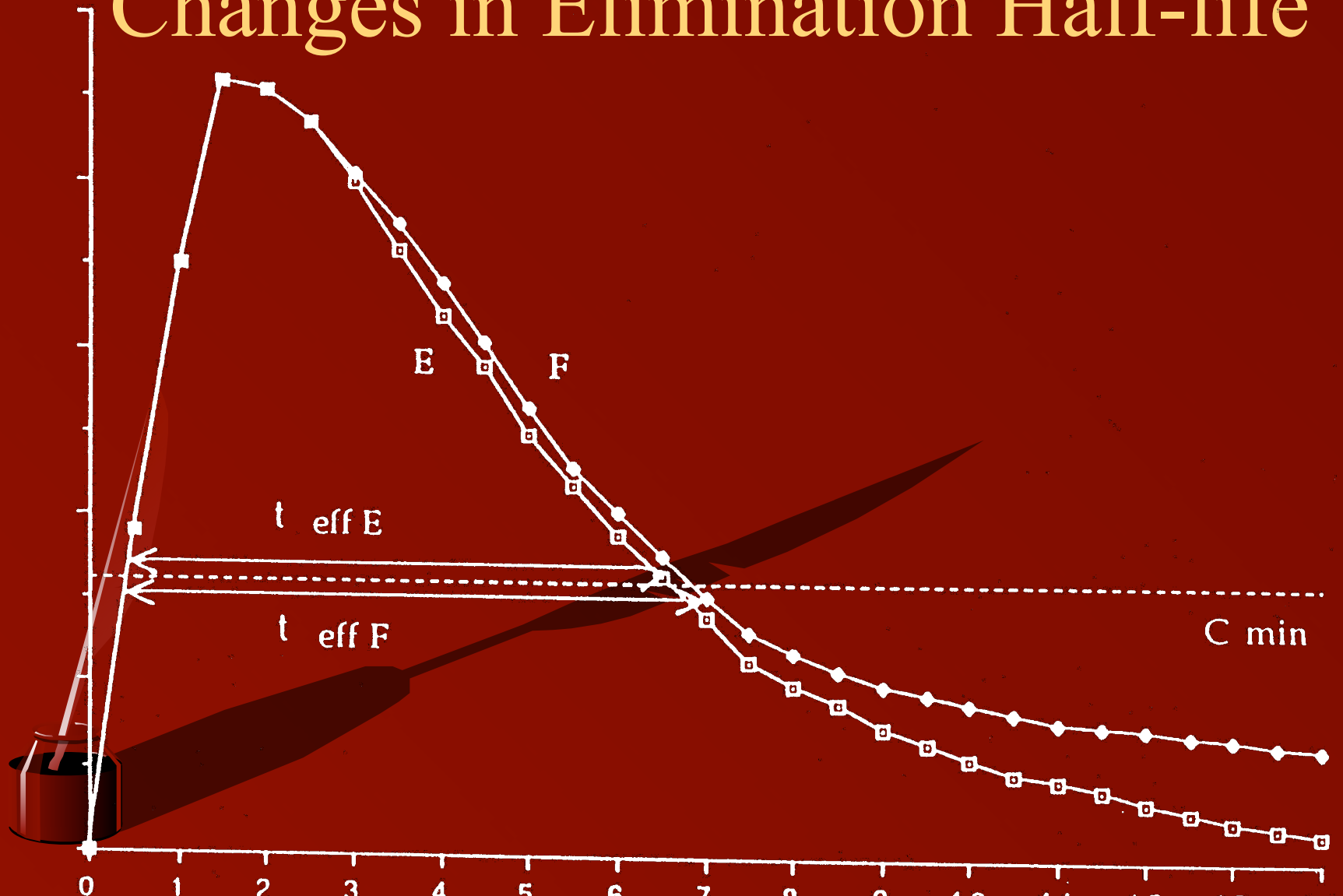
Effects of Volume of Distribution



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 can be bound to lipids, the bigger its volume of distribution.

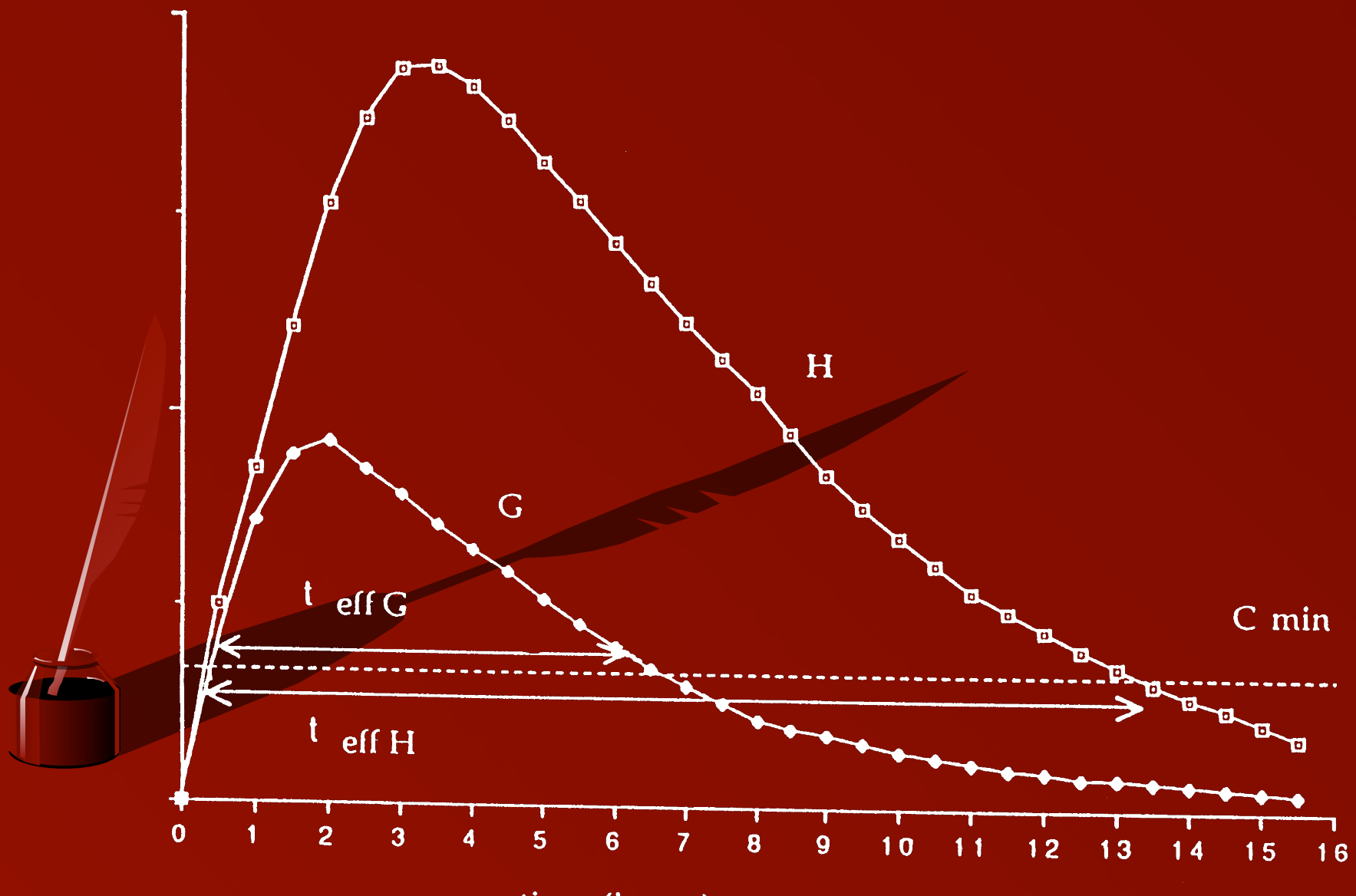
This graph shows that drug C with a higher volume of distribution because of greater lipid solubility, will have a shorter duration of action than drug D.

Changes in Elimination Half-life



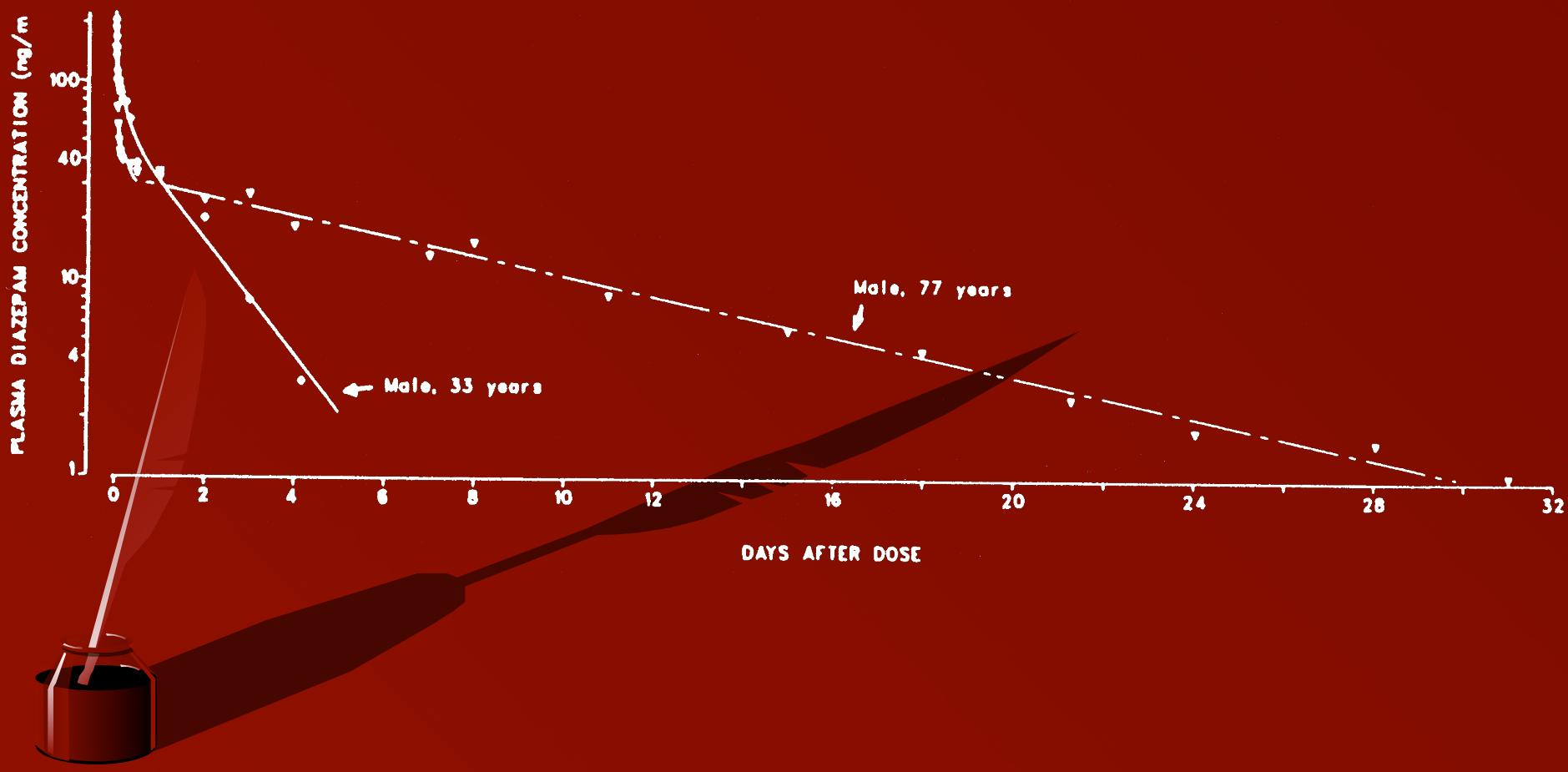
This contrasts with the elimination half-life, which does not affect duration of action when the drug is given in single doses, or doses which are far enough apart.

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.

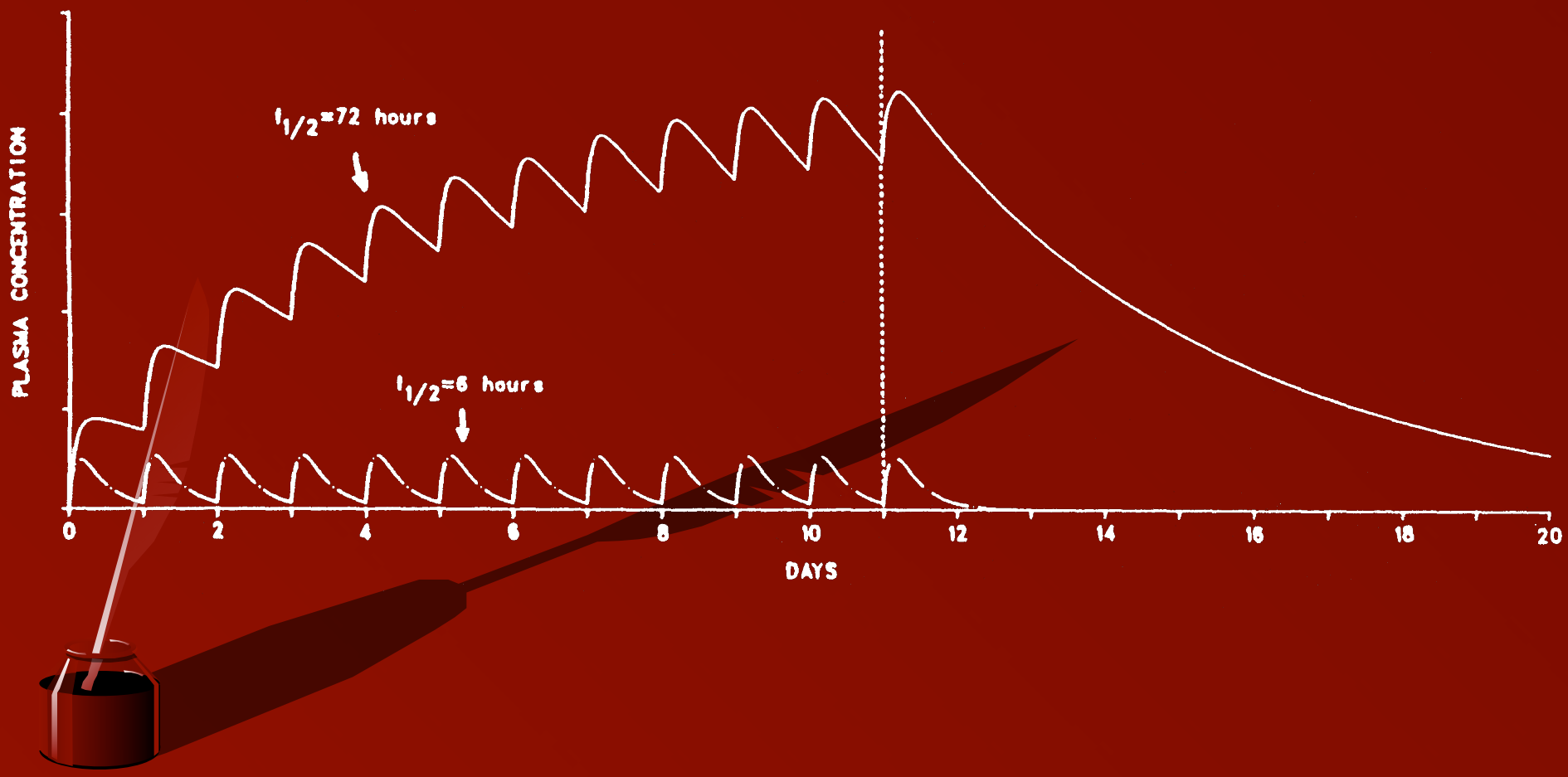
Effects of Age



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



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. 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.

Benzodiazepines

Name	Dose (mg)	Absorption	Active Metabolite	Half-Life
Chlordiazepoxide (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)	0.5-4.0	Intermediate	No	10-20 h

Benzodiazepines & Others

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)	0.125-0.5	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

I've never prescribed midazolam for sleep problems, but I've heard reports that it works so quickly that if you take the medication in your kitchen prior to climbing the stairs to your bedroom, you might fall asleep on the landing. Clearly, this could result in dangerous falls.

Zolpidem is not available in Canada.

Zopiclone is disliked by some patients because it leaves a metallic taste in the mouth.

Zaleplon is eliminated very quickly, which leads to its use as a "rescue" medication. In other words, you don't use it at bedtime in anticipation of difficulty falling asleep, but you could take it at any time during the night up to 4 hours before the desired wake time, if you actually experience sleep difficulties.

Other Hypnotics

Name	Dose (mg)	Absorption	Active Metabolite	Half-Life
Chloral Hydrate	500-1000 mg	Rapid	Yes	4-12 h
Propofol (Diprivan)	2-2.5 mg/kg	Intravenous	No	α: 1.8-8.3 min β: 34-66 min
Valerian root	500 mg			

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.

melatonin

- Derived fom serotonin
- Synthesized in pineal gland
- Rises in evening, peaks between 3 & 5 am, decreases to low levels during day
- Elderly:lower night-time levels
- Elderly insomniacs: oral dose of 0.3 mg 30 min before bedtime restored sleep efficiency
- 3 mg dose: worse sleep
- Not useful as a hypnotic
- Possibly helpful in jet lag, delayed sleep phase syndrome

Melatonin is a hormone derived from serotonin, is synthesized and released by the pineal gland. It begins to rise in the evening, reaches peak values between 3 and 5 am, and decreases to low levels during the day. In the elderly, melatonin levels do not rise as high during the night. A recent study of elderly insomniacs found that an oral dose of 0.3 mg given 30 minutes before bedtime returned nighttime levels to normal and restored sleep efficiency; a dose of 3 mg led to worse sleep, however.

In general, melatonin has not been found useful as a hypnotic. It might be helpful in treating jet lag, or delayed sleep phase syndrome.

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 and cognition
- 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

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

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 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
  - Methamphetamine
  - Pemoline
  - Modafinil

Narcolepsy: medication

- For cataplexy, sleep paralysis, hypnagogic hallucinations:
  - Tricyclic antidepressants
    - Protriptyline: 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
- 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

Breathing-related sleep disorder is very common, and is likely becoming more so, as the prevalence of obesity is increasing. The diagnostic criterion shown hererepresents very mild illness, as it is not uncommon to see people who stop breathing for 60 to 120 seconds, hundreds of times per night.

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

Night Terrors

- Repeated abrupt wakings with:
  - Intense fear
  - Panicky screams
  - Autonomic arousal
  - Amnesia for episode
  - Comforting useless
- Usually during delta sleep
- Synonyms: pavor nocturnus, incubus
- Begins ages 4-12, resolves in adolescence
- Adults: < 1%; M = F; begins ages 20-30; chronic; often assoc. with psychiatric disorder
- Familial relationship to enuresis, somnambulism
- Rx: BDZ (suppress delta sleep)
- Children: 1-6%, M > F

This disorder is defined as repeated abrupt awakenings from sleep characterized by intense fear, panicky screams, autonomic arousal (tachycardia, rapid breathing, and sweating), absence of detailed dream recall, amnesia for the episode, and relative unresponsiveness to attempts to comfort the person. [87] [88] Because sleep terrors occur primarily during delta sleep, they usually take place during the first third of the night. These episodes may cause distress or impairment, especially for caretakers who witness the event. Sleep terrors may also be called night terrors, pavor nocturnus, or incubus.

The prevalence of the disorder is estimated to be about 1% to 6% in children and less than 1% adults. In children, it usually begins between the ages of 4 and 12 years and resolves spontaneously during adolescence. It is more common in boys than in girls. It does not appear to be associated with psychiatric illness in children. In adults, it usually begins between 20 and 30 years of age, has a chronic undulating course, is equally common in men and women, and may be associated with psychiatric disorders, such as posttraumatic stress disorder, generalized anxiety disorder, borderline personality disorder, and others. An increased frequency of enuresis and somnambulism has been reported in the first-degree relatives of patients with night terrors.

Nocturnal administration of benzodiazepines has been reported to be beneficial, perhaps because these drugs suppress delta sleep, the stage of sleep during which sleep terrors typically occur.

Sleepwalking

- Usually during delta sleep (first third of night)
- Blank staring face
- Unresponsive
- Disoriented on arousal
- Amnesia next day
- May involve danger
- 10-30% of children have at least one episode
- Begins ges 4-8; resolves during adolescence
- Triggers: sitting the patient up; fever; sleep deprivation
- Adult onset: look for underlying cause
- Rx: some patients respond to BDZ or sedating antidepressants
- 1-5% repeated episodes

This disorder is characterized by repeated episodes of motor behavior initiated in sleep, usually during delta sleep in the first third of the night. While sleepwalking, the patient has a blank staring face, is relatively unresponsive to others, and may be confused or disoriented initially on being aroused from the episode. Although the person may be alert after several minutes of awakening, complete amnesia for the episode is common the next day. Sleepwalking may cause considerable distress, for example, if a child cannot sleep away from home or go to camp because of it. By DSM-IV definition, pure sleepwalking is excluded if it occurs as a result of a medication or substance or is due to a medical disorder. However, sleepwalking may be an idiosyncratic reaction to specific drugs, including tranquilizers and sleeping pills.

Most behaviors during sleepwalking are routine and of low-level intensity, such as sitting up, picking the sheets, or walking around the bedroom. More complicated behaviors may also occur, however, such as urinating in a closet, leaving the house, running, eating, talking, driving, or even committing murder. [90] A real danger is that the individual will be injured by going through a window or falling from a height.

Whereas about 10% to 30% of children have at least one sleepwalking episode, only about 1% to 5% have repeated episodes. The disorder most commonly begins between the ages of 4 and 8 years and usually resolves spontaneously during adolescence. Genetic factors may be involved, because sleepwalkers are reported to have a higher than expected frequency of first-degree relatives with either sleepwalking or sleep terrors. [91] Sleepwalking may be precipitated in affected patients by gently sitting them up during sleep, by fever, or by sleep deprivation. Adult onset of sleepwalking should prompt the search for possible medical, neurological, psychiatric, pharmacological, or other underlying causes, such as nocturnal epilepsy.

No treatment for sleepwalking is established, but some patients respond to administration of benzodiazepines or sedating antidepressants at bedtime. The major concern should be the safety of the sleepwalker, who may injure herself or himself or someone else during an episode.

REM Sleep Behaviour Disorder

- Complicated behaviours during sleep (eg, walking, talking, singing)
- Usually 2nd half of night
- During REM sleep
- Loss of muscle atonia
- Good memory of dream
- Idiopathic form: men in 50s & 60s

- Causes:
  - Neuro disorders, eg dementia
  - EtOH or sedative withdrawal
  - During Rx with TCAs

- Rx: clonazepam 0.5-1 mg qhs
- Educate patients & bed partners re risk of injury

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. 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.

The Scientific Literature

- "As the olde englysshe prouerbe sayth in this wyse,
  who soo woll ryse erly
  shall be holy helthy and zely."
  —Wynkyn de Worde: A Treatyse of Fysshynge wyth an Angle, 1496, Westminster
- "Diluculo surgere saluberrimum est."
  —William Lily (c. 1468-1522): Latin Grammar, 1513

Just to make sure that you don't go away with the impression that my emphasis on getting up early puts me way out there in left field, here is some of the literature on early rising.

The earliest reference dates back to 1496, but it is clear that this proverb was already considered old at that time. The word "zely" means happy or fortunate.

The latin proverb translates as: "To rise early is very healthy".

The Scientific Literature

- "At grammar-scole I lerned a verse, that is this,
  Sanat, sanctificat, et ditat surgere mane.
  That is to say,
  Erly rysyng maketh a man hole in body, holer in soule, and rycher in goodes."
  —Anthony Fitzherbert (1470-1538): the Book of Husbandry, 1523

- "Earley to bed and earley to rise,
  makes a man healthy, wealthy, and wise."
  —John Clarke (1596-1658): proverb collection Paroemiolgoia Anglo-Latina, 1639

Here's another latin proverb.

In 1639, John Clarke cited the proverb that we all know, and which was erroneously attributed to Benjamin Franklin over a century later. Note, however, that this is the only one that talks about going to bed early; all the others focus only on getting up early.

The Scientific Literature

- "One hour's sleep before midnight is worth two hours after."
  —John Rays (1627-1705): A Compleat Collection of English Proverbs, 1670
- "Plough deep while sluggards sleep."
  —Benjamin Franklin (1706-1790): Maxim prefixed to Poor Richard's Almanac, 1757
- "The early bird catches the worm."
- "My formula for success?
  Rise early, work late, strike oil."
  —J. Paul Getty

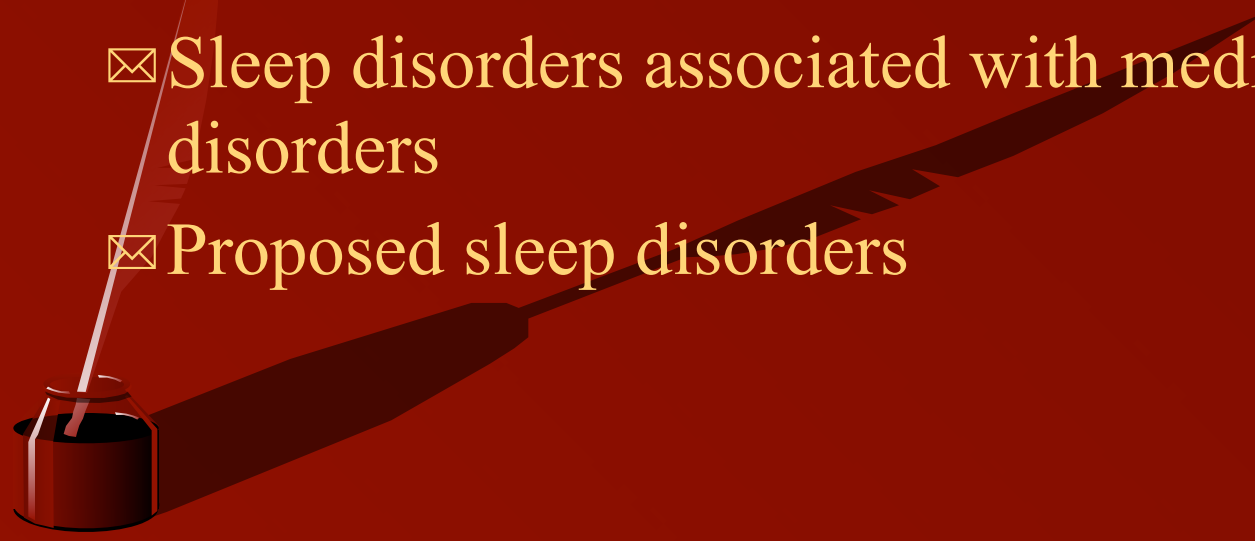
My favourite is the one at the bottom, by billionaire oilman J. Paul Getty.

Thank you for being such a great audience!

Sleep Disorders: Classification

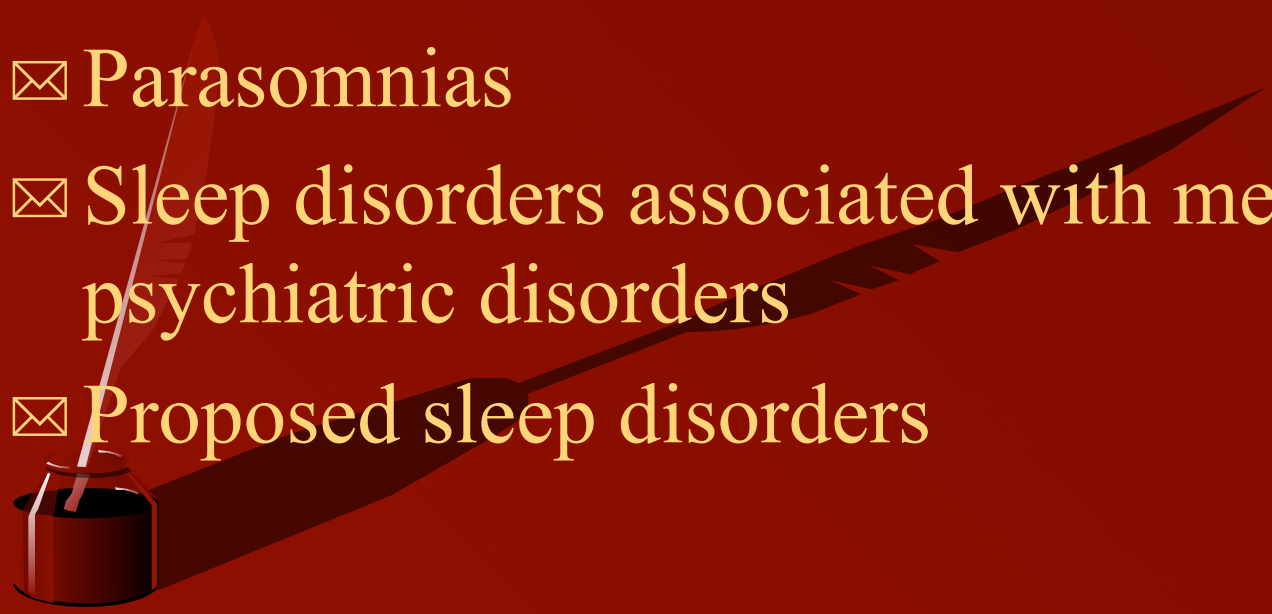
International Classification of Sleep Disorders (1997)

- 4 categories: (82 diagnoses)
  - Dyssomnias
  - Parasomnias
  - Sleep disorders associated with medical or psychiatric disorders
  - Proposed sleep disorders



Sleep Disorders: Classification

- Dyssomnias (28)
  - Intrinsic
  - Extrinsic
  - Circadian-rhythm disorders
- Parasomnias
- Sleep disorders associated with medical or psychiatric disorders
- Proposed sleep disorders



Sleep Disorders: Classification

- Dyssomnias
  - Intrinsic (11)
    - Psychophysiologic insomnia
    - Sleep state misperception
    - Idiopathic insomnia
    - Narcolepsy
    - Recurrent hypersomnia
    - Idiopathic hypersomnia
    - Obstructive sleep apnea syndrome
    - Central sleep apnea syndrome
    - Central alveolar hypoventilation syndrome
    - Periodic leg movements in sleep disorder
    - Restless legs syndrome
  - Extrinsic

Sleep Disorders: Classification

- Dyssomnias
  - Intrinsic
  - Extrinsic (14)
    - Inadequate sleep hygiene
    - Environmental sleep disorder
    - Altitude insomnia
    - Adjustment sleep disorder
    - Insufficient sleep disorder
    - Limit-setting sleep disorder
    - Sleep-onset association disorder
  - Circadian-rhythm sleep disorders
- Parasomnias
- Sleep disorders associated with medical or

Sleep Disorders: Classification

- Dyssomnias
  - Intrinsic
  - Extrinsic (14)
    - Food allergy insomnia
    - Nocturnal eating (drinking) syndrome
    - Hypnotic-dependent sleep disorder
    - Stimulant-dependent sleep disorder
    - Alcohol-dependent sleep disorder
    - toxin-induced sleep disorder
    - NOS
  - Circadian-rhythm sleep disorders
- Parasomnias
- Sleep disorders associated with medical or

Sleep Disorders: Classification

- Dyssomnias
  - Intrinsic
  - Extrinsic
  - Circadian-rhythm sleep disorders (7)
    - Time-zone (jet lag) syndrome
    - Shift-work sleep disorder
    - Irregular sleep-wake pattern disorder
    - Delayed-sleep-phase syndrome
    - Non-24 hour sleep-wake disorder
    - Advanced sleep phase syndrome
    - NOS
- Parasomnias
- Sleep disorders associated with medical or

Sleep Disorders: Classification

- Dyssomnias
- Parasomnias (24)
  - Arousal disorders
  - Sleep-wake transition disorders
  - Parasomnias usually associated with REM sleep
  - Other parasomnias
- Sleep disorders associated with medical or psychiatric disorders
- Proposed sleep disorders

Sleep Disorders: Classification

- Dyssomnias
- Parasomnias
  - Arousal disorders (3)
    - Confusional insomnia
    - Sleepwalking (somnambulism)
    - Sleep terrors (pavor nocturnus, incubus attacks)
  - Sleep-wake transition disorders
  - Parasomnias usually associated with REM sleep
  - Other parasomnias
- Sleep disorders associated with medical or psychiatric disorders
- Proposed sleep disorders

Sleep Disorders: Classification

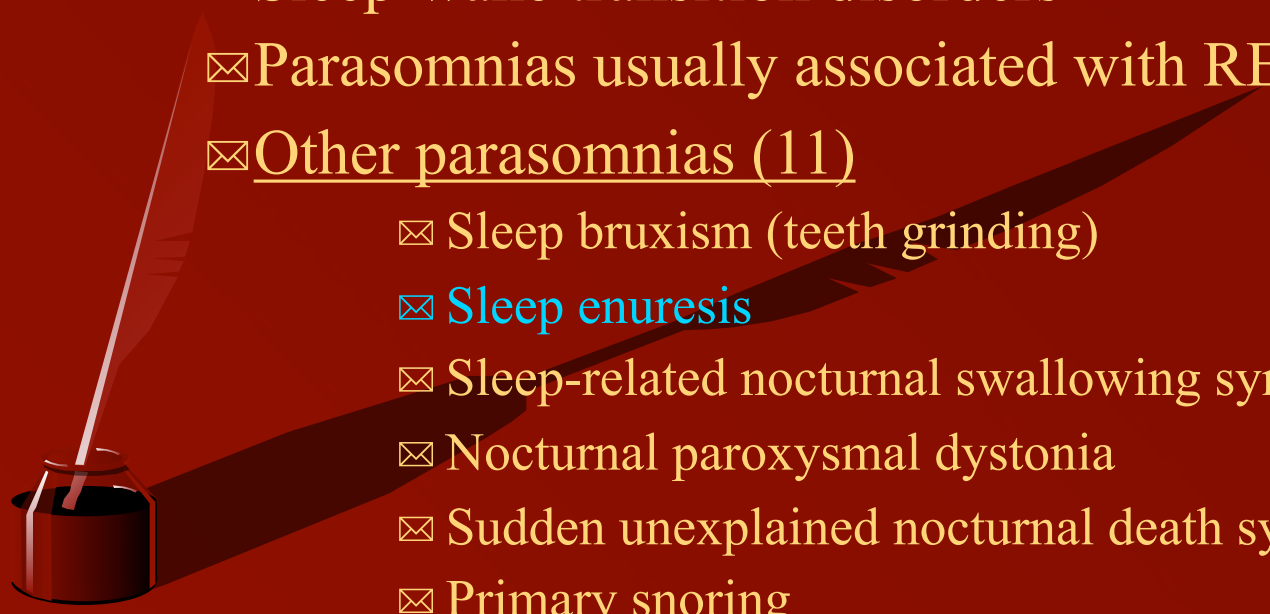
- Dyssomnias
- Parasomnias
  - Arousal disorders
  - Sleep-wake transition disorders (4)
    - Rhythmic movement disorder
    - Sleep starts (hypnic jerks)
    - Sleep talking
    - Nocturnal leg cramps (nocturnal myoclonus)
  - Parasomnias usually associated with REM sleep
  - Other parasomnias
- Sleep disorders associated with medical or psychiatric disorders

Sleep Disorders: Classification

- Dyssomnias
- Parasomnias
  - Arousal disorders
  - Sleep-wake transition disorders
  - Parasomnias usually associated with REM sleep (6)
    - Nightmares
    - Sleep paralysis
    - Impaired sleep-related penile erections
    - Sleep-related painful erections
    - REM sleep-related sinus arrest
    - REM sleep behavior disorder
  - Other parasomnias
- Sleep disorders associated with medical or

Sleep Disorders: Classification

- Dyssomnias
- Parasomnias
  - Arousal disorders
  - Sleep-wake transition disorders
  - Parasomnias usually associated with REM sleep
  - Other parasomnias (11)
    - Sleep bruxism (teeth grinding)
    - Sleep enuresis
    - Sleep-related nocturnal swallowing syndrome
    - Nocturnal paroxysmal dystonia
    - Sudden unexplained nocturnal death syndrome
    - Primary snoring



- Sleep disorders associated with medical or

Sleep Disorders: Classification

- Dyssomnias
- Parasomnias
  - Arousal disorders
  - Sleep-wake transition disorders
  - Parasomnias usually associated with REM sleep
  - Other parasomnias (11)
    - Infant sleep apnea
    - Congenital central hypoventilation syndrome
    - Sudden infant death syndrome
    - Benign neonatal sleep myoclonus
    - NOS
- Sleep disorders associated with medical or psychiatric disorders

Sleep Disorders: Classification

- Dyssomnias
- Parasomnias
- Sleep disorders associated with medical or psychiatric disorders (19)
  - Mental disorders
  - Neurologic disorders
  - Other medical disorders
- Proposed sleep disorders

Sleep Disorders: Classification

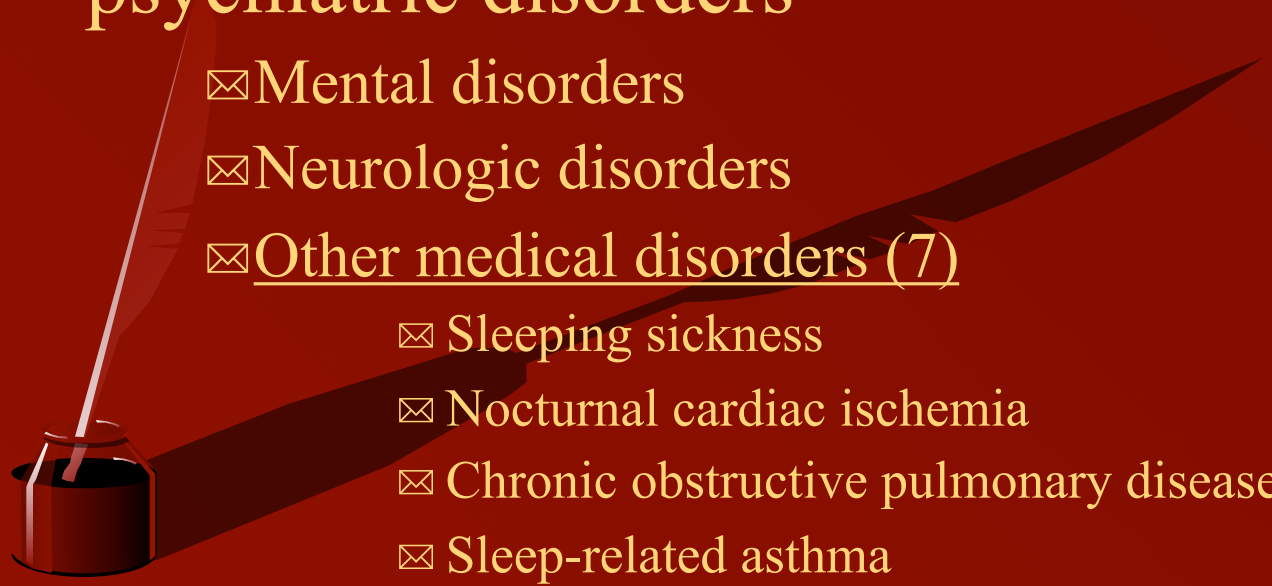
- Dyssomnias
- Parasomnias
- Sleep disorders associated with medical or psychiatric disorders
  - Mental disorders (5)
    - Psychoses
    - Mood disorders
    - Anxiety disorders
    - Panic disorders
    - alcoholism
  - Neurologic disorders
  - Other medical disorders

Sleep Disorders: Classification

- Dyssomnias
- Parasomnias
- Sleep disorders associated with medical or psychiatric disorders
  - Mental disorders
  - Neurologic disorders (7)
    - Cerebral degenerative disorders
    - Dementia
    - Parkinsonism
    - Fatal familial insomnia
    - Sleep-related epilepsy
    - Electrical status epilepticus of sleep
    - Sleep-related headaches

Sleep Disorders: Classification

- Dyssomnias
- Parasomnias
- Sleep disorders associated with medical or psychiatric disorders
  - Mental disorders
  - Neurologic disorders
  - Other medical disorders (7)
    - Sleeping sickness
    - Nocturnal cardiac ischemia
    - Chronic obstructive pulmonary disease
    - Sleep-related asthma



- Proposed sleep disorders

Sleep Disorders: Classification

- Dyssomnias
- Parasomnias
- Sleep disorders associated with medical or psychiatric disorders
  - Mental disorders
  - Neurologic disorders
  - Other medical disorders (7)
    - Sleep-related gastroesophageal reflux
    - Peptic ulcer disease
    - fibromyalgia
- Proposed sleep disorders

Sleep Disorders: Classification

- Dyssomnias
- Parasomnias
- Sleep disorders associated with medical or psychiatric disorders
- Proposed sleep disorders (11)
  - Short sleeper
  - Long sleeper
  - Subwakefulness syndrome
  - Fragmentary myoclonus
  - Sleep hyperhydrosis
  - Menstrual-associated sleep disorder

Sleep Disorders: Classification

- Dyssomnias
- Parasomnias
- Sleep disorders associated with medical or psychiatric disorders
- Proposed sleep disorders (11)
  - Pregnancy-associated sleep disorder
  - Terrifying hypnagogic hallucinations
  - Sleep-related neurogenic tachypnea
  - Sleep-related laryngospasm
  - Sleep choking syndrome