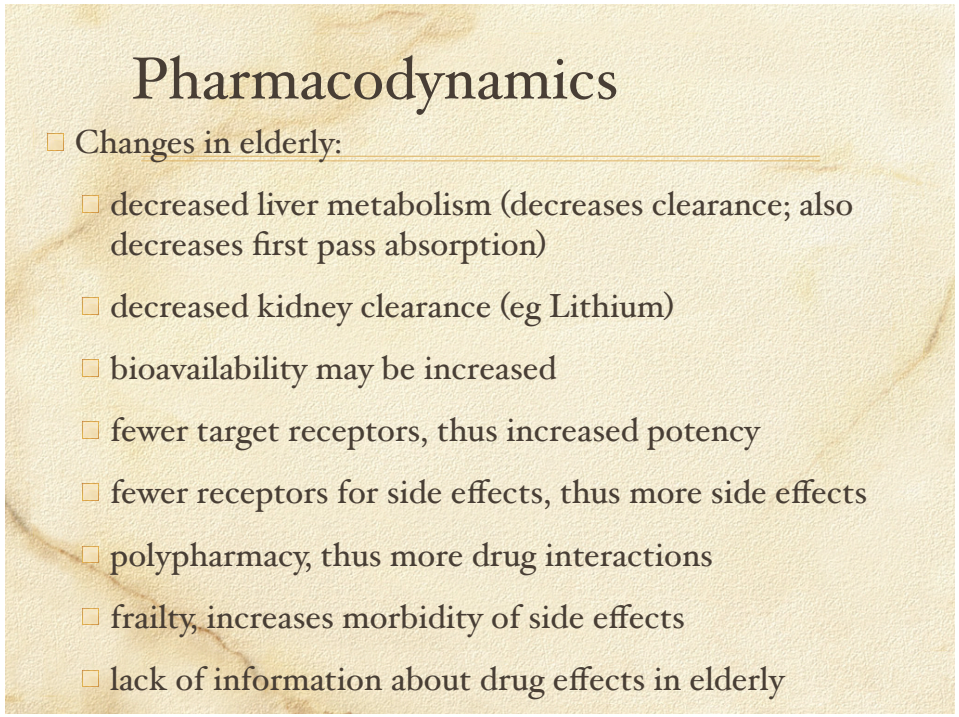
Geriatric Psychopharmacology

Henry Olders, MD, FRCPC
McGill University
SMBD - Jewish General Hospital

Outline

- Pharmacodynamics
- How patients present to psychiatry
  - affective disorder is common
- hypothesis: connection between sleep patterns and affective disorder
- treatment of bipolar spectrum disorders
- next week: sleep, delirium, dementia, psychosis
  omega-3; vitamin B12



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certain drugs take 3-4 x as long to be metabolized, eg desmethyldiazepam (active metabolite of diazepam). t 1/2 80-120 hours in young adults; say 300 in elderly, almost 2 weeks.

bioavailability

eg reduced density of muscarinic receptors - increases risk for cognitive impairment with anticholinergics
reduced dopamine D2 receptor density - increased risk of EPS with antipsychotics
up to 35% of drug trials exclude subjects on the basis of age.

Pharmacodynamics - 2

- ⇓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
- Bottom line: Start low, go slow!

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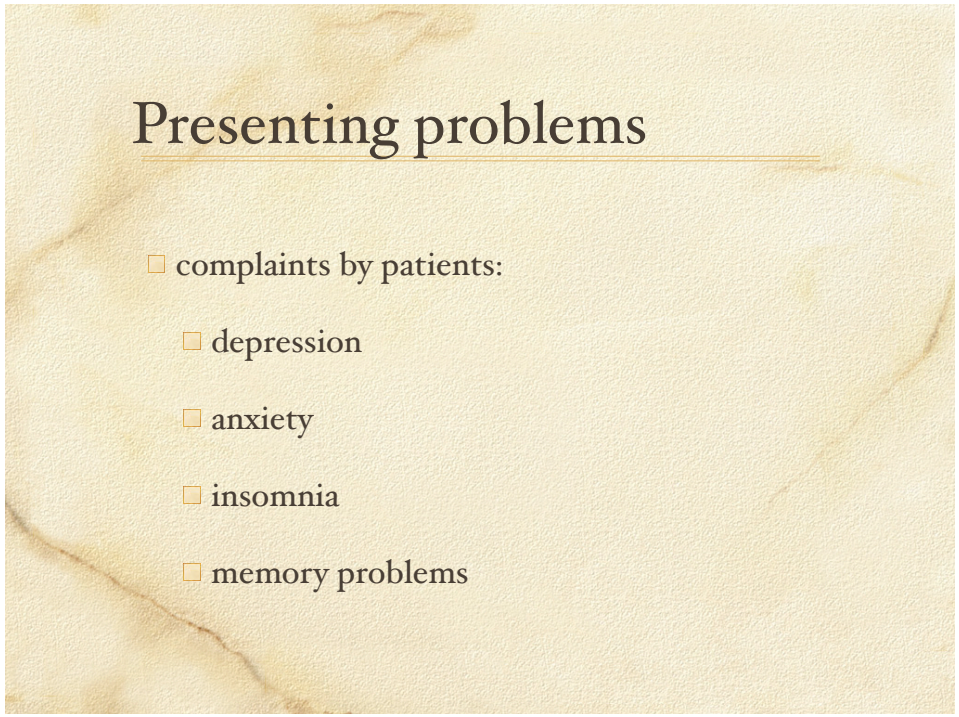
So that's it – all you need to know about geriatric psychopharmacology!



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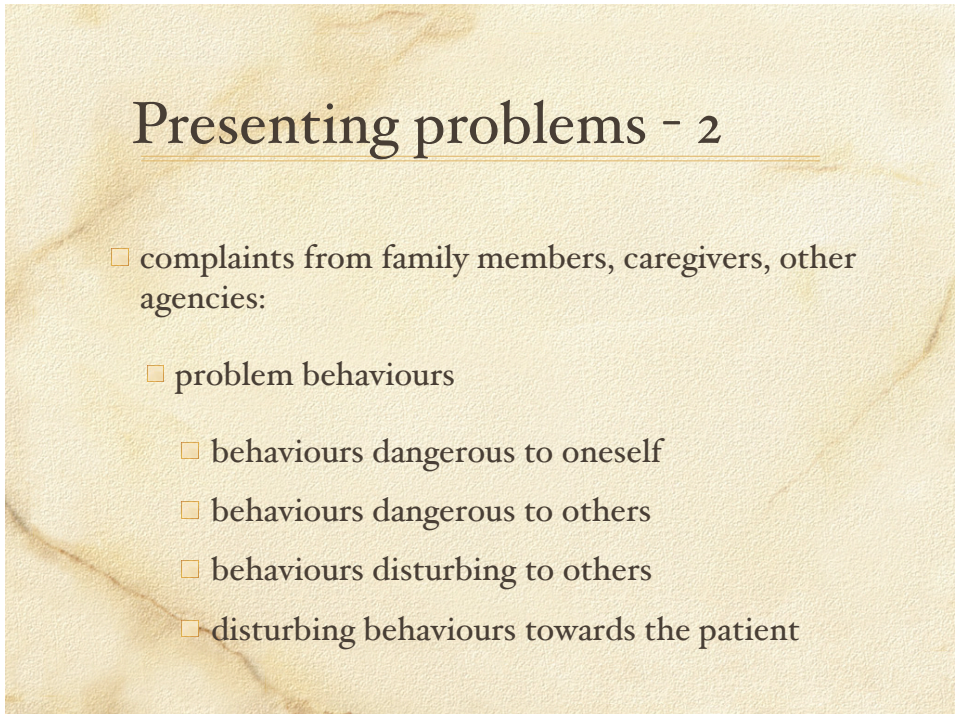
Fortunately, the complaints that patients themselves bring to a psychiatrist are quite straightforward in terms of arriving at a diagnosis and in formulating a treatment plan, which often includes medication.



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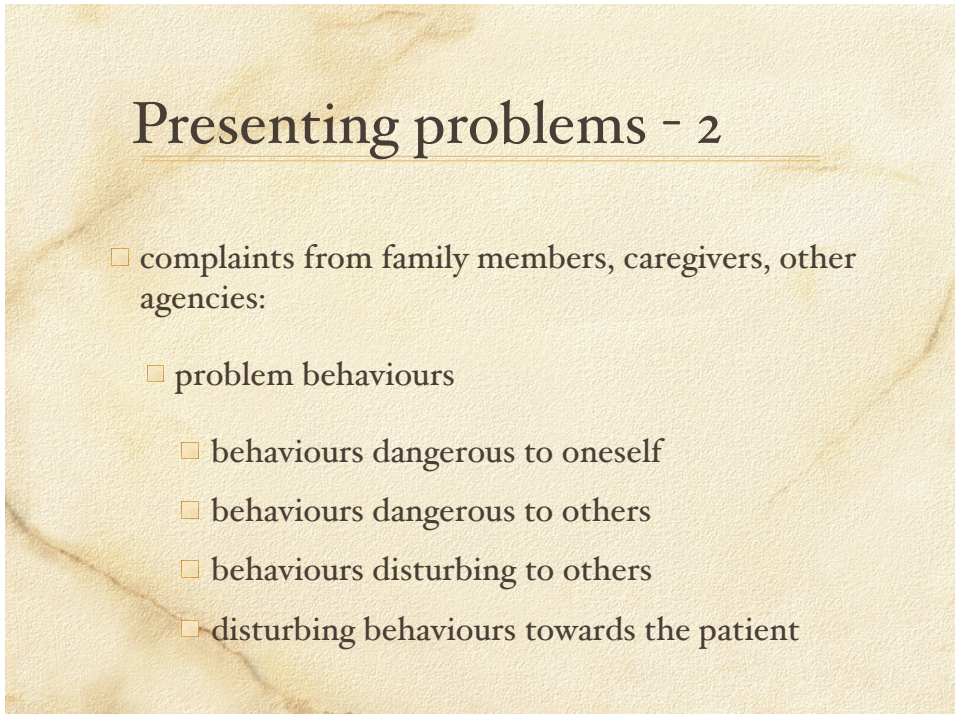
When a patient is brought to the psychiatrist by family members, a foster home proprietor, the CLSC, or the police, things are rarely as straightforward. Here are some examples of the types of problems which prompt intervention.

behaviours dangerous to oneself:

taking inappropriate risks, eg in mania
failing to provide oneself with the necessities of life
forgetfulness resulting in dangerousness to self
refusal of essential services
suicidal behaviour



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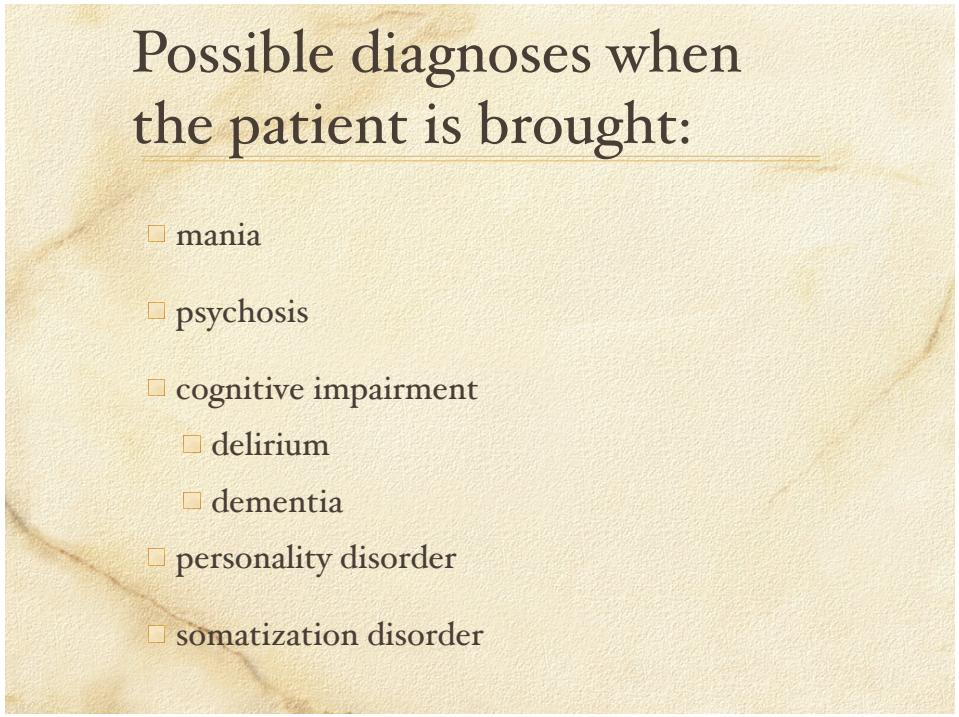
behaviours dangerous to others:
physical violence or threats of violence
taking inappropriate risks with others' welfare
forgetfulness resulting in dangerousness to others

behaviours disturbing to others:
excessive charity or spending; living in filth; poor personal hygiene; refusing health evaluations or interventions.

disturbing behaviours towards the patient:
financial, physical, or psychological abuse of the patient; neglect



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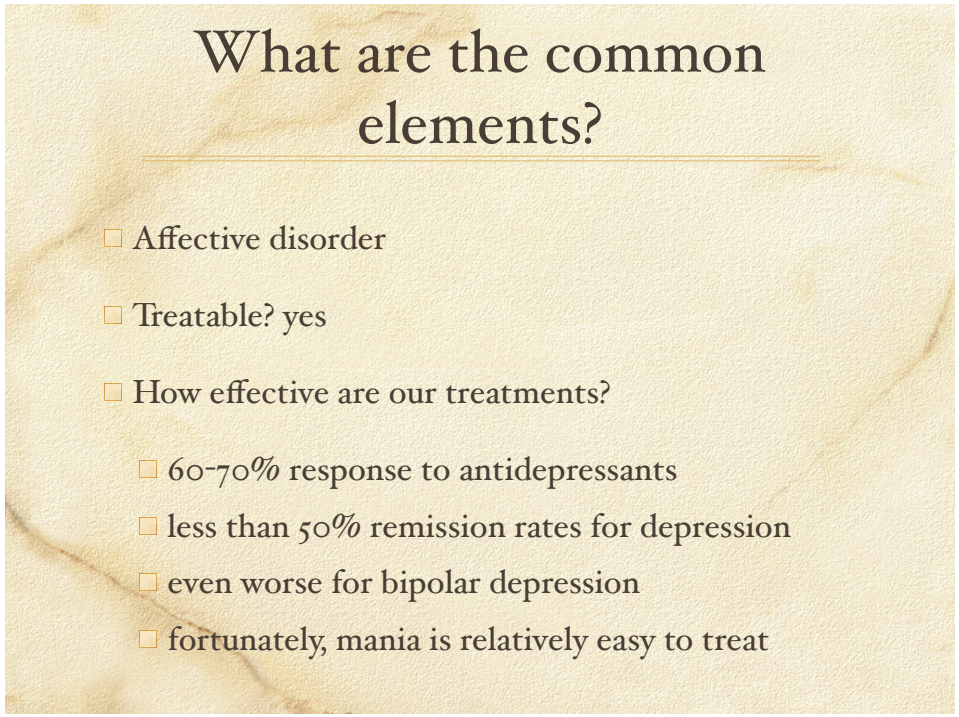
What all of these problems have in common is a lack of insight on the part of the patient. This occurs in manic states, psychoses, and in cognitive impairments, whether due to delirium or dementia. Patients with personality disorders or somatization disorders also often deny psychiatric problems.

My clinical experience is that in many of these cases where the patient presents with problem behaviours and a lack of insight into their behaviour, one will see some manic symptoms such as irritability, impulsivity, and pressured speech. What this means in practice is that if we intervene to deal with these manic symptoms, we can reduce or eliminate the problem behaviour which prompted the consultation, even if the underlying dementia or personality disorder remains unchanged.



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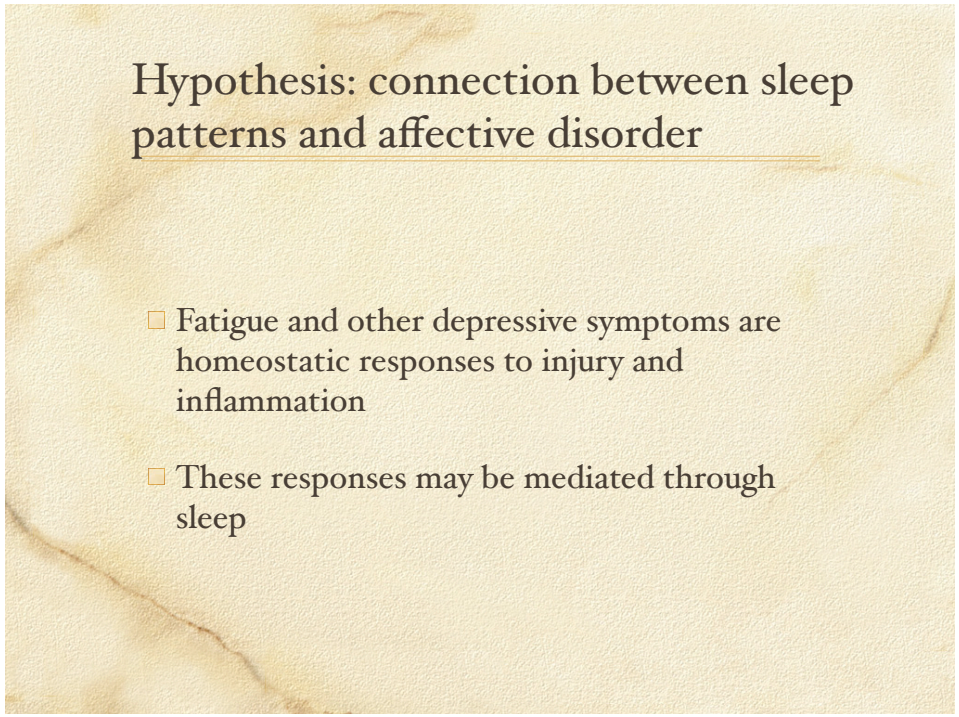
Thus, we have a group of disorders including depression, anxiety, mania, as well as a variety of conditions where the problem behaviours prompting a request for psychiatric intervention, may be caused by manic symptoms. Of course, the commonality here is the affective disorder, which we should be able to treat easily.

The fact that we have good treatments for mania may be why most patients with bipolar disorder spend most of their lives being depressed.



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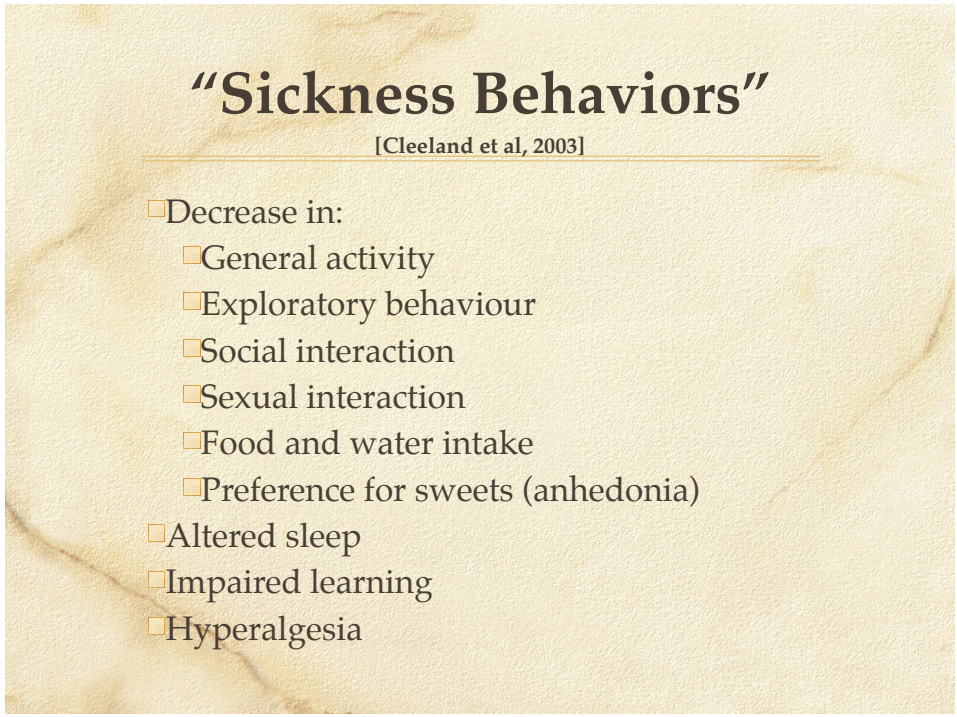
Suppose you're a wild animal, say a wolverine, and you are in a fight, and get a deep gash from your shoulder down to your groin. Obviously, you can't go to your friendly neighbourhood veterinarian to get stitches. So what do you do? The best thing to do would be to keep as still as possible, while the wound knits together enough so it won't rip open when you do move around. How can you stay as still as possible?
One way is to stay asleep. If you develop other depressive symptoms such as fatigue, lack of energy, lack of appetite, lack of sexual interest, you will also be less likely to go looking for food or a mate. Even better if you have pain all over, like in fibromyalgia, so that any movement is avoided.

My hypothesis is that there is a mechanism which connects the injury to the depressive symptoms, built in by evolution because it has survival value.



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Here's what I think happens: the injury causes inflammation; one of the inflammatory responses is for white blood cells to produce a number of different signalling molecules called cytokines, which have a number of physiological effects. Certain cytokines, such as interleukin-2 or interferon-alpha, induce what is known as "sickness behaviour". We don't know how these pro-inflammatory cytokines induce these changes in behaviour.
Another effect of cytokines is to increase the amount of sleep.
Although there may be a direct effect on cytokines in producing symptoms of fatigue, anorexia, and so on, there is evidence that increased sleep, particularly increased REM sleep, can produce those symptoms even without inflammation.
What I'm positing is that at least some of the sickness behaviour symptoms are indirectly caused by inflammation through its role in increasing sleep.
The implication is that excessive sleep, specifically excessive REM sleep, can cause depressive symptoms, even in the absence of inflammation or injury.
Sleeping patterns affect how much sleep and what type of sleep we get, and sleep patterns are a behaviour, thus modifiable.

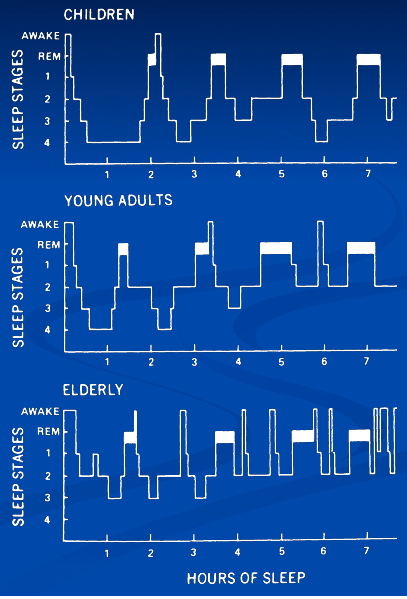
Characteristics of Sleep

- 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%

What are the characteristics of sleep?

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



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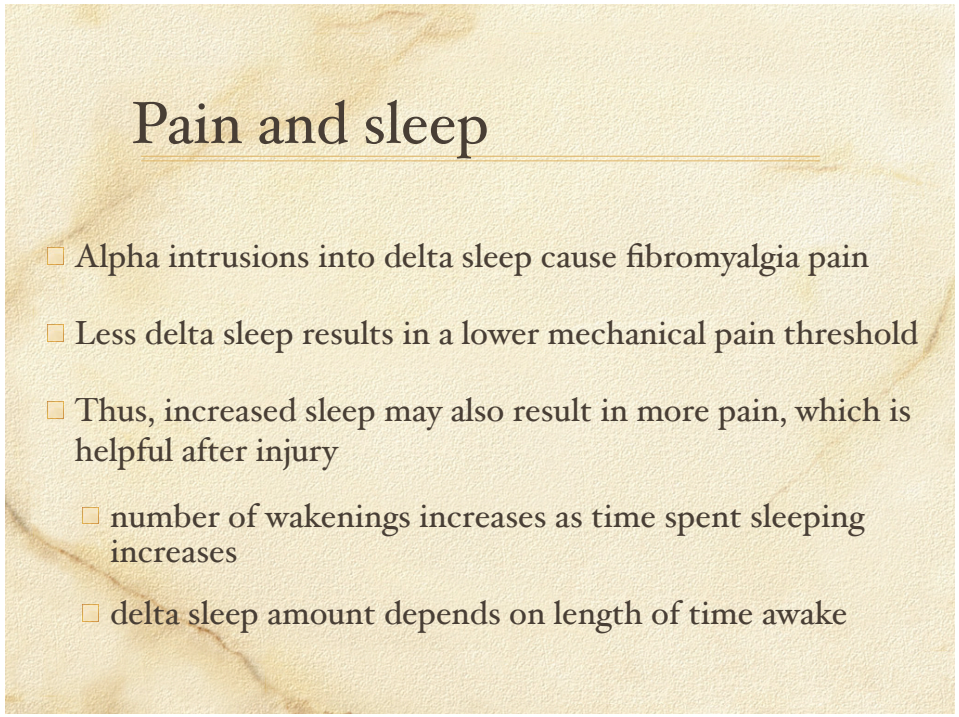
Here we have three typical somnograms, showing the stages of sleep, in children, young adults, and the elderly.



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This suggests that one can reduce pain by increasing the quantity and quality of delta sleep.

The less time spent in bed, the better the quality of sleep.

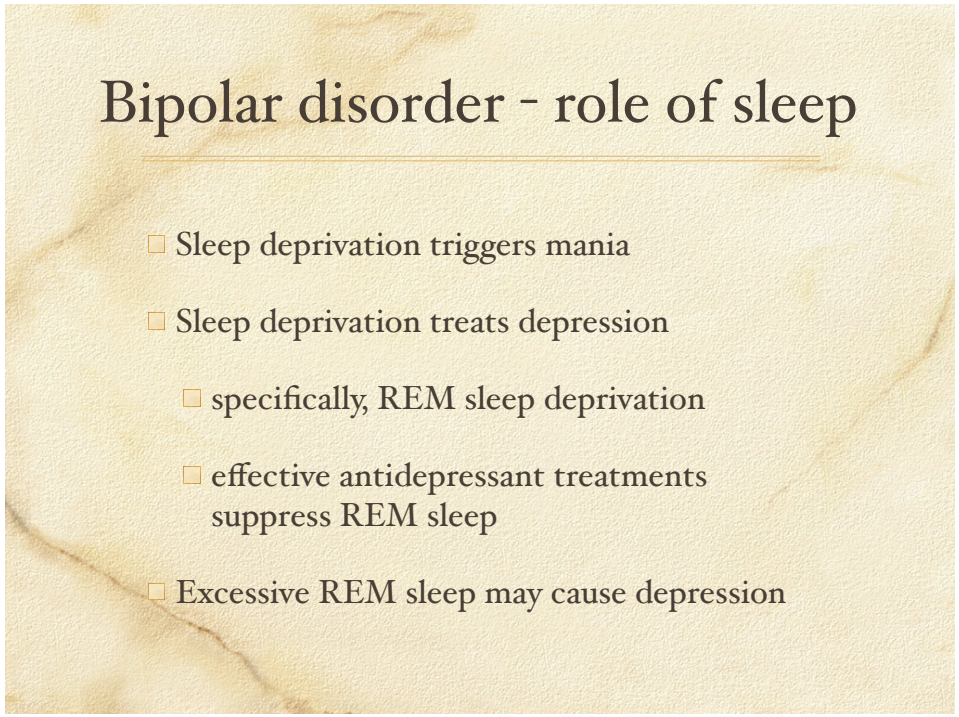
The longer time spent awake, the more delta sleep.

Certain medications increase delta sleep, eg amitriptyline (Elavil), gabapentin (neurontin), olanzapine (Zyprexa), trazodone.

Delta Sleep

- Delta sleep is associated with perceived good sleep [Silberfarb et al, 1985]. Its absence is associated with waking up exhausted [van Diest & Appels, 1994]
- Delta sleep and pain:
  - Selective disruption of delta sleep mimics fibromyalgia [Lentz et al, 1999]
  - Increased delta sleep may improve mechanical pain tolerance [Onen et al, 2001]
  - IBS patients have 70% less delta sleep than controls [Rotem et al, 2003]
  - Noise stimuli that disrupt delta sleep in normals causes unrefreshing sleep, diffuse musculoskeletal pain, and tenderness [Moldofsky, 2001]

If you want references for this stuff, here is a slide from a talk I gave to the McGill Palliative Care people last fall.



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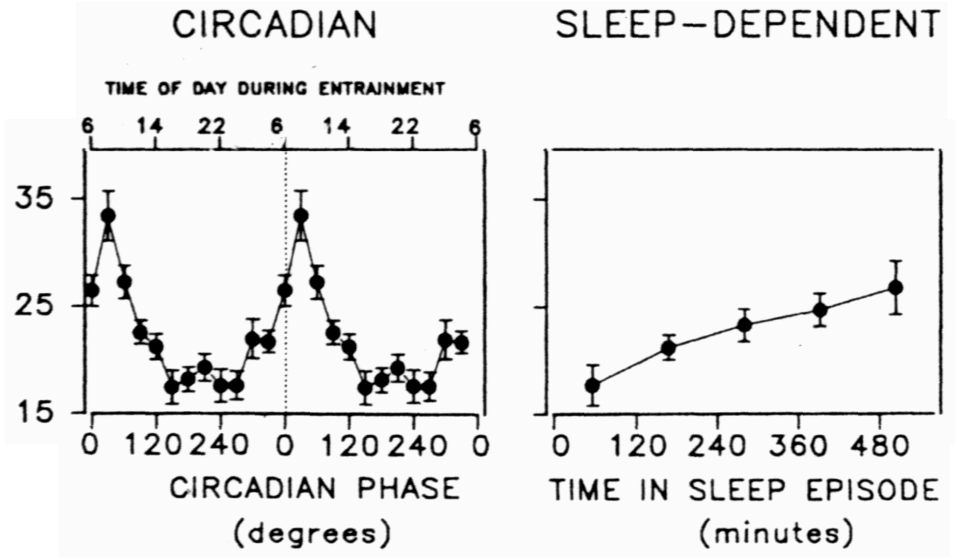
Even partial sleep deprivation which reduces REM sleep is effective against depression.

Effective antidepressant treatments which suppress REM sleep include tricyclics, SSRIs, ECT, exercise, and vagus nerve stimulation.

How does one get too much REM sleep?
Some medications increase REM sleep: reserpine and benzos are two examples; self-medication with alcohol also increases REM sleep. Reserpine is no longer used to treat hypertension because it causes depression. Benzos and alcohol have a paradoxical effect - they suppress REM sleep initially, but as blood levels drop, there is a rebound increase in REM sleep. Also, these medications increase the likelihood of sleeping longer or later, thus increasing the total amount of REM sleep.

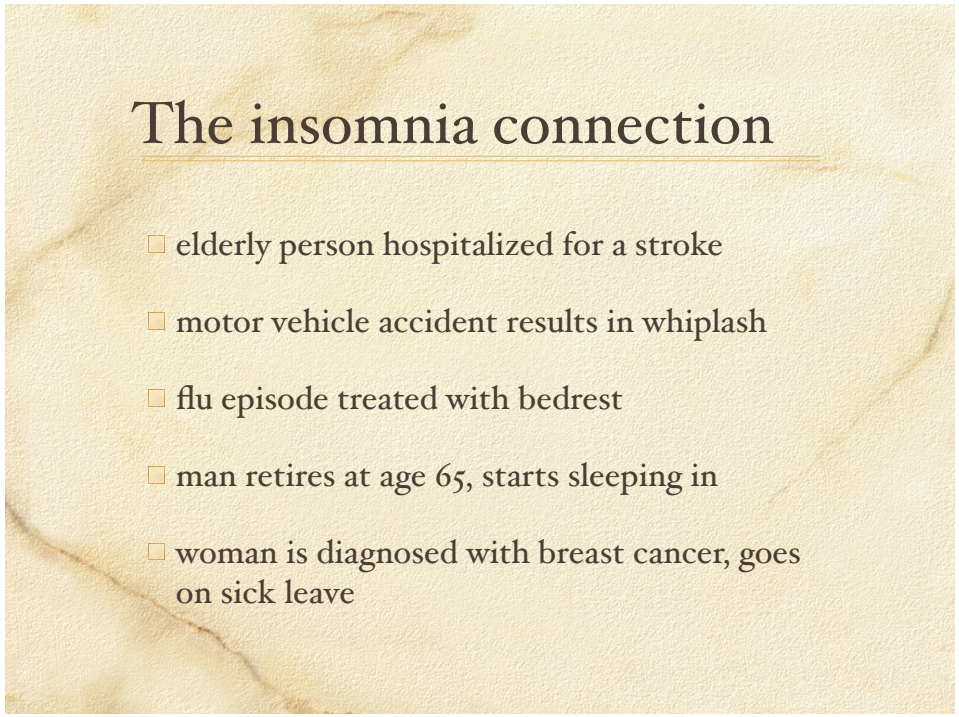
However, a very effective way to increase REM sleep is by sleeping longer or getting up later, even without medication.

REM sleep (% of TST)



this slide shows how REM sleep peaks in the morning, around 8 or 9 am, if we are sleeping at that time.

Thus, even a small amount of additional sleep in the morning has a major impact on REM sleep, whereas afternoon or evening sleep has very little effect.



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The stroke victim, if bedridden, has little choice but to sleep more, with or without the influence of inflammatory cytokines.

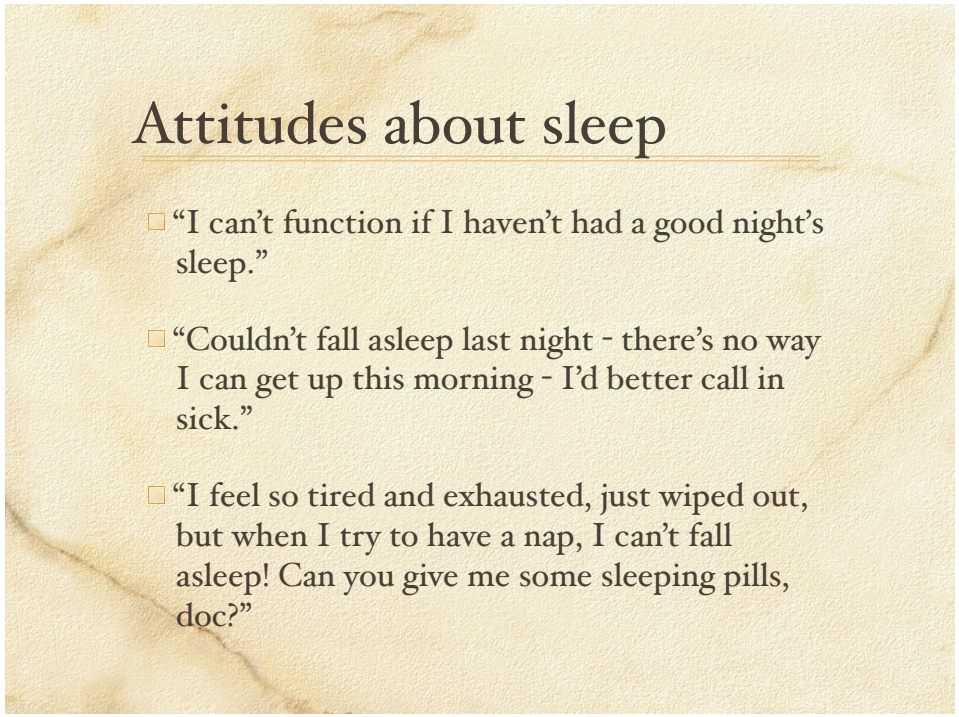
A relatively minor injury may be treated with bedrest and time off work, especially if there may be a claim against the other driver. What if the disability lasts longer than the injury requires?

Any sort of viral illness results in cytokines such as interferon being produced, thus the sickness behaviours and the increased sleep. When the illness wanes, what if the person continues to spend excess time in bed?

Retirees may sleep more than they need, without any medical reason, simply because of increased opportunity and possibly a lack of other activities to fill in the time.

People diagnosed with a serious illness, or other people dealing with a significant loss, may attempt to use sleep to escape psychological pain.

In each of these scenarios, when the person starts sleeping more than they need, they will develop insomnia – difficulty falling asleep or staying asleep.



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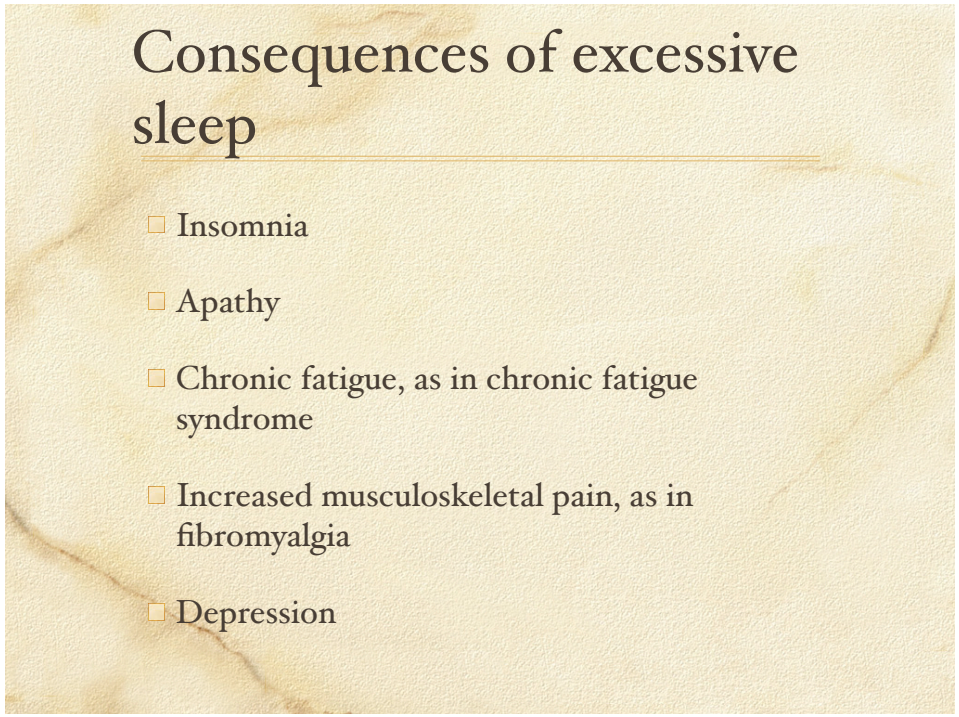
All of us have nights when we don't sleep well. Perhaps too much coffee or alcohol the night before; anxiety; or for no apparent reason. As medical students, we learn that even being up all night doesn't prevent functioning the next day. We may not like it, but we know it can be done.

Some people don't believe that. Poor sleep, even for one night, may prompt changes in sleep patterns, such as getting up late or going back to bed. How does this affect their sleep the next night?

What's worse, sleeping late increases the amount of REM sleep drastically. This seems to cause depression in people, although there are other factors, such as genetic predisposition or omega-3 fatty acids that play a role. For those not prone to depression, excessive REM sleep seems to produce other symptoms of "sickness behaviour"; fatigue is the most crippling of these symptoms.

If the person interprets their fatigue as being caused by lack of sleep, they will attempt to sleep even more, or take more sleeping pills to try to overcome their insomnia. Both



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When you try to sleep longer than you need, you develop insomnia. If the additional sleep is in the morning, you will get too much REM sleep, which produces symptoms of fatigue, apathy, anhedonia, loss of appetite. If the extra time in bed causes you to be awake for a shorter period of time, the amount of delta sleep decreases, which decreases mechanical pain threshold. If your sleep is disturbed, you may develop fibromyalgia symptoms.

So it may be that changes in sleep patterns cause the post-stroke apathy of the elderly bedridden stroke victim; the fibromyalgia that sets in for the whiplash patient; the chronic fatigue syndrome that develops after a viral infection; the insomnia and depression in the retired person; the fatigue and depression which plague the person with cancer.

Rising time and mood

Sleep pattern	effect on sleep	effect on mood
Early rising	insufficient REM	manic symptoms
Late rising	excessive REM	depressive symptoms
Variable rising times	circadian desynchronisation	affective instability

21

As people age, they tend to become more like morning larks, whereas young people are more likely to be night owls. This dimension is called “morningness-eveningness” and studies show that depressives report greater eveningness compared to controls; in other words, depressives get up later.

But what about early morning awakening - isn’t that strongly associated with depression? Yes, it is; and you might even consider it as a homeostatic mechanism to reverse the depression, as early rising reduces REM sleep and thus would have an antidepressant effect. But unfortunately, many elderly who have this symptom stay in bed or go back to bed; if asked the right questions, they will report that they sleep soundly from 6 to 9 am. So these people are really late risers, consistent with the table above.

Early rising becomes more common with age. I recall the orthodox Jewish woman who, every passover, would start getting up at 3 am to clean her house to ensure there were no crumbs of leavened bread anywhere. Within a few days, she would become frankly manic and get hospitalized.

Rising time and mood

Sleep pattern	effect on sleep	effect on mood
Early rising	insufficient REM	manic symptoms
Late rising	excessive REM	depressive symptoms
Variable rising times	circadian desynchronisation	affective instability

22

In nursing homes, it's not uncommon for patients to be put to bed soon after supper. This is mostly for the convenience of the nursing staff, but patients rarely complain because there's usually little to occupy them in the evening. What do you think happens?

An eighty-year old needs about 6 hours of sleep, maybe even less, as sleep need decreases with age. So if they're in bed at 8 pm, they'll be wide awake at 2 or 3 am, either wandering around, or banging on the bedrails, or crying out for someone to help them to the toilet. And chances are that their cognition is even more impaired at this time of night than it usually is in the daytime, as brain functioning is strongly influenced by circadian rhythm.

The early rising stimulates manic symptoms, such as irritability and aggression, talking too much and talking loudly, and uninhibited behaviours such as sexual acting out. Up to 80% of nursing home patients may manifest activity disturbances or aggression.

Those behaviours are unacceptable, so the usual reaction of staff is to sedate the patient, often with antipsychotic medication. Now the patient may sleep, but they're getting too much sleep, and so they may become depressed. 42% of nursing home patients have depressive symptoms.

Rising time and mood

Sleep pattern	effect on sleep	effect on mood
Early rising	insufficient REM	manic symptoms
Late rising	excessive REM	depressive symptoms
Variable rising times	circadian desynchronisation	affective instability

Of course, you don't have to be in a nursing home to get up too early and develop manic symptoms. And a bit of euphoria can't be too bad.
Unfortunately, dysphoric mania seems much more common in the elderly than euphoria.

Many patients present with a complaint of depression, but may have prominent symptoms of irritability, verbal or even physical aggression, loud and/or pressured speech. Whether we call this a mixed state, or dysphoric mania, or agitated depression, these conditions are very difficult to treat. They may be difficult to recognize, even; younger patients are often labeled as borderline personality disorders.

If we obtain an good sleep history, we may find a pattern of variable rising times, early one day, late the next, with mood and energy levels which fluctuate accordingly.

My feeling is that all of these patients that have prominent mood fluctuations in response to changes in sleep patterns, have a bipolar spectrum disorder.

Treating bipolar spectrum disorders

- First, get an adequate picture of symptoms and sleep patterns
- If the patient's sleep pattern corresponds to their mood, modify the sleep pattern

Mania: aim for longer, later sleep

- Use sedating meds:
  - sedating mood stabilizers
  - sedating antipsychotics
  - benzodiazepines
- Control timing of medications:
  - avoid daytime sedation

Depression: sleep shorter, get up earlier

- Reduce REM sleep without triggering mania
- go to bed later; get up earlier, consistently
- daytime naps should be very brief
- morning psychostimulant if early rising problematic
- coffee, bright light helpful
- antidepressant if on a mood stabiliser
- consider lamotrigine for resistant cases
- ECT as a last resort

Mood stabilisers - Lithium

- lithium toxicity can be a big problem
  - medication interactions, eg diuretics
  - occult infections, eg UTIs
  - vomiting or diarrhea
  - intentional or unintentional overdosing
  - gradually decreasing kidney functioning

Mood stabilisers - valproate

- Parkinsonian syndrome
  - can develop after a year or more
  - can be totally debilitating
  - probably more likely in individuals who are sensitive to parkinsonism with atypical antipsychotics

Mood stabilisers - topiramate

- narrow-angle glaucoma
  - both a side effect and a contra-indication
  - consult an opthalmologist

Antipsychotics - olanzapine

- May be more effective against mania than lithium
- Effects on sleep:
  - sedative
  - increases delta sleep
  - suppresses REM sleep

Antipsychotics - flupenthixol

- Believed to have antidepressant effects
- Possibly has mood-stabilizing effects (Gruber & Cole 1991)
- Available as a depot preparation

Antipsychotics - methotrimeprazine (Nozinan)

- 2-3 times as sedating as chlorpromazine
- not available in the U.S.
- po liquid, im preparations

Depression vs. agitated depression

- Why make the distinction?
  - Agitated depressions may be mixed states of BAD
  - agitation worsens with antidepressants
  - antidepressants may worsen suicide risk

Diagnosis of agitated depression

- Look for manic symptoms:
  - irritability
  - agitation
  - pressured speech
  - flight of ideas
  - sleep:
    - inability to sleep
    - reduced sleep
    - advanced sleep phase

Past psychiatric history

- periods of manic or hypomanic behaviour
- prior treatment with mood stabilisers, ECT
- alcohol or drug abuse
- seasonal symptoms
- in women:
  - postpartum depression or psychosis
  - peri-menopausal depression (involutional melancholia
  - premenstrual symptoms

Family psychiatric history

- Bipolar affective disorder
  - treatment with mood stabilisers
- Depression
  - suicidality
  - hospitalization
  - treatment with ECT
- Psychotic disorders
  - schizophrenia
  - paranoia
- Alcohol and drug abuse

Treatment of retarded depression

- Stimulant antidepressants
- Early rising
- Psychostimulants
- order of treatments

Treatment of agitated depression

- Antidepressants alone
- Mood stabilizers
- Addition of antidepressants
- Regulation of sleep pattern

Sedating antidepressants: remeron; elavil; trazodone

Delirium

- Look for causes:
  - elderly females: UTI
  - 15-25% of over-65s have B12 deficiency
- Aim to correct a disturbed sleep-wake cycle
- Apathetic delirium: psychostimulants
- Agitated delirium:
  - olanzapine may worsen delirium
  - haloperidol

Dementia

- Rule out delirium
- Treat depression
- Give B12
- Cholinesterase inhibitors:
  - donepezil (Aricept) easiest to use
  - galantamine (Reminyl) may be more effective
  - rivastigmine (Exelon) targets more receptor types

Psychosis

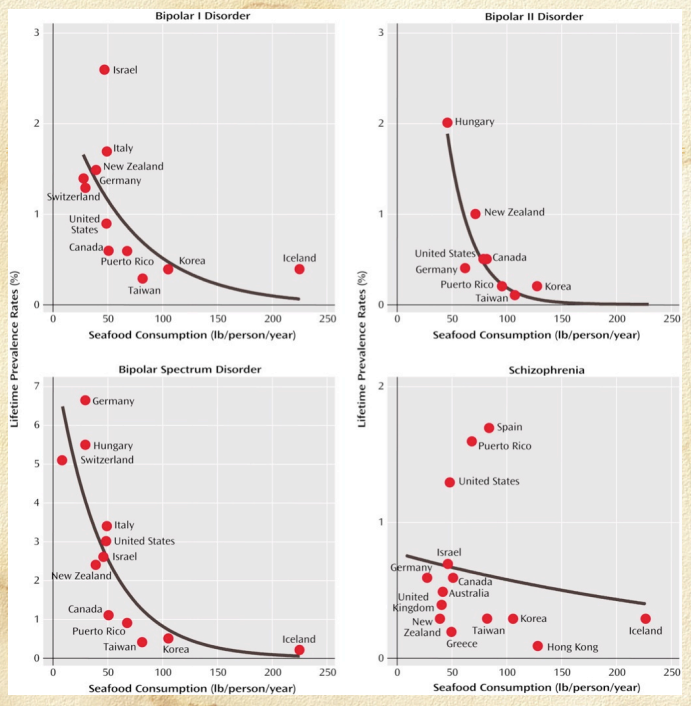
- If first-onset, probably organic
- steroid psychosis may be related to sleep deprivation
- give B12

Sleep

- Sleep restriction for insomnia
- enhance slow wave sleep
- most sedatives:
  - may cause depression
  - are disinhibiting
  - contribute to falls
  - impair memory
  - are ineffective after a couple of weeks

Omega-3 fatty acids

- important component of cell membranes which use electrical signals: heart, retina, brain
- anti-inflammatory (omega-6s are pro-inflammatory)
- current diets: 1:25 omega-3:omega-6 (vs 1:1 pre-agrarian)
- cold-water fatty fish only good source


Bipolar I Disorder
Israel
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New Zealand
Germany
Switzerland
United States
Canada
Puerto Rico
Korea
Iceland
Taiwan
Bipolar II Disorder
Hungary
New Zealand
United States
Canada
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Puerto Rico
Korea
Taiwan
Bipolar Spectrum Disorder
Germany
Hungary
Switzerland
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United States
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New Zealand
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Puerto Rico
Taiwan
Korea
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Schizophrenia
Spain
Puerto Rico
United States
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Germany
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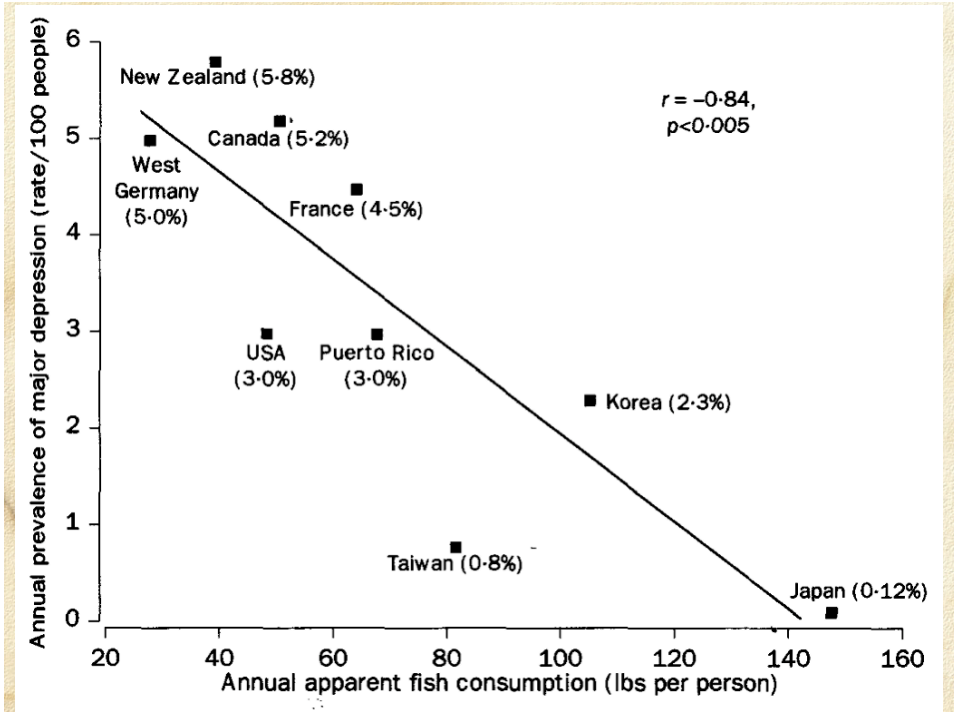
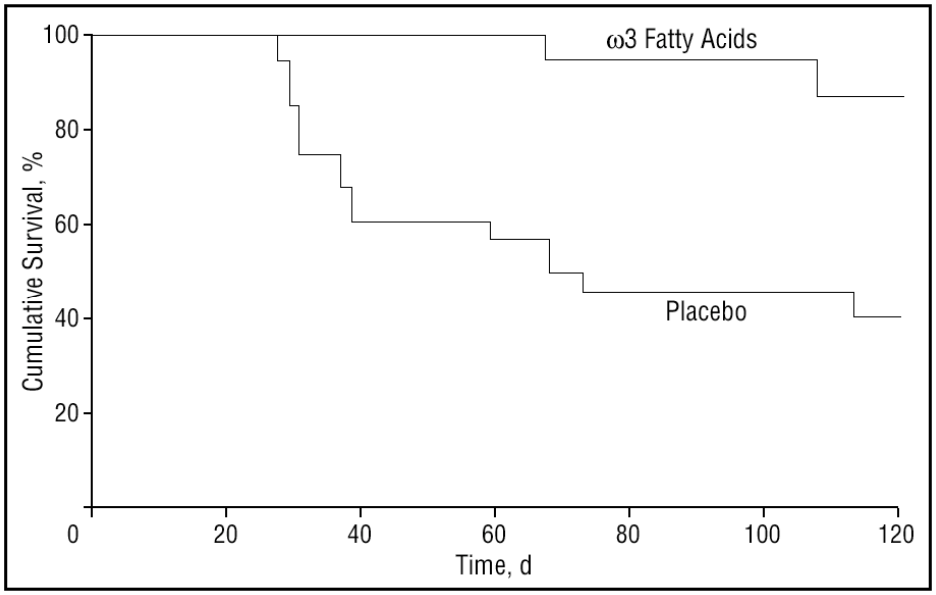
Australia
United Kingdom
New Zealand
Taiwan
Korea
Iceland
Greece
Hong Kong
Lifetime Prevalence Rates (%)
Seafood Consumption (lb/person/year)


Annual prevalence of major depression (rate/100 people)
6
5
4
3
2
1
0
New Zealand (5·8%)
Canada (5·2%)
West Germany (5·0%)
France (4·5%)
USA (3·0%)
Puerto Rico (3·0%)
Korea (2·3%)
Taiwan (0·8%)
Japan (0·12%)
r = –0·84, p<0·005
20
40
60
80
100
120
140
160
Annual apparent fish consumption (lbs per person)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Cumulative Survival, %
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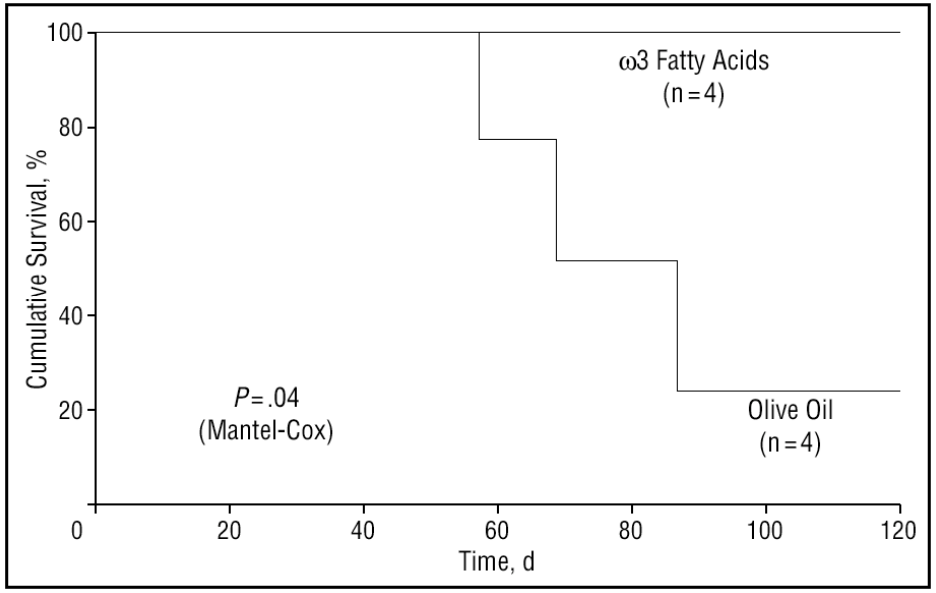
ω3 Fatty Acids
Placebo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Cumulative Survival, %
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Olive Oil
(n = 4)
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80
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http://henry.olders.ca/psychiatry/