

Sleep and Quality of Life in Cancer Patients

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Symptoms in Cancer

- Caused by the cancer or by treatment
 - Pain
 - GI symptoms including nausea and diarrhea
 - Wasting / cachexia
 - Fatigue
 - Cognitive impairment
 - Anxiety
 - Depression
 - Insomnia

Effects of cancer symptoms

- Delay in treatment
- Premature termination of treatment
- Functional impairment
- Significant distress

Outline

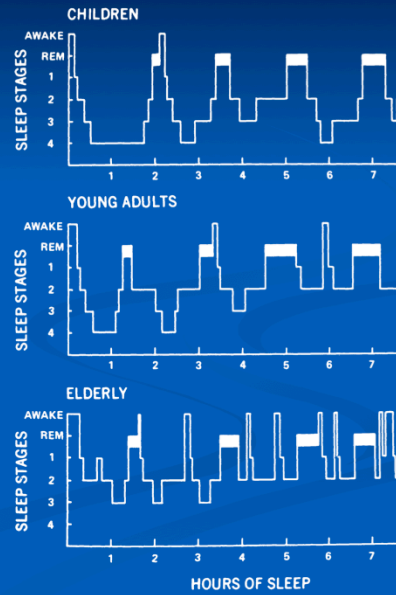
- Sleep 101
- REM sleep and depression
- Cancer-related fatigue
 - Sleep and fatigue
 - Role of insomnia
- Cytokines and sickness behaviors
 - Role of sleep
- Interventions to decrease symptoms
- Strategies affecting sleep

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%

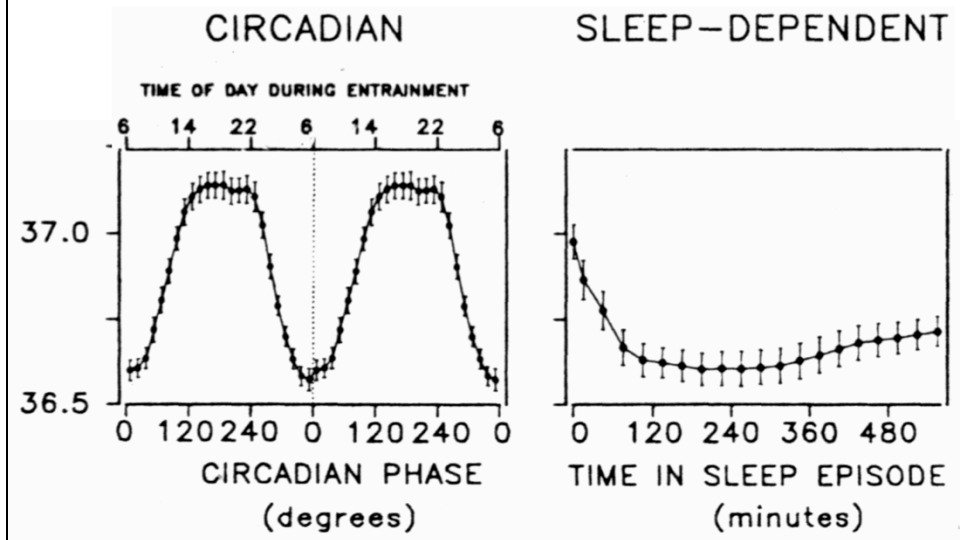
EEG Stages of Normal Sleep

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

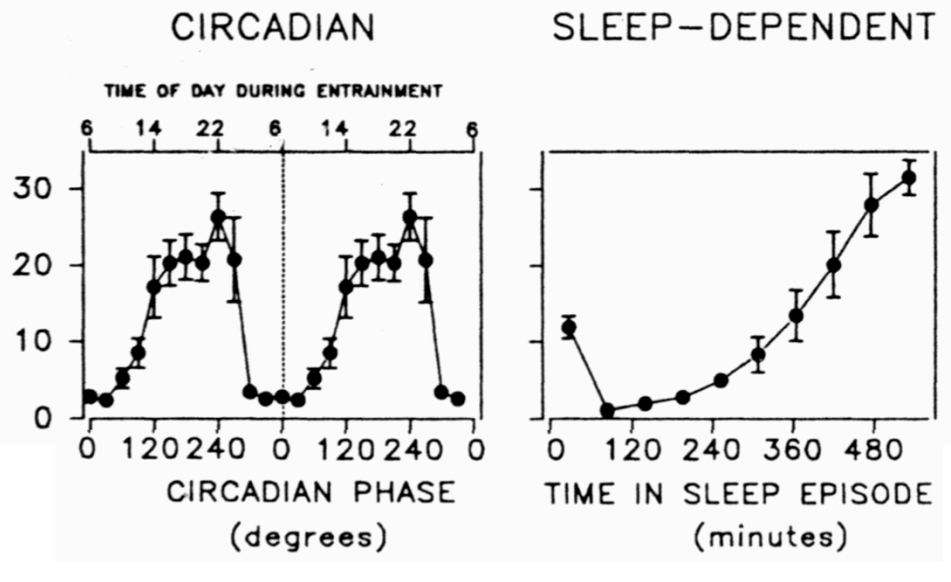


Body Temperature (deg. C)

[Dijk & Czeisler, 1995]



Wakefulness (% of recording time)



Nocturnal Sleep Propensity

Helmus et al 1996



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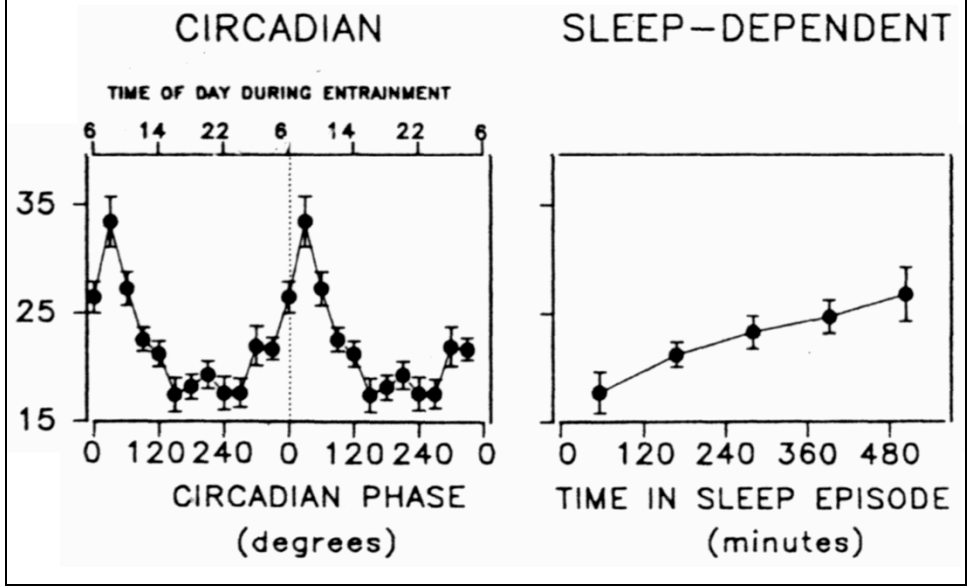
Sleep
Latency
(minutes)

Time of night

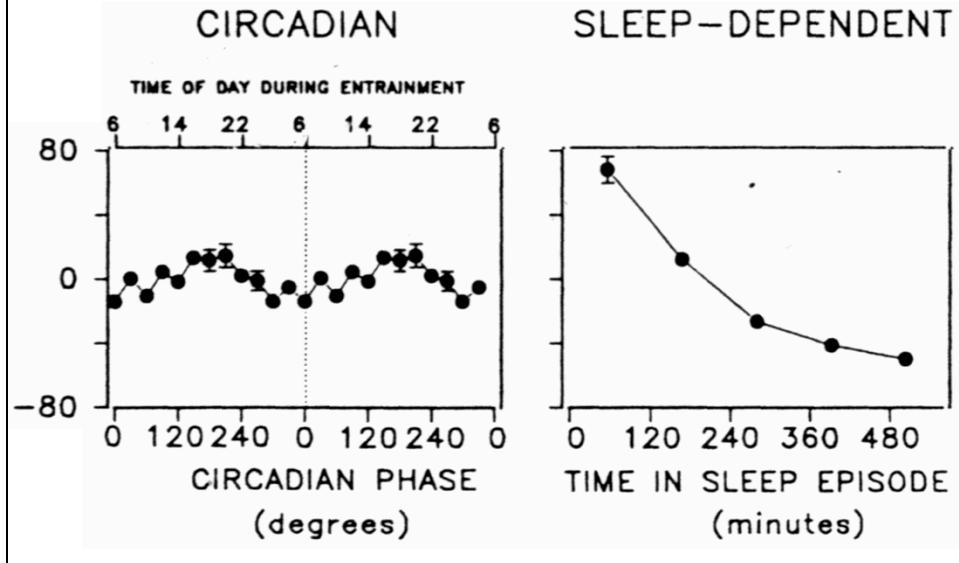
Suppose you took people who were sleeping normally, put them in the sleep lab, and then woke them up at different times during the night. Keep them awake for 10 minutes, then let them go back to sleep and time how long it takes for them to fall back to sleep. What time of the night do you think they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



Slow-wave Activity (deviation from mean, %)



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]

take-home message

- delta sleep
 - restful, refreshing sleep
 - beginning of night
 - increases with length of prior wakefulness
 - Involved with pain
- REM sleep
 - must-have
 - length of each period increases through the night
 - circadian influence very powerful
 - REM propensity peaks at 8 am

Total Sleep Deprivation (TSD)

- brings about antidepressant response in 60%
[Beersma & van den Hoofdakker 1992; Gill et al 1993]
- can trigger mania in BAD pts [Kasper & Wehr 1992]
- Possibly triggers mania in normals [Wright 1993]

Total sleep deprivation leads to an immediate and substantial reduction of depressive symptoms in 60% to 70% of patients with major depression. This effect usually happens the same afternoon after only one night of no sleep. Considering that even the newer antidepressants are effective in the same percentage of patients, and take at least 2 or 3 weeks to work, total sleep deprivation certainly has something to recommend it. So why isn't it used?

Unfortunately, the antidepressant effect is usually very short-lived. Long naps, on average 2 hours, caused a return of depressive symptoms. The presence of REM sleep during the nap was associated with this recurrence of depression.

Total sleep deprivation can also make some of these depressed people manic. Interestingly, total sleep deprivation has triggered mania in normal people.

You don't have to keep people up all night to treat their depression. Partial sleep deprivation late in the night also has a significant antidepressant effect.

REM Sleep and Depression

- Selective REM sleep deprivation has an antidepressant effect [Vogel et al 1975]
- Reserpine, which increases REM sleep, can cause depression [Faber & Havrdova 1981]
- REM sleep is increased in:
 - Depression [Thase et al 1994; Lauer et al 1995]
 - Suicidal patients [Agargun, 2003]
 - post-traumatic stress disorder [Harvey et al, 2003]
 - Irritable bowel syndrome [Orr, 2000]

What other evidence is there for the hypothesis that too much REM sleep is related to depression?

First, if you increase REM sleep, you can cause depression. For example, reserpine, a blood pressure medication which increases REM sleep, has depression as a side effect. Similarly, some beta-blockers, including timolol eye drops for glaucoma, can cause depression. These beta-blockers appear to also increase REM sleep..

A number of researchers have found that in depression, REM sleep is increased. Which came first, the chicken or the egg? In post-traumatic stress disorder, where symptoms of insomnia, decreased concentration, anhedonia, and social withdrawal, overlap symptoms of depression, REM sleep is also increased.

What about decreasing REM sleep? Here, the evidence is more compelling for a direct causal link. Selective REM sleep deprivation has an efficacy equivalent to that of a tricyclic antidepressant such as imipramine.

REM Sleep and Depression

- Antidepressant treatments, including SSRI's, TCA's, MAOIs, ECT, psychostimulants, light, and exercise, suppress REM sleep [eg, Nofzinger et al 1995]
- Amount of REM sleep suppression after initial TCA dose predicts clinical improvement [Höchli et al 1986]

Antidepressant treatments of all types, including medications, shock treatment, and even exercise, suppress REM sleep.

One notable exception is trazodone. But perhaps this explains why so many psychiatrists have given up on trazodone as not being a very effective antidepressant.

“Depressiogenic Theory of Sleep”

- “sleep may induce depression and sleep deprivation relieves it” [Wiegand et al, 1987]
- “the depressiogenic effect of sleep may be specifically due to rapid eye movement (REM) sleep”

Theory: late rising and depression

- Late Partial Sleep Deprivation (PSD), but not early PSD, is antidepressant [Leibenluft & Wehr 1992]
- This makes sense in terms of REM suppression, since REM propensity peaks in the morning, around 8 am
- Theory: Late rising leads to excessive REM sleep leads to depression
- I couldn't find any published studies of depression which looked at rising time

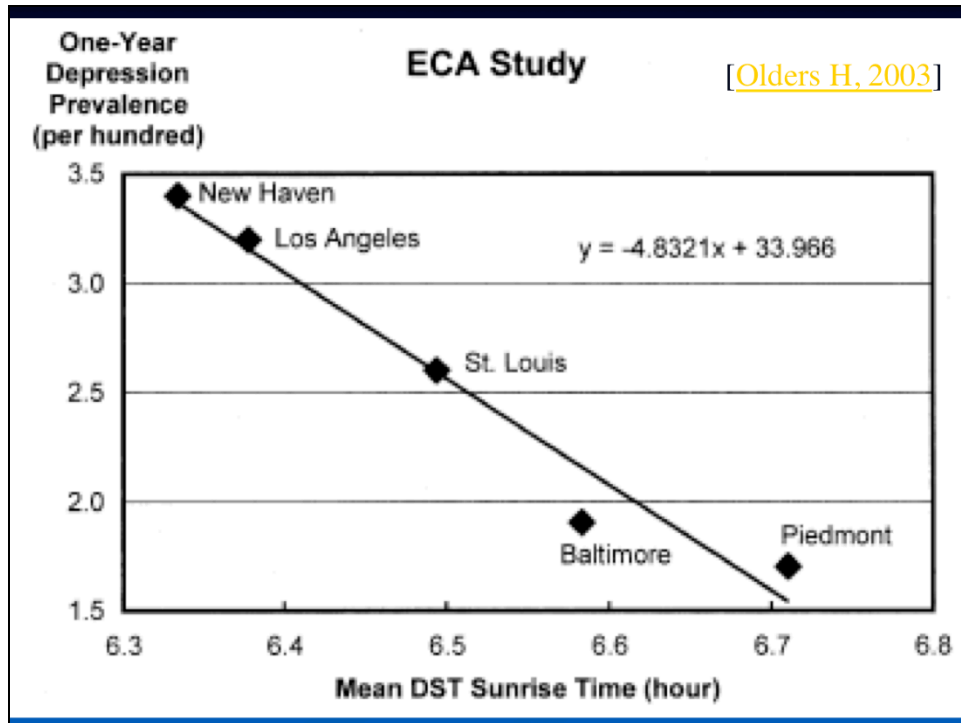
What happens if you sleep too much or get up late?

- Students sleeping 10 or more hours: worn-out, tired, lethargic, irritable, fuzzy thinking, difficulty getting going [[Globus, 1969](#)]
- Extended sleep impairs alertness [[Taub, 1983](#)]
- Late rising correlates with lower GPAs [[Trockel et al, 2000](#)]
- Longer sleep has higher mortality [[Kripke et al, 2002](#)]

If sleep deprivation removes depression, perhaps too much sleep causes depression. What happens when people sleep too much?

The Scientific Literature

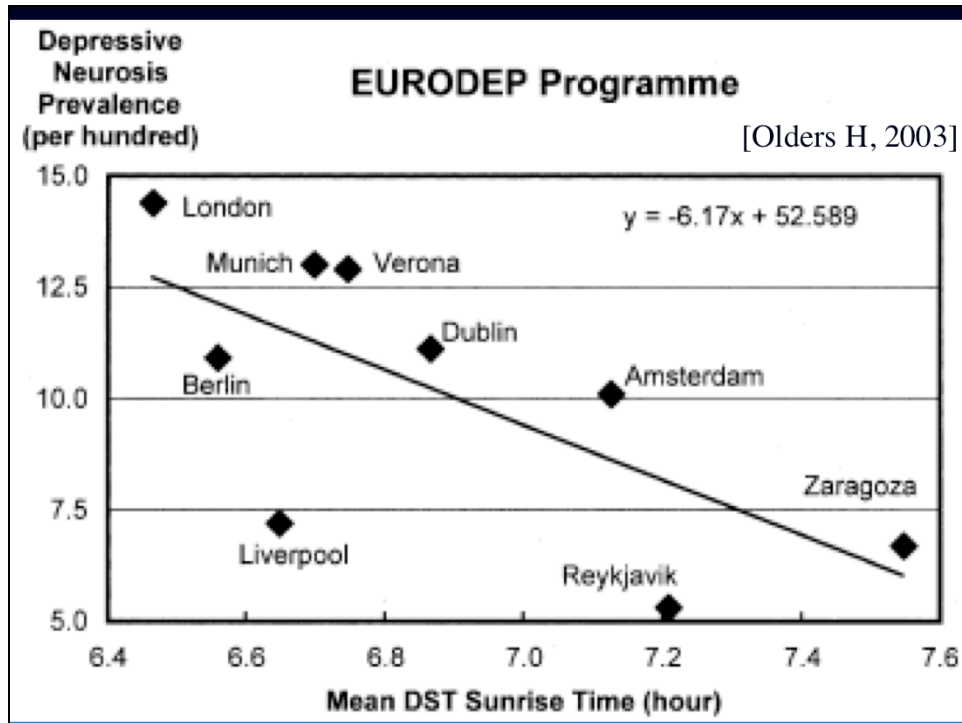
“At grammar-scole I lerned a verse, that is this, Sanat, sanctificat, et ditat surgere mane. That is to say, Erly rysyng maketh a man hole in body, holer in soule, and rycher in goodes.” [Anthony Fitzherbert (1470-1538): the Book of Husbandry, 1523]



When I plotted these prevalence figures against the times for sunrise for the various communities, it looked like this. The sunrise times are averaged over the whole year. The Pearson correlation coefficient was -0.895 ; probability $P = 0.0041$

What is the significance of this? The majority of people who live in urban centres get up by the clock, not by the time of sunrise. So if you live in a city where the sun gets up late in relation to the clock, you will be getting up relatively earlier than you would if you lived where the sunrise is earlier. Thus, residents of New Haven who get up at say, 6:00 am, would be getting up almost 15 minutes after the sun, on average, while people in Piedmont who also get up at 6:00 am would be beating the sun by 8 minutes, on average.

According to my hypothesis, getting up earlier would mean less depression. That's exactly what this graph shows.



If this were the only study for which this relationship existed, it wouldn't mean much. But a study which was published this past April in the British Journal of Psychiatry, termed the EURODEP Programme, looked at the prevalence of affective disorder in the geriatric population in 9 European cities. Again, when I plotted the prevalence figures for depressive neurosis against average sunrise times, I got a Pearson correlation coefficient of -0.776, $P = 0.0395$

- However, many cancer patients complain of fatigue. Most of these are not depressed.
- about 20% of cancer patients develop clinical depression (same order of magnitude as in the general population)
- Could it be that excessive REM sleep would result in depression in some people and fatigue in the rest?

Hypothesis: Excess REM Sleep causes Fatigue or Depression

- Chronic Fatigue caused by too much REM sleep occurs in:
 - Cancer
 - Chronic illnesses, eg
 - SLE
 - Arthritis
 - AIDS
 - Fibromyalgia
 - Chronic fatigue syndrome
- Depression caused by too much REM sleep occurs in:
 - Individuals with a genetic predisposition to depression
 - (those with high ratio of omega-6 to omega-3 fatty acids)

I think that if you get too much REM sleep, you will develop chronic fatigue. If you also have a genetic predisposition, the fatigue will become a full-blown depression.

This hypothesis that REM sleep might cause depression, known as the “depressiogenic sleep theory”, was put forward by Wiegand and his colleagues in 1987.

So, how can you get too much REM sleep? The easiest way would be to simply sleep more. However, this is often not as easy as it sounds. While some people are naturally long sleepers, most people who try to sleep longer, either by going to bed earlier, by getting up later, or by taking daytime naps, very soon develop difficulty sleeping, or insomnia. They would experience problems falling asleep, or they would wake frequently, or they would wake up too early. Or possibly all three.

If their insomnia gets treated with benzodiazepines, then the person will be able to sleep more than they need.

Definition of Fatigue

a subjective, unpleasant symptom which incorporates total body feelings ranging from tiredness to exhaustion creating an unrelenting overall condition which interferes with individuals' ability to function in their normal capacity [

[Ream & Richardson 1996](#)]

When talking about fatigue, there are many different ideas about what constitutes fatigue.

Cancer-related Fatigue

- Affects up to 99% of cancer patients [Blesch et al, 1991]
- Frequently is the most distressing symptom [Degner & Sloan 1995]
- Closely linked to insomnia [Graydon, 1994]
- May be identical to the fatigue in other chronic medical conditions or in Chronic Fatigue Syndrome [[Olders & Winningham, 2000](#)]


Sleep and Fatigue

- Cancer patients experience insomnia and fatigue even before treatment [Cimprich 1999]
- Fatigue is associated with inactivity, daytime napping, and fragmented nighttime sleep [Ancoli-Israel et al, 2001]
- More sleep is associated with more fatigue [Greenberg et al, 1993]

Questionnaire study: cancer fatigue and sleep

- Convenience sample of oncology outpatients
- Questions about sleep patterns and problems, fatigue, Beck depression inventory, demographics
- 125 useable questionnaires returned: 87 females, 32 males, mean age 55
- 53% had breast cancer
- BDI >20 (clinical depression): 11 patients

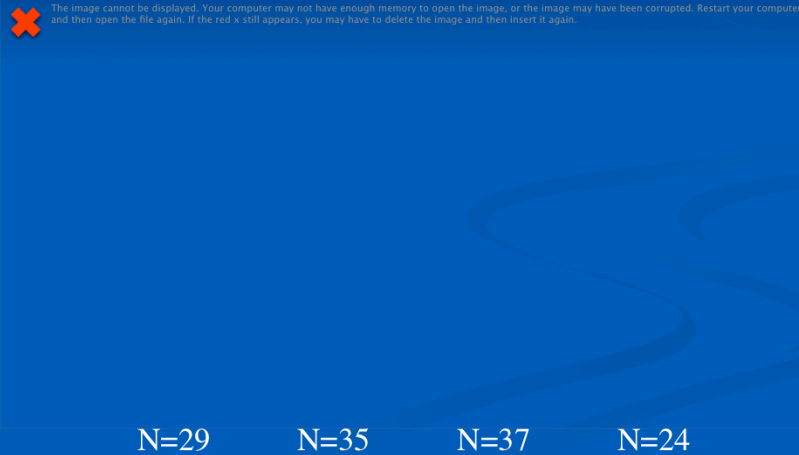
Low vs. High Fatigue

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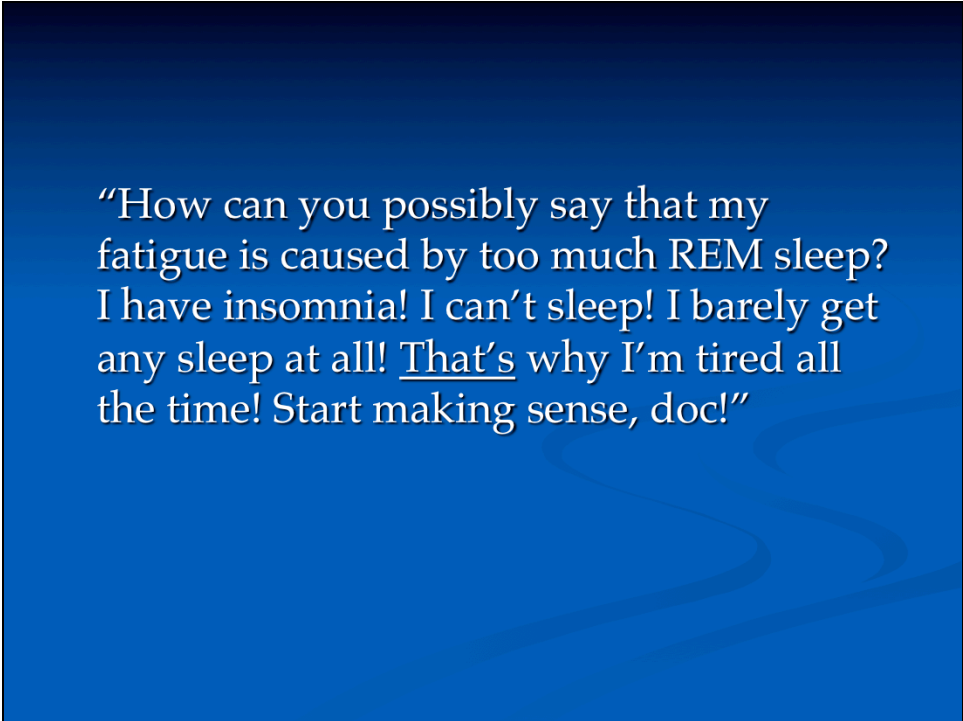
When I divided the respondents into two groups based on their chronic fatigue scores, using a cutoff of 5.21 (the average fatigue level for the entire group), I obtained the results shown in this table. As you can see, the high fatigue group was younger; they scored considerably higher on the Beck Depression Inventory; they were more likely to complain of insomnia; to use hypnotic medication; to get up later; to spend more time in bed; including naps, after 6 am; and to spend more time overall in bed. In addition, they were more likely to agree with the sleep attitude question: "Sometimes it's necessary to miss work or school because of lack of sleep or really poor sleep".

There was also a non-significant trend for high fatigue sufferers to take more and longer naps, and to agree with the attitude question: "If I don't get enough sleep during the night, I should make up for it by sleeping late or taking a long nap."

Chronic Fatigue and Time in Bed after 6 am



This slide illustrates the progression in chronic fatigue scores with time in bed after 6 am.



“How can you possibly say that my fatigue is caused by too much REM sleep? I have insomnia! I can’t sleep! I barely get any sleep at all! That’s why I’m tired all the time! Start making sense, doc!”

I’m sure many of you are skeptical about this hypothesis. If it’s so simple and so straightforward, why haven’t I heard about it before? You might well ask.

Well, you aren’t any more skeptical than most of my patients when I suggest that their fatigue or their depression may be caused by too much REM sleep. The slide shows a typical reaction.

And you are right to be skeptical. Because this insomnia business does throw a monkey wrench into the gears. Studies show that the fatigue experienced by cancer patients is strongly associated with sleep disturbances.

Insomnia

- The most common type of sleep difficulty is called psychophysiological insomnia
- This seems to be caused by attempting to exceed one's need for sleep [Chambers & Keller, 1993]
- Sleep restriction / constriction is the most effective treatment [Morin et al, 1994]
- Thus, it is possible to have fatigue caused by excessive REM sleep even when one has insomnia

- So now we have a theory linking excessive sleep and late rising to fatigue and depression
- we've addressed the issue of insomnia coexisting with fatigue
- A troubling complication: cytokines are implicated in a whole range of cancer symptoms, including fatigue

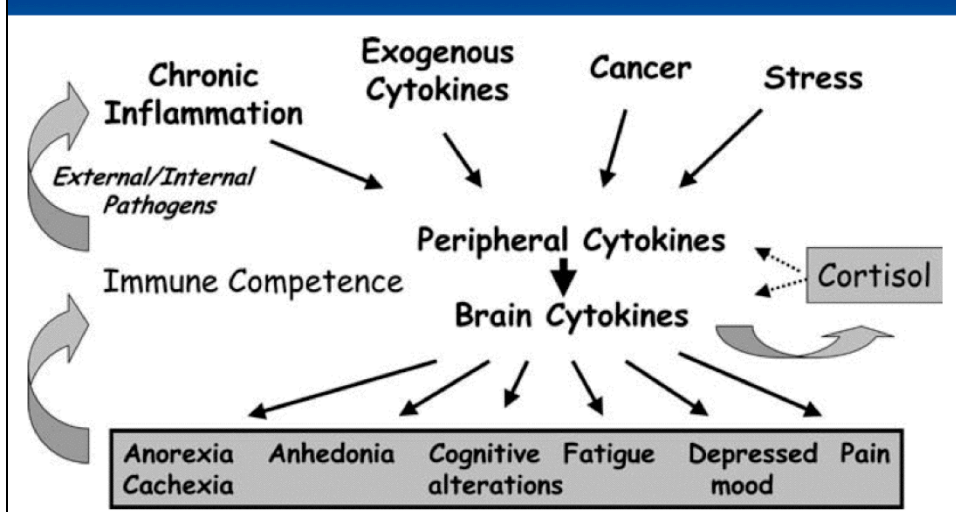
Evolution of understanding of cytokines

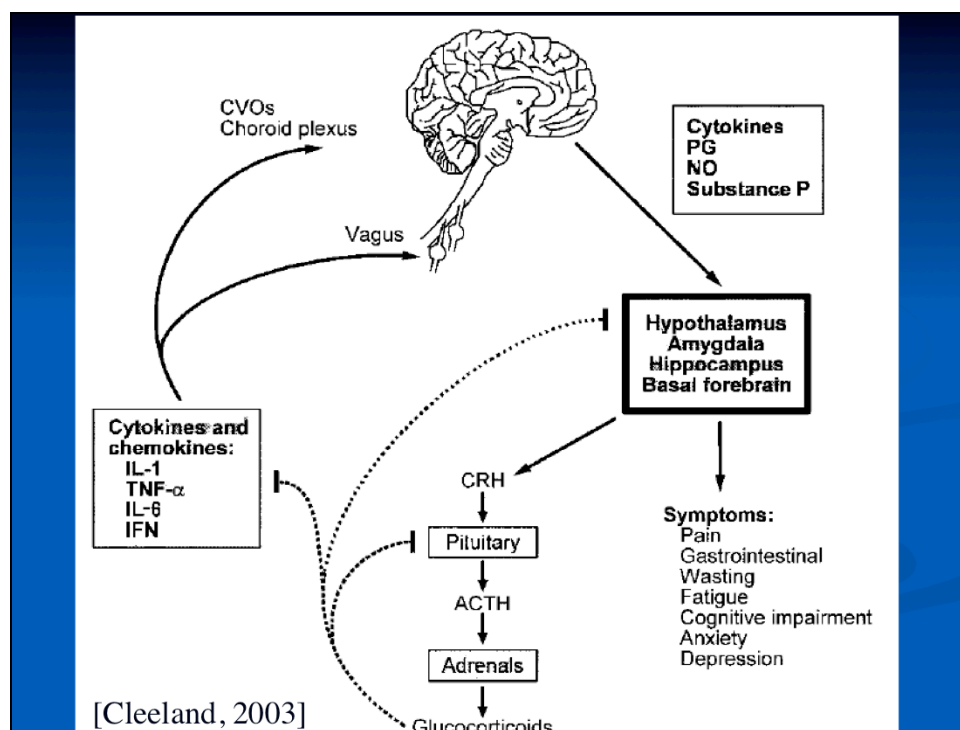
- IL-1 and 2 were identified and synthesised using recombinant techniques
- When used to treat certain cancers and other conditions, behavioural changes were observed
- These behavioural changes were also seen in animal experiments, and were identical to the responses to injections of endotoxins and lipopolysaccharide
- These “sickness behaviors” are believed to exert a homeostatic role in enabling the organism to fight infection, eg through energy conservation
[Maier & Watkins, 1999]

“Sickness Behaviors” [[Cleeland et al, 2003](#)]

- Decrease in:
 - General activity
 - Exploratory behaviour
 - Social interaction
 - Sexual interaction
 - Food and water intake
 - Preference for sweets (anhedonia)
- Altered sleep
- Impaired learning
- Hyperalgesia

Cytokines and Sickness Behavior





Is Sickness Behavior Homeostatic?

- For infection, a fever helps to kill or slow down the infectious organism
- Decreases in activity, exploration, etc help to conserve energy which helps with maintaining a fever
- But what does a fever have to do with cancer or stress? What adaptive role does sickness behavior play in these conditions?

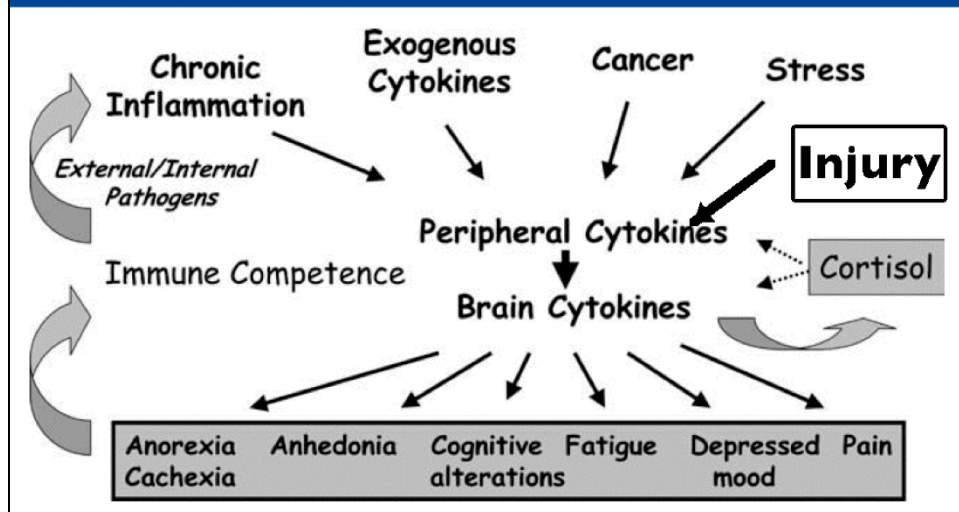
Hypothesis: depression is a homeostatic response to injury

- A wounded animal will heal best if keeps still:
 - Hypersomnia
 - Anorexia
 - Fatigue
 - Anhedonia
 - Reduced sex drive
- Injury is likely the most common cause of inflammation in animals in the wild

Putative mechanism

- Acute phase response in injury involves production of cytokines: IL-1, IL-6, TNF [Brandt, 2001]
- Cytokines cause “sickness behaviour”

Injury and Sickness Behavior

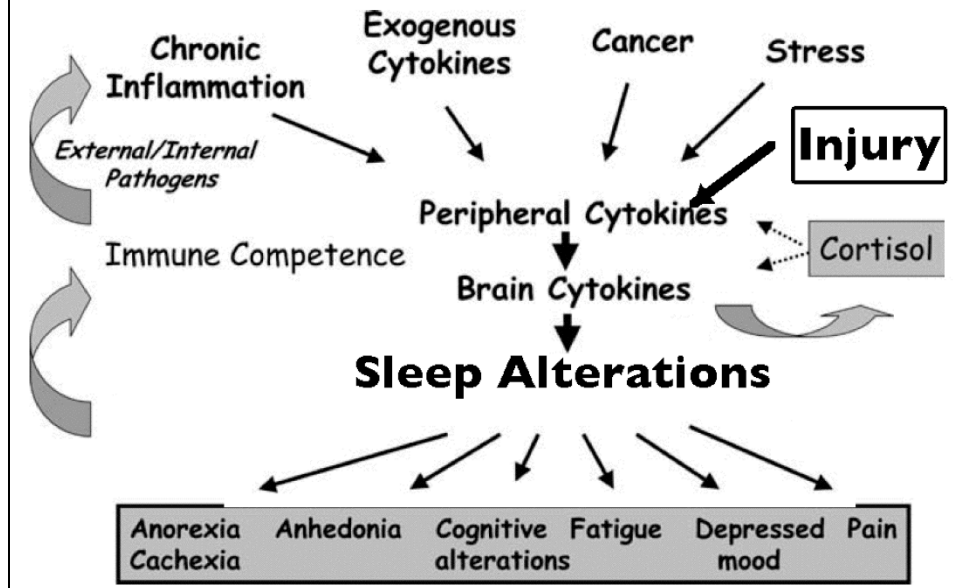


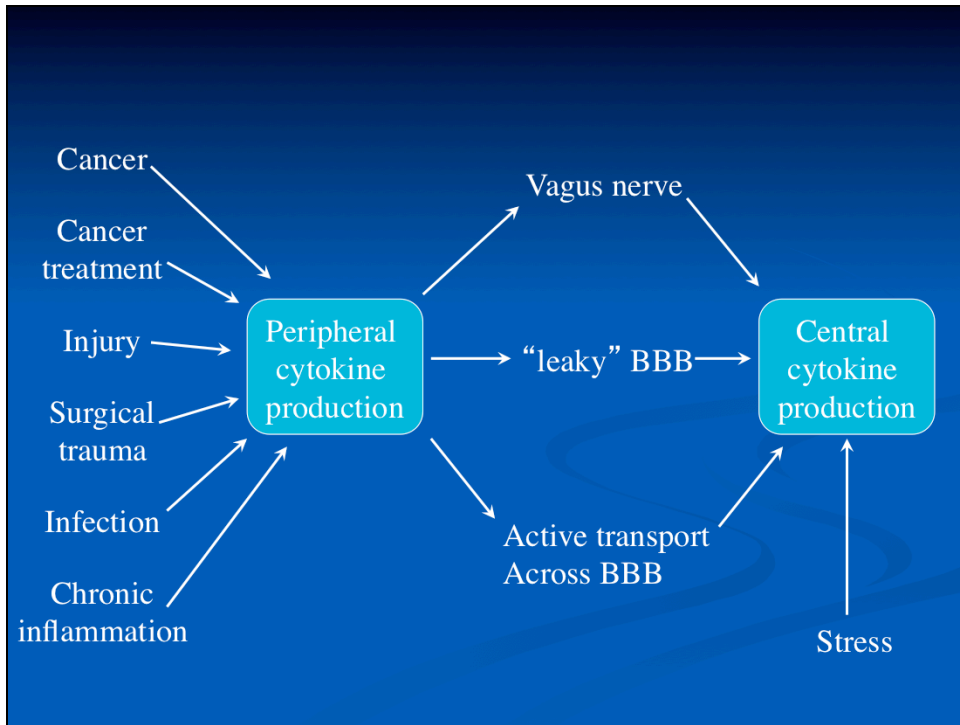
- However:
 - Acute phase response often does not cause sickness behaviour
 - Depression often occurs in absence of acute phase response

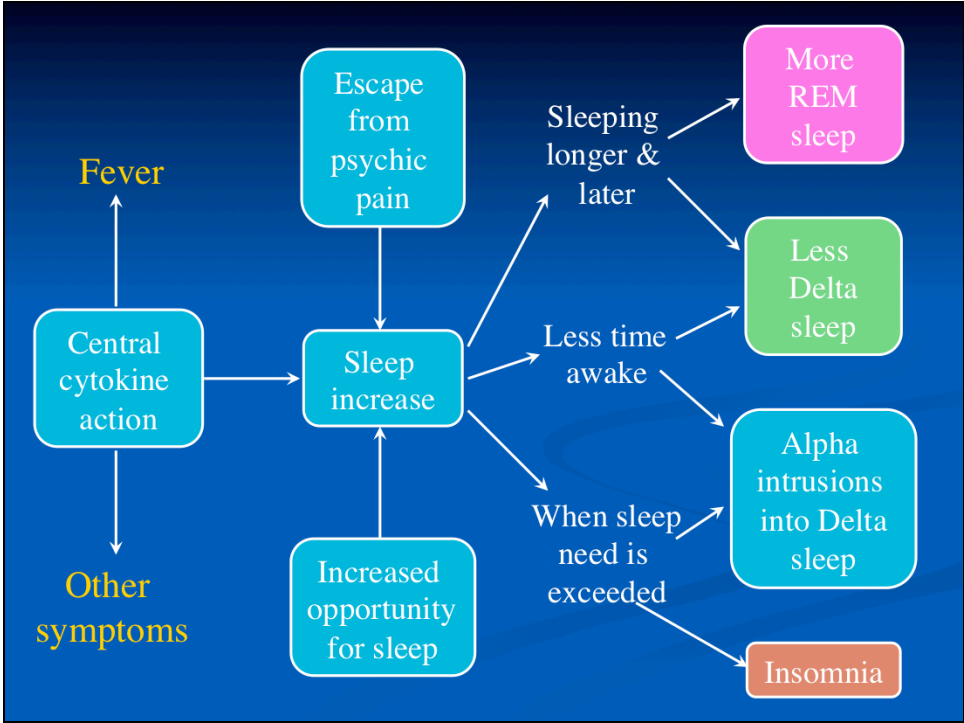
What if there's an intermediate factor?

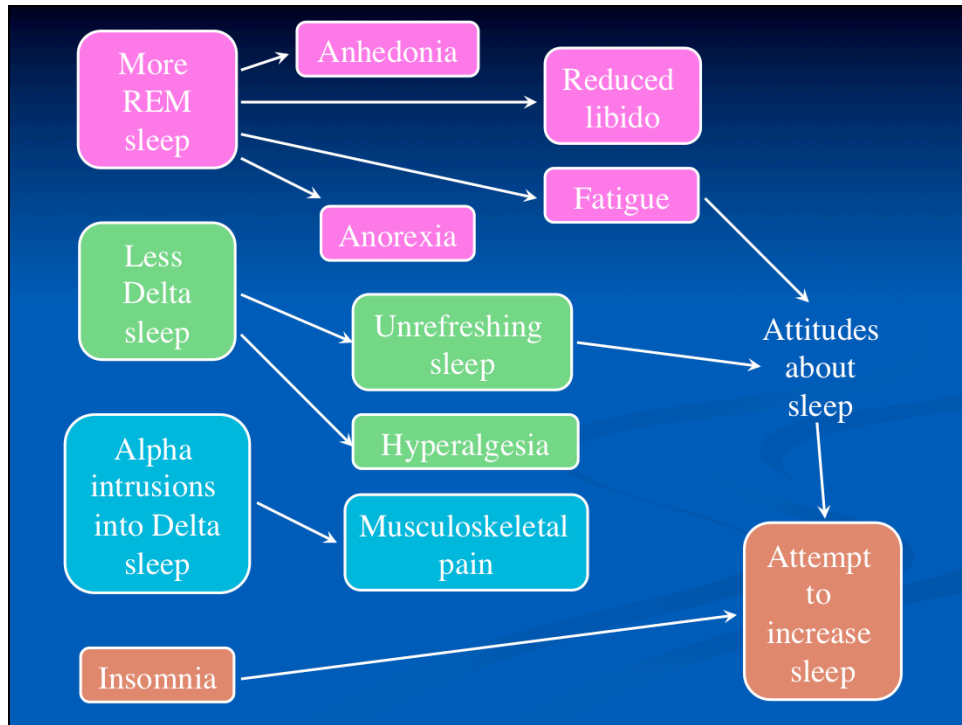
- Cytokines increase sleep
- Increased REM sleep is thought to trigger depression
- Fatigue, anhedonia, anorexia, reduced sex drive, impaired cognition are all depressive symptoms

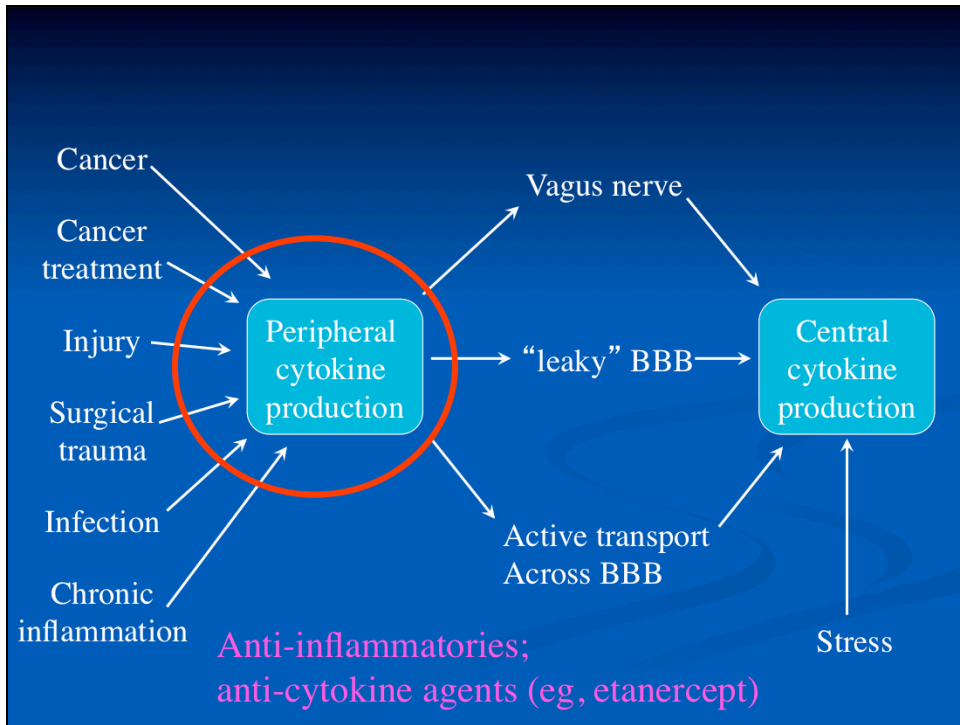
The Role of Sleep

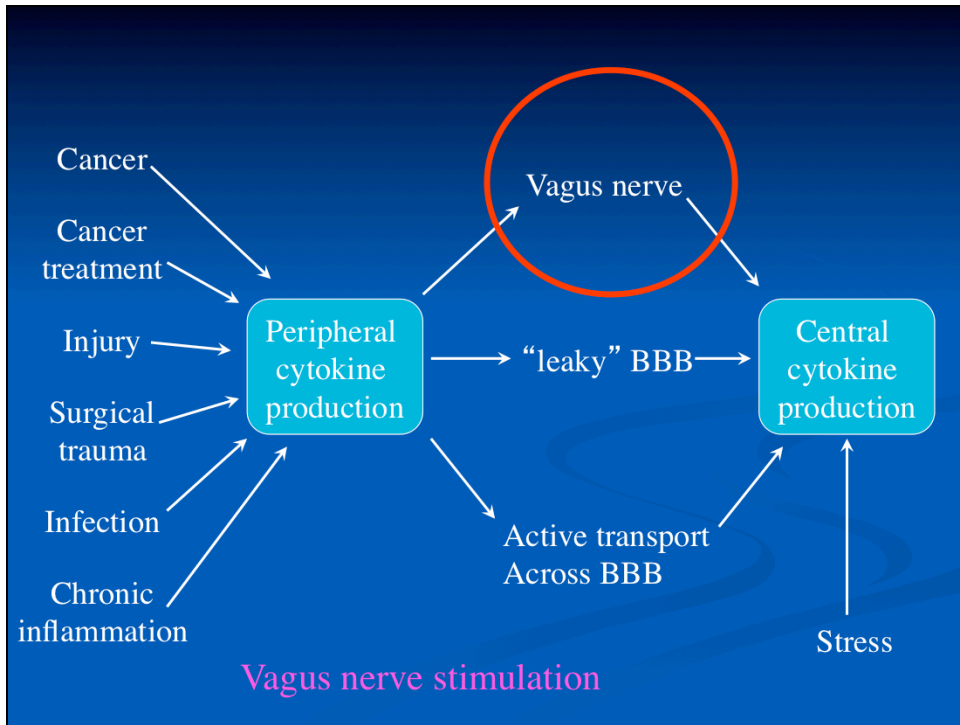


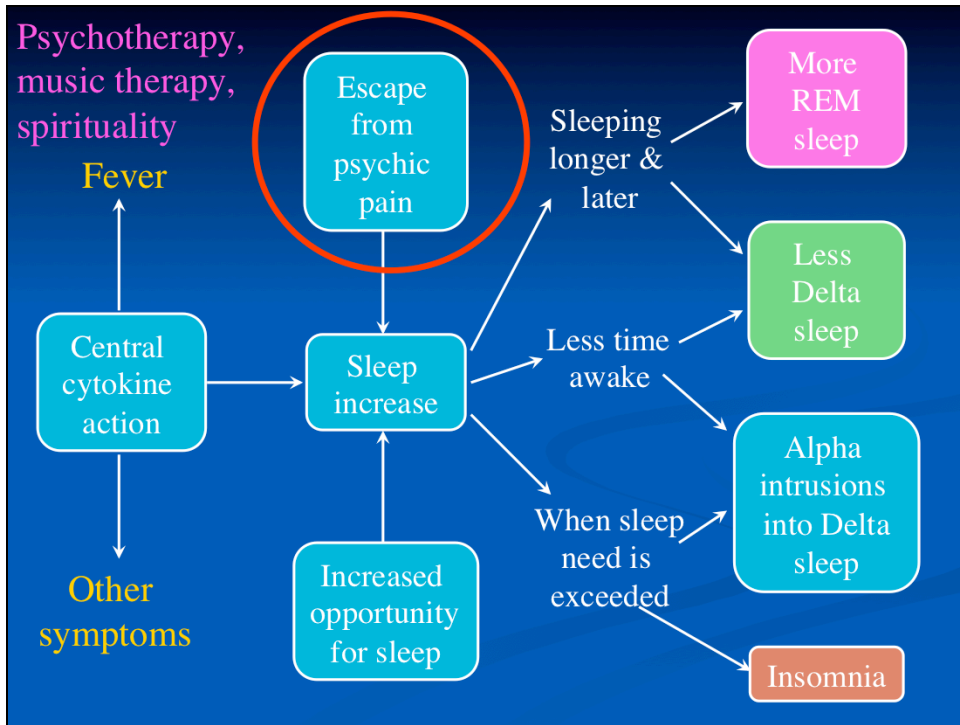


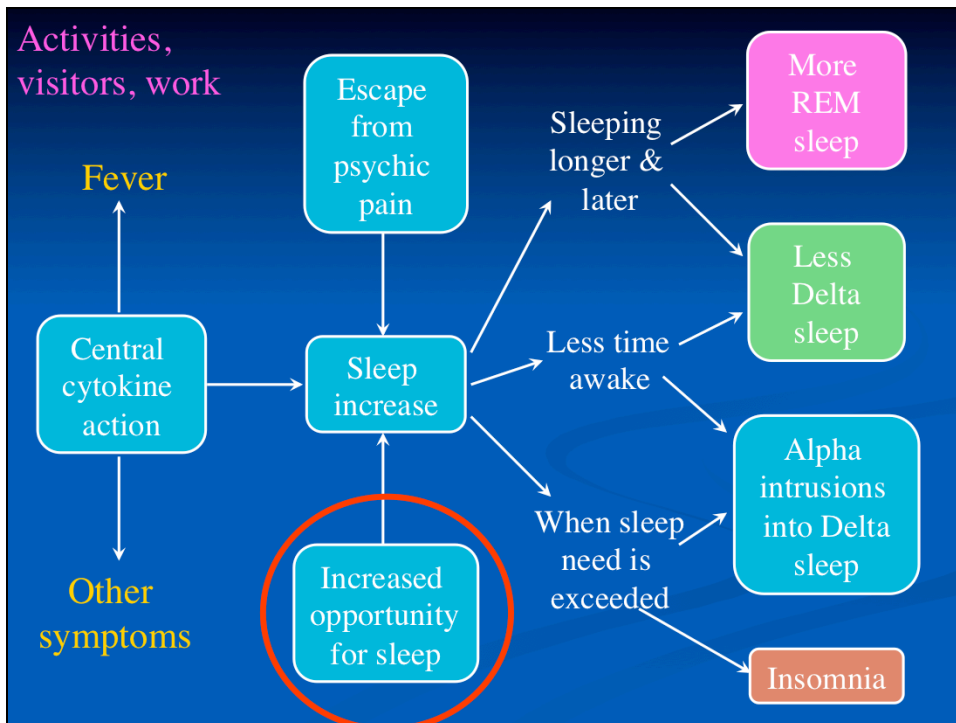


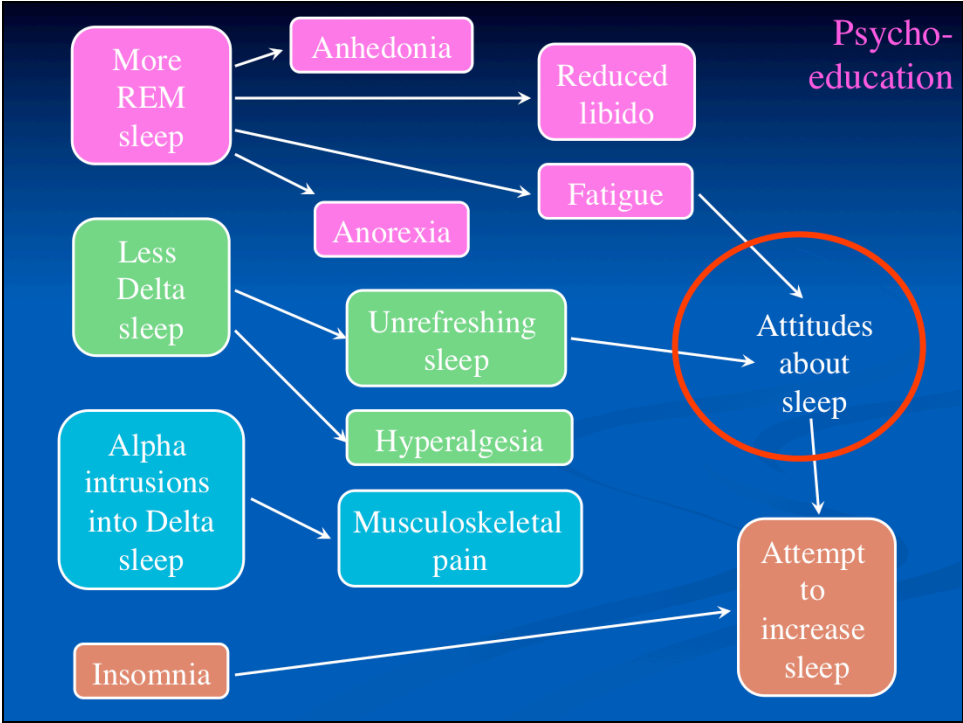


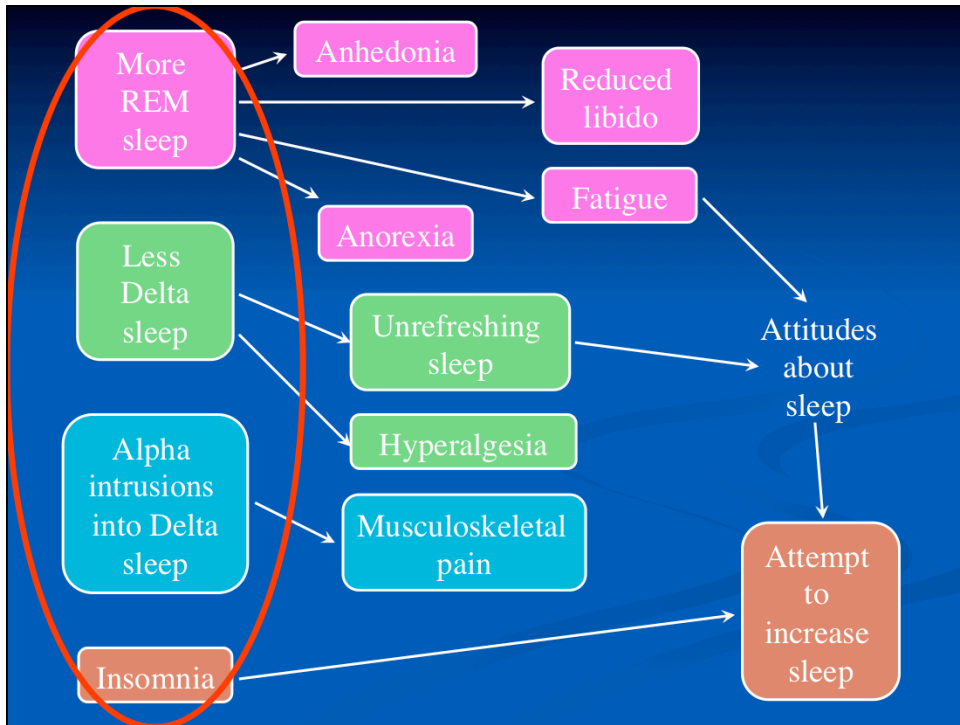












Strategies to improve sleep quality

- Decrease time in bed (adjust for age) [[Kripke et al, 2002](#)]
- Get up at a consistent time, even if didn't sleep
- If daytime sleepiness: short naps (< 10 min) [Takahashi & Arito, 2000]
- Consistent caffeine consumption [Kawachi et al, 1996]
- Other sleep hygiene principles:
 - Temperature, light, noise, distractions, classical conditioning, avoid clock-watching, use alarm.

Strategies to improve sleep quality

- Morning bright light exposure
 - Improves subjective sleep quality
 - Improves daytime alertness
 - Reduces time in bed
- Sleep constriction / sleep restriction

Strategies to reduce REM sleep

- Early rising (eg, 6 am)
- Partial sleep deprivation
- Psychostimulants
 - Eg, Ritalin 5-20 mg at 6 am
- Exercise [Youngstedt et al, 1997]
- Antidepressants
- Bright light [Dietzel et al, 1986]

Strategies to Increase Delta Sleep

- Stay awake longer
 - Get up earlier
 - Go to bed later
 - Avoid long naps
 - Psychostimulants to maintain daytime wakefulness

Strategies to Increase Delta Sleep

- Medication to increase SWS
 - Some antidepressants:
 - Trazodone [[Yamadera et al, 1999](#)]
 - Mirtazapine [[Schittcattte et al 2002](#)]
 - ?amitriptyline [Staner et al, 1995]
 - Atypical antipsychotic: olanzapine [Sharpley et al, 2000]
 - GABA mimetics:
 - GHB [Scharf et al, 1998]
 - Gabapentin [[Foldvary-Schaefer et al, 2002](#)]
 - Pregabalin [Kubota et al, 2001]
 - Several of these medications are used to treat pain

Words of wisdom from Homer

- "Even where sleep is concerned, too much is a bad thing" [Homer, *Odyssey*, 9th century BCE]
- "There is a time for many words, and there is also a time for sleep"