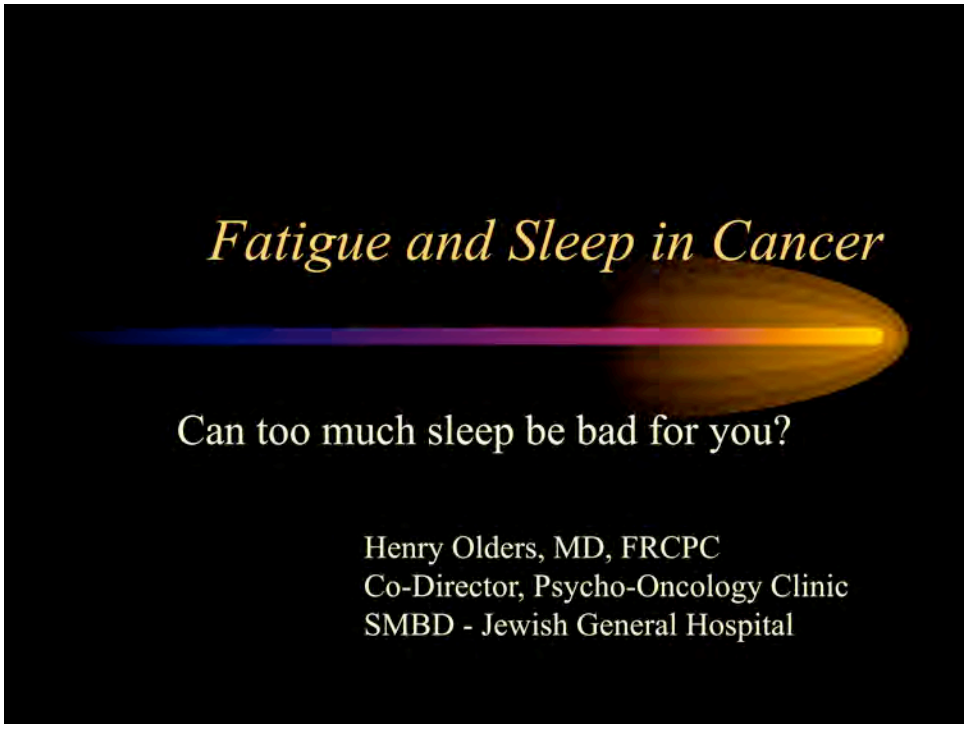
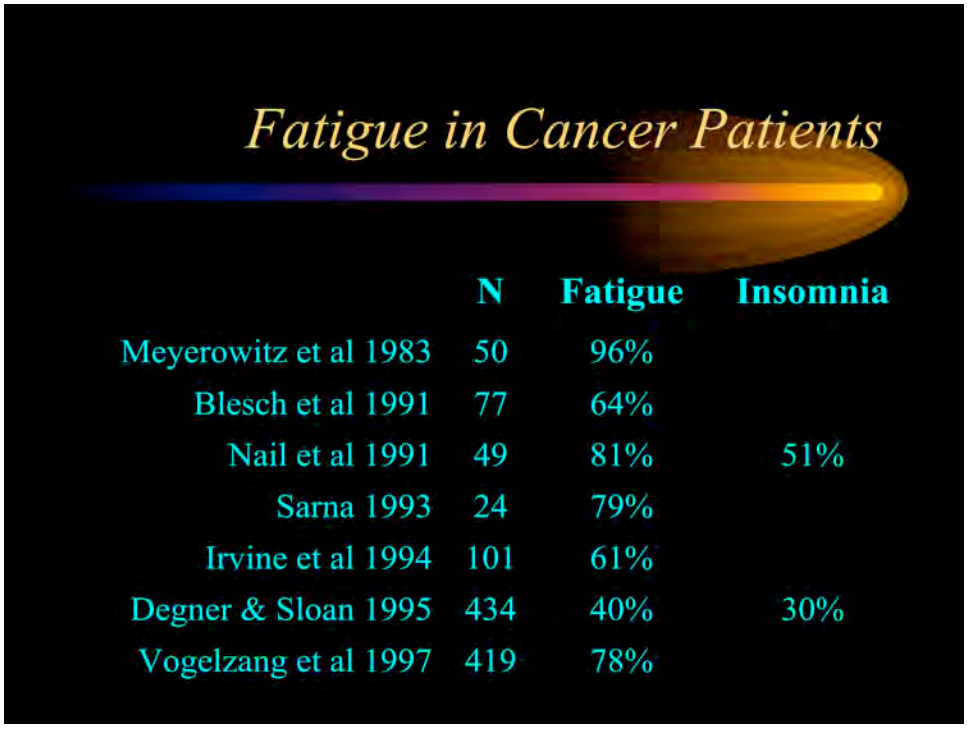


Today I'm going to talk about fatigue in cancer patients, and its relationship to sleep, insomnia, and depression. I will present the results of a questionnaire study I did with cancer patients at the Jewish General Hospital, and then present a hypothesis which I think explains the findings. This hypothesis leads directly to a clinical approach which I have found successful with my patients in the Psycho-Oncology Clinic, and also helpful with fatigue and depression in the patients I see in the Consultation-Liaison Psychiatry Service and in the Psychogeriatrics Clinic. I'm excited about the possibilities, and I hope I can share that with you.

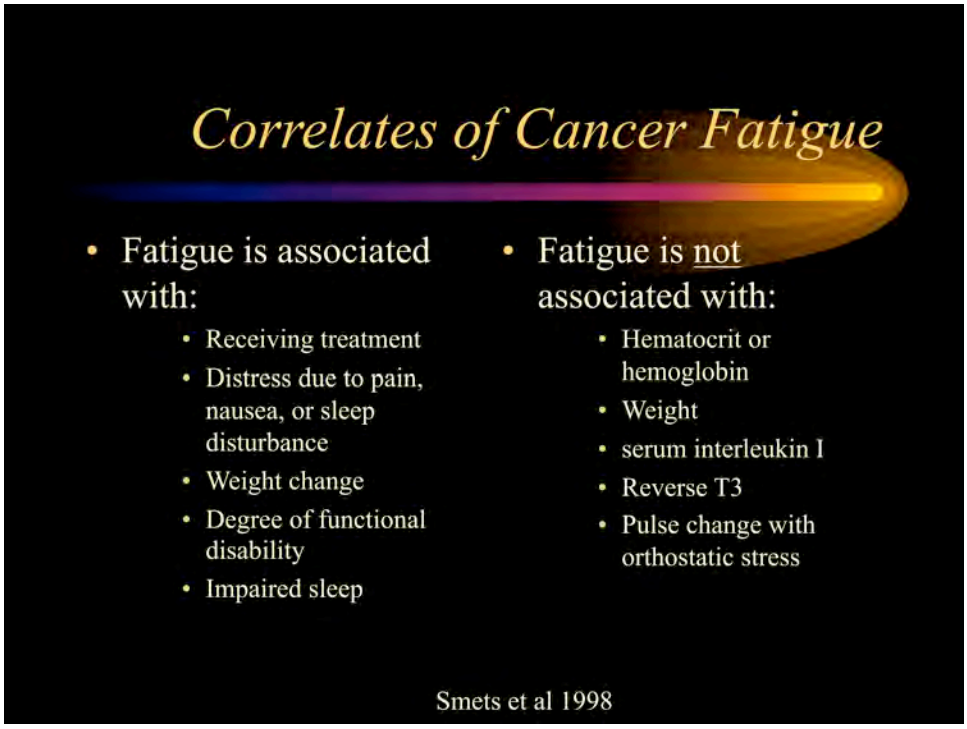


This slide shows a small sampling of the many studies, mostly from the nursing literature, looking at fatigue in cancer patients.

The Meyerowitz study interviewed 50 breast cancer patients receiving adjuvant chemotherapy; 96% of their group reported fatigue, and most of these viewed fatigue as the most disruptive symptom.

The Blesch article described 33 lung cancer and 44 breast cancer patients receiving chemo and/or radiotherapy. 99% of their sample had fatigue, although only 64% reported it as moderate or severe in intensity. They found no difference in fatigue level between the two cancer types, and while fatigue correlated with pain severity and mood disturbance, there were no correlations with any biochemical parameters.

Nicholas Vogelzang and his group found that 32% of the patients reported that fatigue significantly affected their daily routines. They also sent questionnaires to oncologists, 61% of whom believed that pain affected their patients to a greater degree than fatigue, whereas only 19% of patients felt pain affected their lives more.



This slide shows the factors associated with cancer fatigue. I found it interesting that none of the physical factors one would suspect, such as anemia, are associated.

Fatigue, of course, doesn't limit itself to cancer patients. It is a significant factor in other medical illnesses; for example, in 80% of patients with rheumatoid arthritis, and in 68% of patients with primary biliary cirrhosis. Fatigue is also common in AIDS.

Fatigue can also cause significant disability even in the absence of a clearly causative medical illness. For example, most patients with chronic fatigue syndrome are unable to work fulltime because of their fatigue.

Finally, fatigue figures prominently in depression and its milder variant, dysthymic disorder.

The experience of fatigue appears to be treatment related in cancer patients receiving radiotherapy. For example, groups with different radiation fields have different prevalence rates of fatigue. Fatigue seems to increase gradually over the course or radiotherapy treatment, but decreases on weekends when no treatment is given.

Fatigue is also associated with distress, with weight change, with degree of functional impairment, and with sleep disturbance. Fatigue was <u>not</u> found to be related with various physical factors, such as degree of anemia or weight.

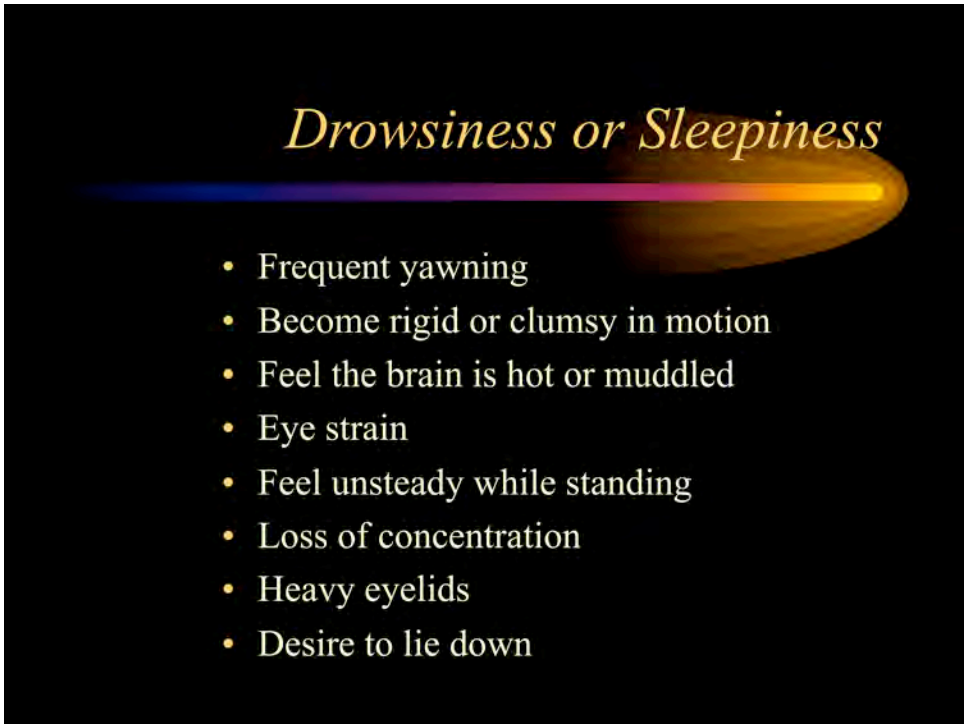
Unfortunately, the word fatigue means different things to different people.

The words tiredness, fatigue, and sleepiness, are frequently used interchangeably, both by lay people and by researchers. The slide illustrates some of the meanings for tiredness that have been used.

For example, there are many articles about long-distance truck drivers having accidents when they fall asleep behind the wheel because they 're not getting enough sleep. Even though the accidents are clearly due to sleepiness, the articles invariably talk about "fatigue"! Widely used fatigue questionnaires such as the Piper Fatigue Self-Report Scale includes "sleepy" and "drowsy" as fatigue sensations. No wonder most people believe that fatigue is caused by insufficient sleep!

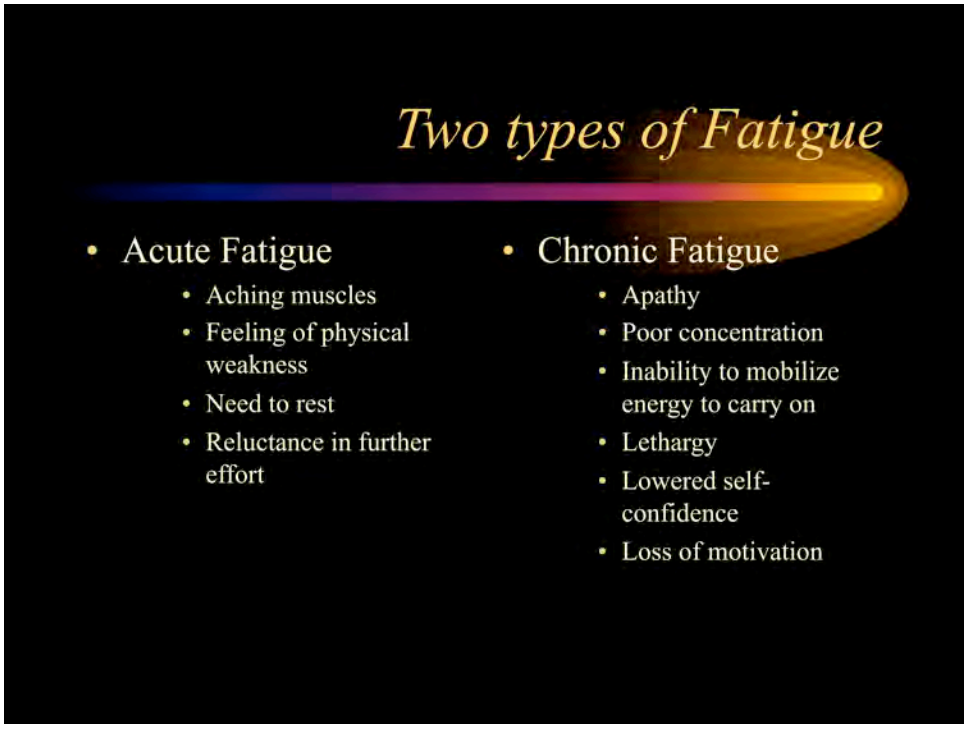
Unfortunately, this confusion of terminology means that a lot of the research on fatigue has to be looked at critically to ensure that what is being investigated is really fatigue, and not sleepiness.

In an attempt to clarify the terminology, I propose we use the following three terms: chronic fatigue, acute fatigue, and sleepiness.



Let's first look at sleepiness. You all know what this is. Some of you are probably experiencing it right now.

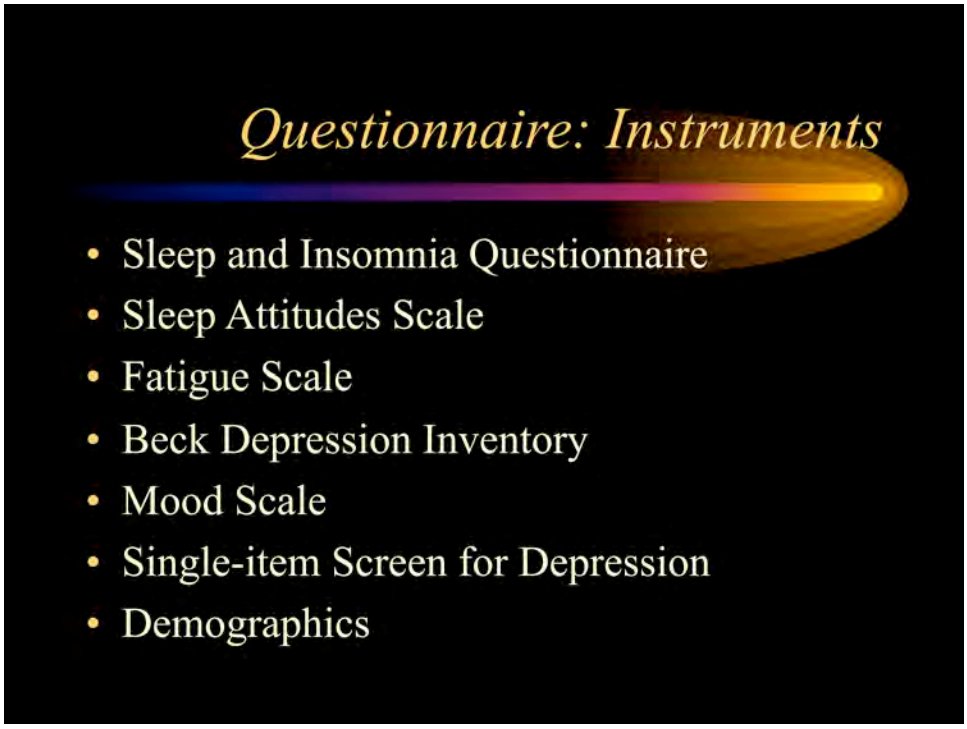
Everyone who has had to stay awake hours past their usual bedtime is familiar with drowsiness or sleepiness. It's characterized by a temporary loss of alertness, difficulty staying awake, and an overpowering desire to sleep. For most people it occurs twice daily, at mid-afternoon and at night, and it's usually relieved by a short nap. The slide shows some typical symptoms of drowsiness.



This slide shows the two types of fatigue, acute and chronic.

Acute fatigue is something just about everyone experiences. It's the kind of fatigue caused by hard physical work, such as running a marathon race. It is usually experienced as a temporary loss of efficiency, and it can be relieved by rest. The fatigue experienced after a concentrated lengthy mental effort, such as writing a 6-hour exam, is also acute fatigue.

Chronic fatigue, on the other hand, is the kind of fatigue typically found in disorders such as depression, and is frequently part of chronic medical illnesses like cancer. It is characterized by loss of initiative, boredom, and progressive anxiety; it is less likely to be relieved by rest; and it seems to accumulate from the effects of chronic stress or tension.



In order to explore the connection between fatigue and sleep in cancer patients, I undertook a questionnaire study of a convenience sample of outpatients attending the Oncology or Radio-Oncology Clinics at the Jewish General Hospital.

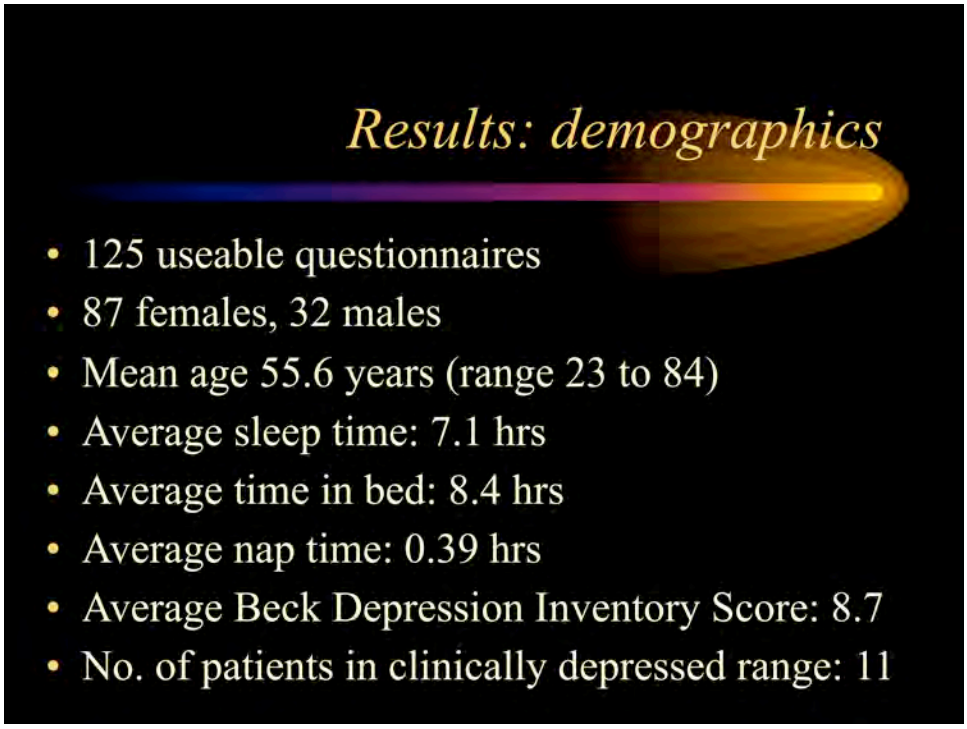
The questionnaire, which took about 30 minutes to fill in, was ditributed by clinical secretarial personnel to outpatients. It included a sleep and insomnia questionnaire, designed by Cathy Fichten, Eva Libman, and their colleagues in the Sleep Research Unit at the Jewish General Hospital. It taps self-report data on sleep patterns, sleep difficulties, insomnia, and the use of hypnotic medication.

The sleep attitudes scale includes six visual analogue scales to rate an individual's attitudes about sleep or its lack.

The fatigue scale rates the three dimensions of acute fatigue, chronic fatigue, and sleepiness, independently. It also asks the respondent to rate the distress and impact on daily life of chronic fatigue.

The Beck Depression Inventory is probably the most widely used self-report questionnaire for screening for depression. There are 21 items, each scored from 0 to 3. Scores above 20 are considered indicative of clinical depression, while 10 or less is considered non-depressed. For this study, I removed the two items dealing with sleep.

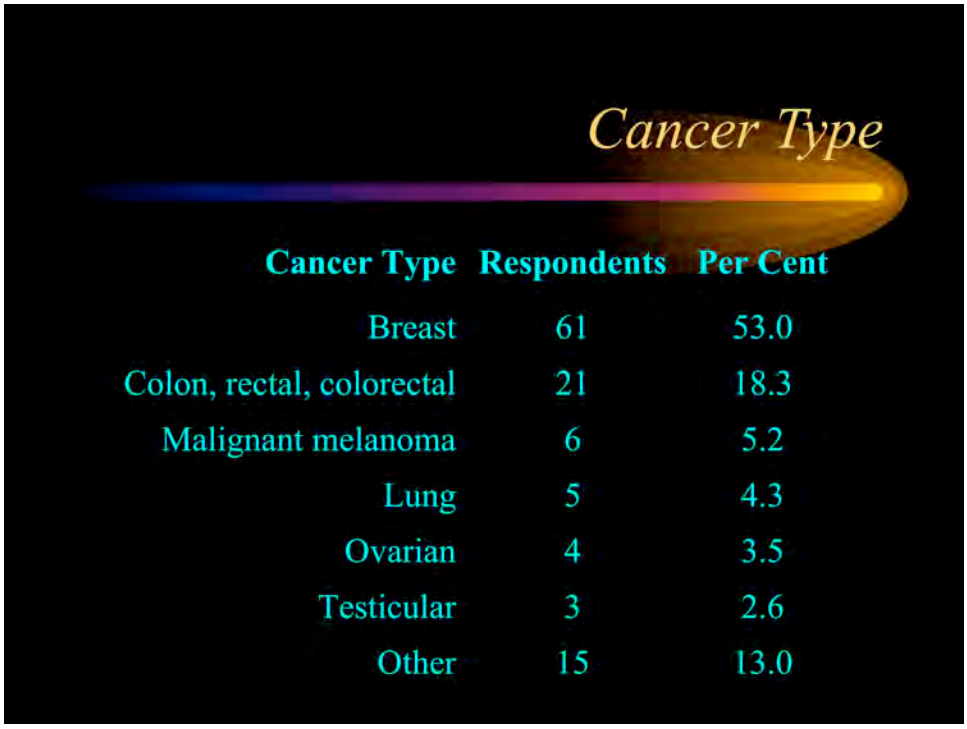
The demographics questions dealt with age, gender, type of cancer, treatment, and use of medication for anxiety, depression, or insomnia.



This slide gives some data for the whole sample. The figure for average nap time of just under .4 hours, or 24 minutes, includes those people who didn't nap. If we include only those people who napped, nap length was .8 hours for women and 1.1 for men.

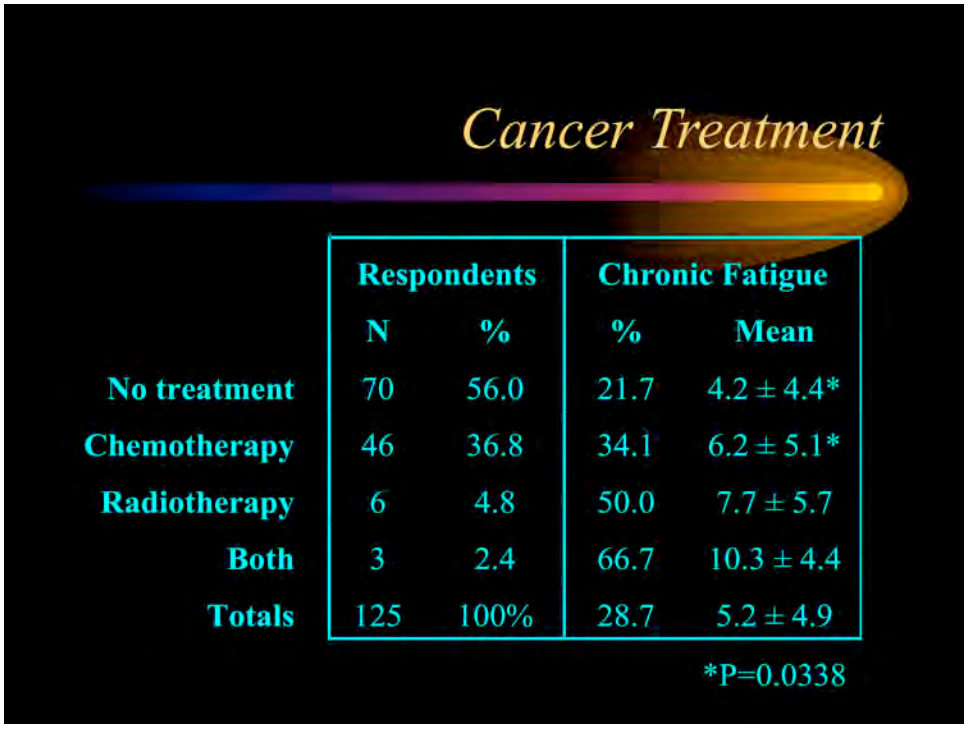
While men took longer naps, they had fewer insomnia problems.

The Beck scores averaged out to 8.7, which lies well within the non-depressed range of 0 to 10. Only 11 out of the total sample of 125 scored over 20 on the Beck Depression Inventory, indicating the likelihood of a clinical depression.



This slide gives a breakdown by cancer type. More than half of the people that reported cancer type had breast cancer.

The "other" category includes responses of adenocarcinoma, renal cancer, astrocytoma, bone cancer, brain cancer, germ cell, multiple myeloma, pelvis, stomach, synovial cell sarcoma, throat, tongue, and unknown primary in the neck.



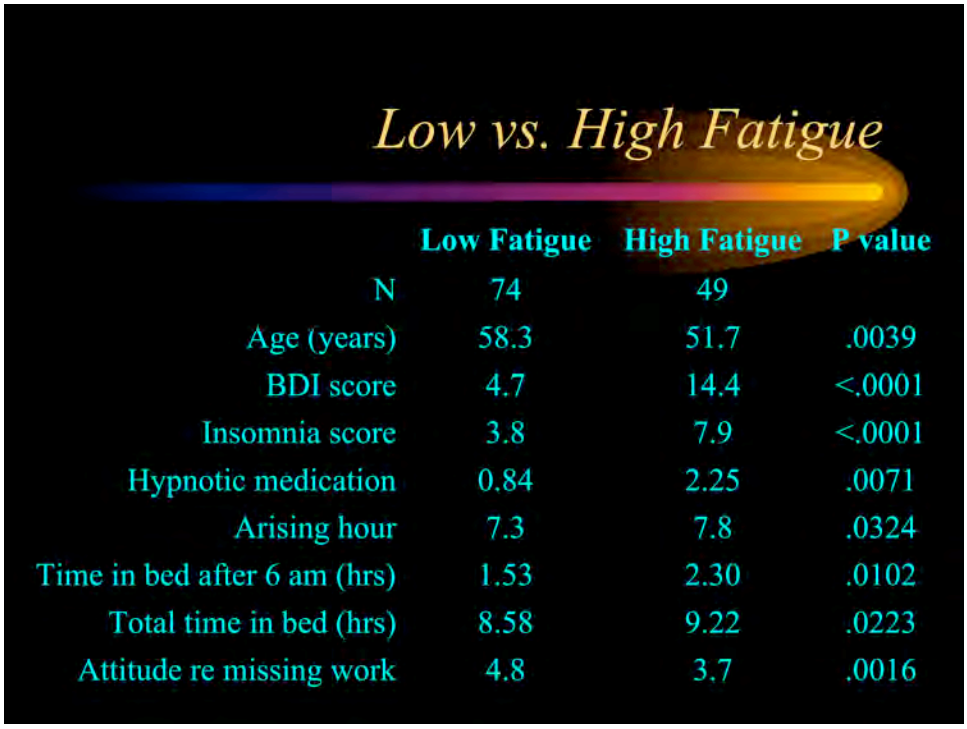
This slide shows a breakdown by type of cancer treatment.

The third column gives the percentage of patients in each group who scored in the moderate to severe range on a combined measure of chronic fatigue and distress due to this fatigue. The fourth column shows the mean chronic fatigue score* for each treatment group.

Clearly, the chemotherapy group had more fatigue than the group not getting treatment. The radiotherapy group had higher fatigue levels still, and those getting both treatments the highest fatigue levels of all. However, the numbers of patients in the last two groups were much too small to tell us if these fatigue figures are meaningful.

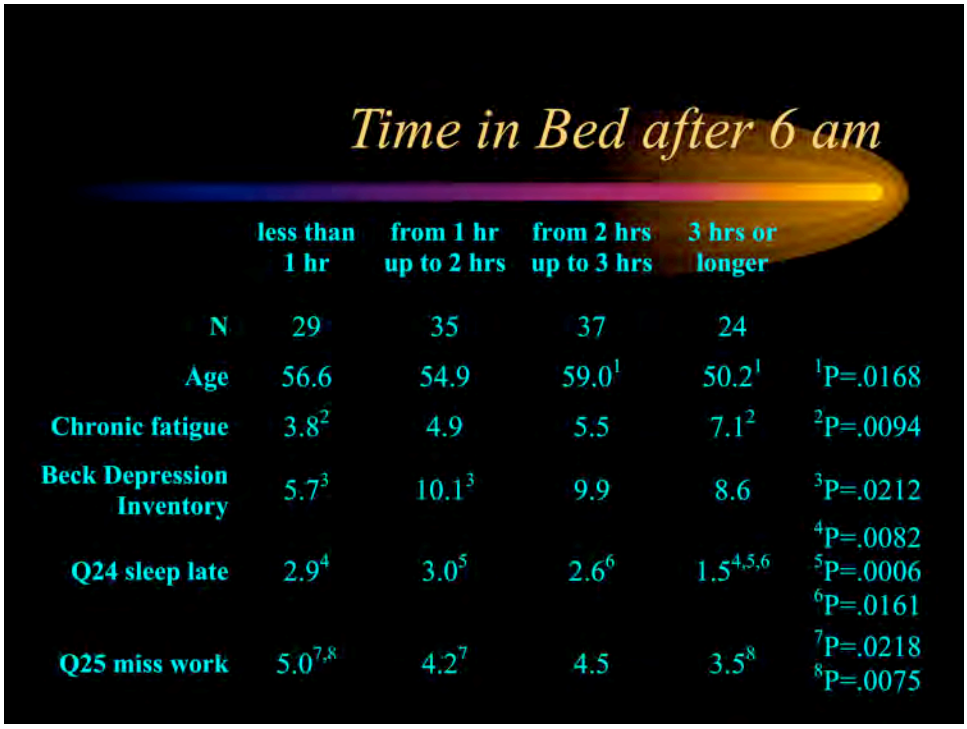
These results partially agree with Bessie Woo and her colleagues, in the June 1998 issue of Oncology Nursing Forum, who found higher fatigue for combined therapy than for radiotherapy or chemotherapy.

* The range for this measure is 0 to 16, with 8 being used as the cutoff for moderate to severe fatigue and fatigue distress.



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."

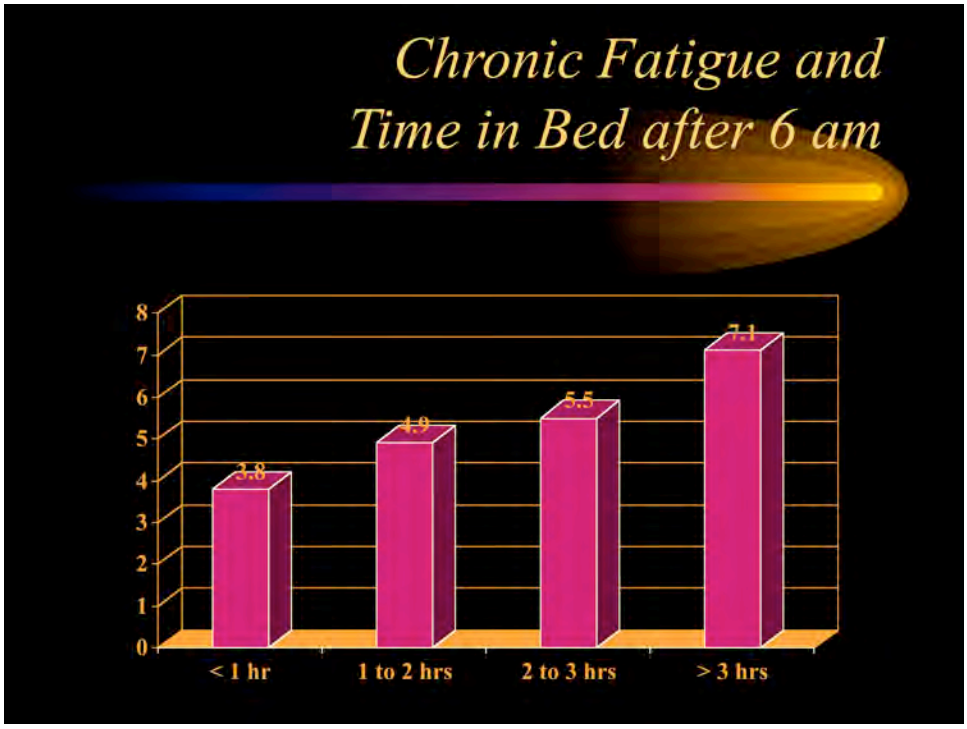


	less than 1 hr	from 1 hr up to 2 hrs	from 2 hrs up to 3 hrs	3 hrs or longer	
N	29	35	37	24	
Age	56.6	54.9	59.0[1]	50.2[1]	[1]P=.0168
Chronic fatigue	3.8[2]	4.9	5.5	7.1[2]	[2]P=.0094
Beck Depression Inventory	5.7[3]	10.1[3]	9.9	8.6	[3]P=.0212
Q24 sleep late	2.9[4]	3.0[5]	2.6[6]	1.5[4,5,6]	[4]P=.0082 [5]P=.0006 [6]P=.0161
Q25 miss work	5.0[7,8]	4.2[7]	4.5	3.5[8]	[7]P=.0218 [8]P=.0075

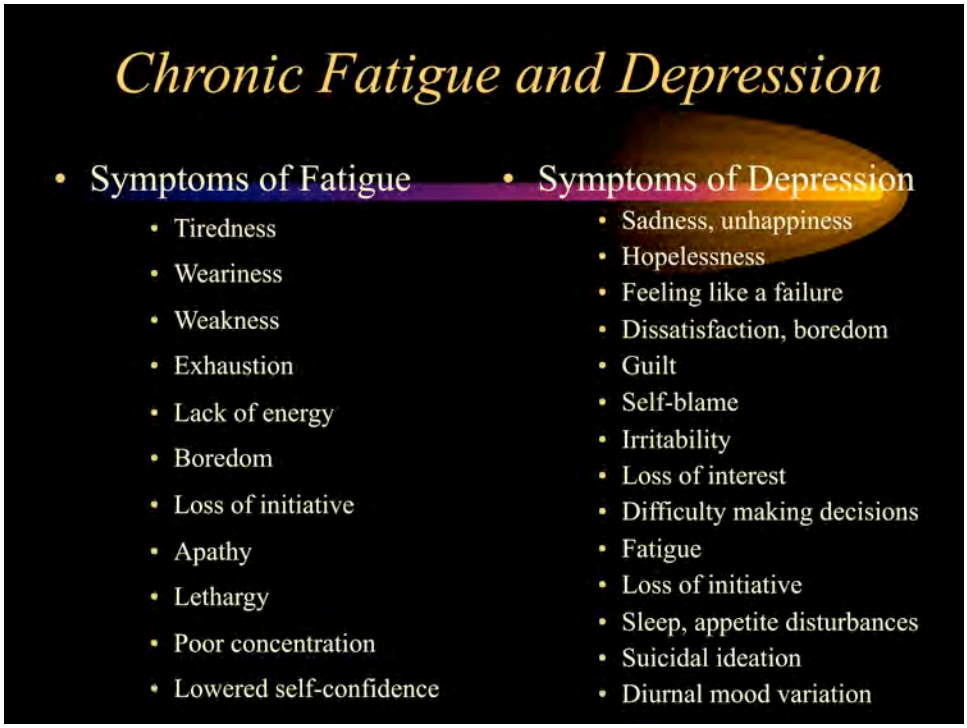
I was particularly interested in the association between getting up late and higher levels of fatigue, so I looked at the data from another perspective. When I divided the respondents into groups based on the amount of time they spent in bed after 6 am, again including daytime napping, I got the results shown here.

However, the chronic fatigue mean scores for each group increase as the time in bed after 6 am increases.

Not surprisingly, the scores on the two sleep attitude questions correspond with the time in bed groups: the persons who slept later were more likely to agree with the attitude that they should sleep later or take a nap if they had a poor sleep, including missing work or school to do so.



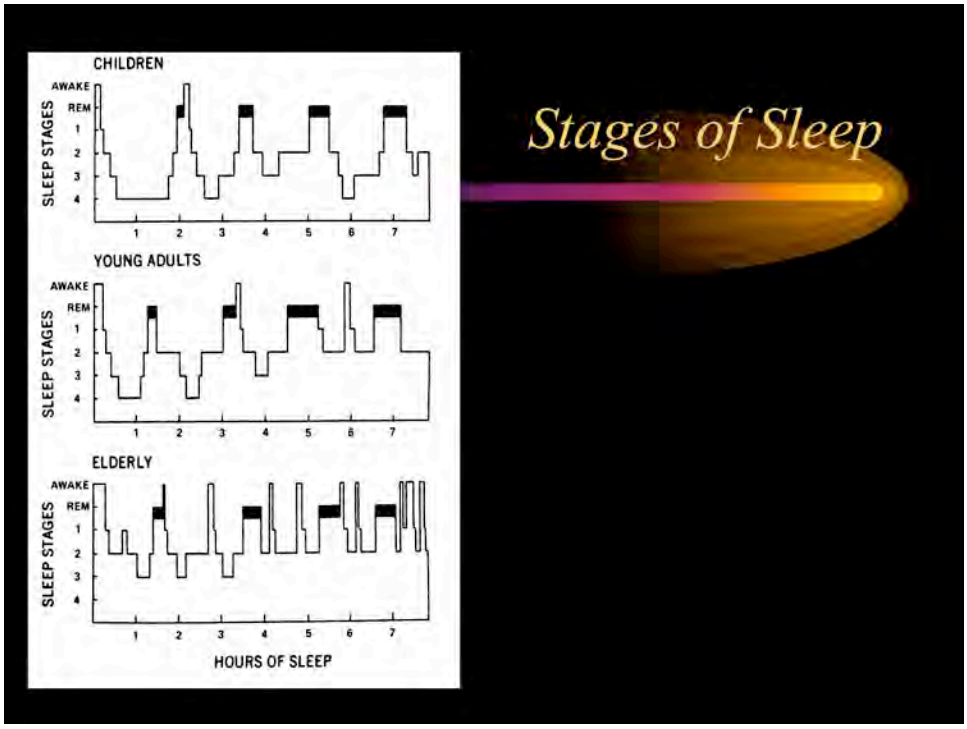
This slide illustrates the progression in chronic fatigue scores with time in bed after 6 am.



How to explain this association between getting up late and chronic fatigue? Keep in mind that this study doesn't say anything about cause and effect, and I couldn't find any other studies about this association. Further research is needed.

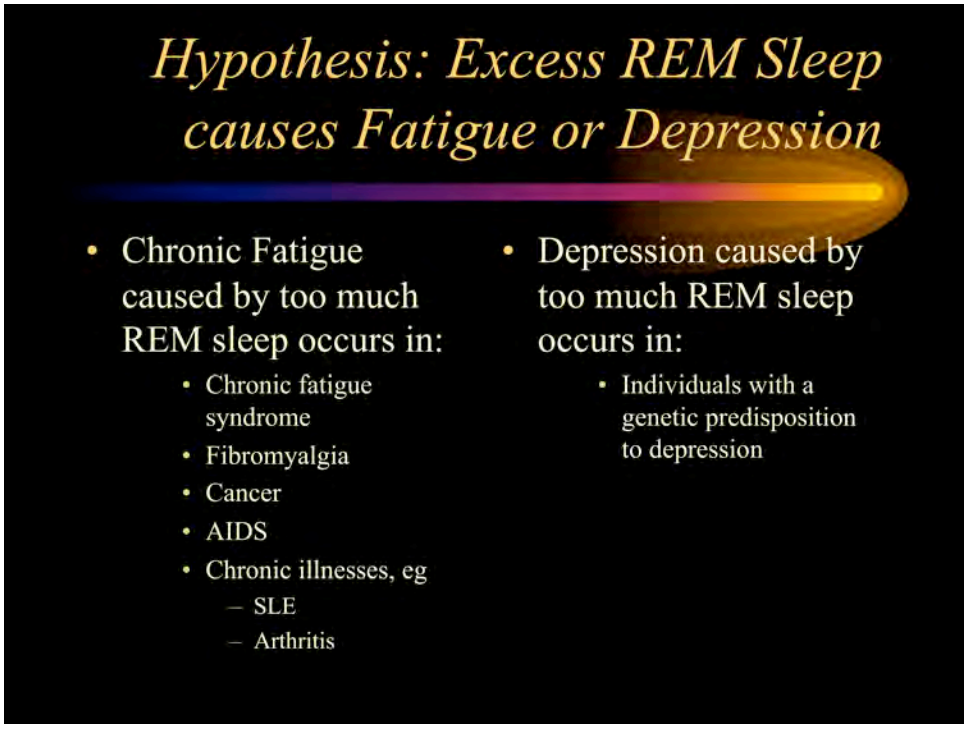
This slide compares symptoms of fatigue with those of depression. Notice any similarities? It seems to me that chronic fatigue might just be a mild form of depression, and that whatever causes depression, could also cause chronic fatigue.With the right environmental trigger, just about anybody could develop chronic fatigue, but only those who are genetically predisposed would become clinically depressed.

While there is little research on the relationship between fatigue and sleep, there is lots about depression and sleep, and this may help us to understand chronic fatigue.



This slide shows three typical somnograms, or graphs showing the various stages of sleep, for a child, a young adult, and an elderly person. Each somnogram has the awake state at the top, with REM sleep immediately below, and the four stages of non-REM sleep below that. Stages 3 and 4 are also called slow-wave sleep. In general, REM sleep occupies 20 to 25% of our total sleep time. Notice also that the first period of REM sleep occurs about an hour and a half after we first fall asleep, and recur with a periodicity of about 1 1/2 hours, or 90 minutes. As we go through the night, each period of REM sleep lasts longer, in general.

The body and mind will not tolerate a total absence of REM sleep; depriving someone will induce a REM rebound. It is believed that REM sleep is necessary for the consolidation of long-term memory. Is it possible to have too much REM sleep? Well, can you think of anything which we need where too much does not cause a problem?We need food; too much food causes obesity, diabetes, heart disease, etc. Too much water causes water intoxication. Too much oxygen in premature infants leads to blindness.

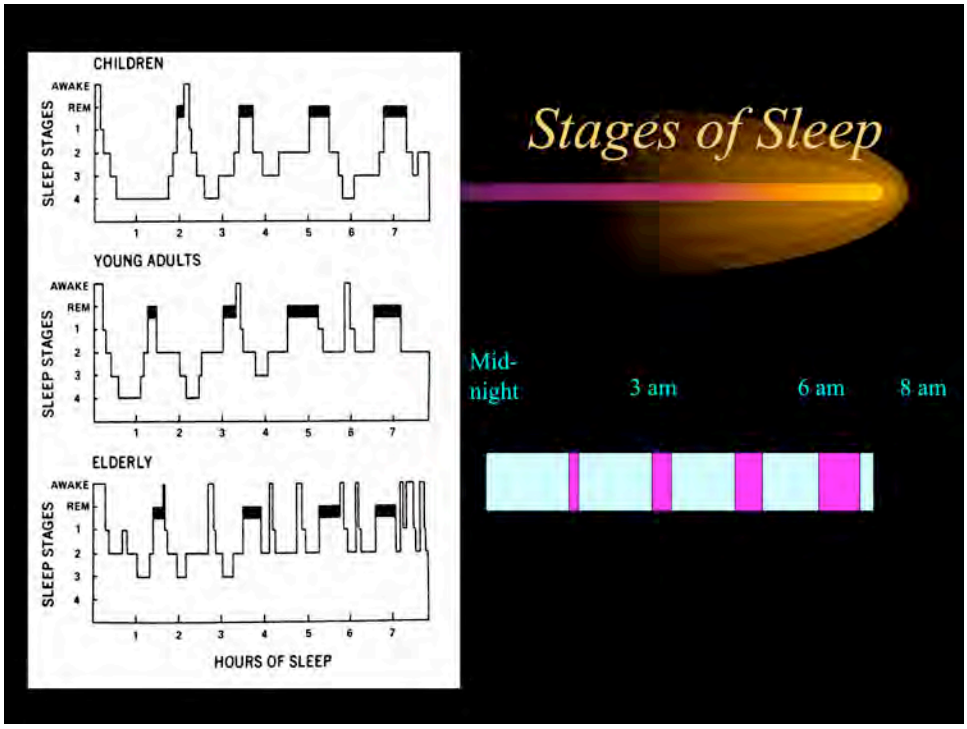


I think that if you get too much REM sleep, you will develop chronic fatigue. If you also have a genetic predisposition, the fatigue will become a full-blown depression.

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

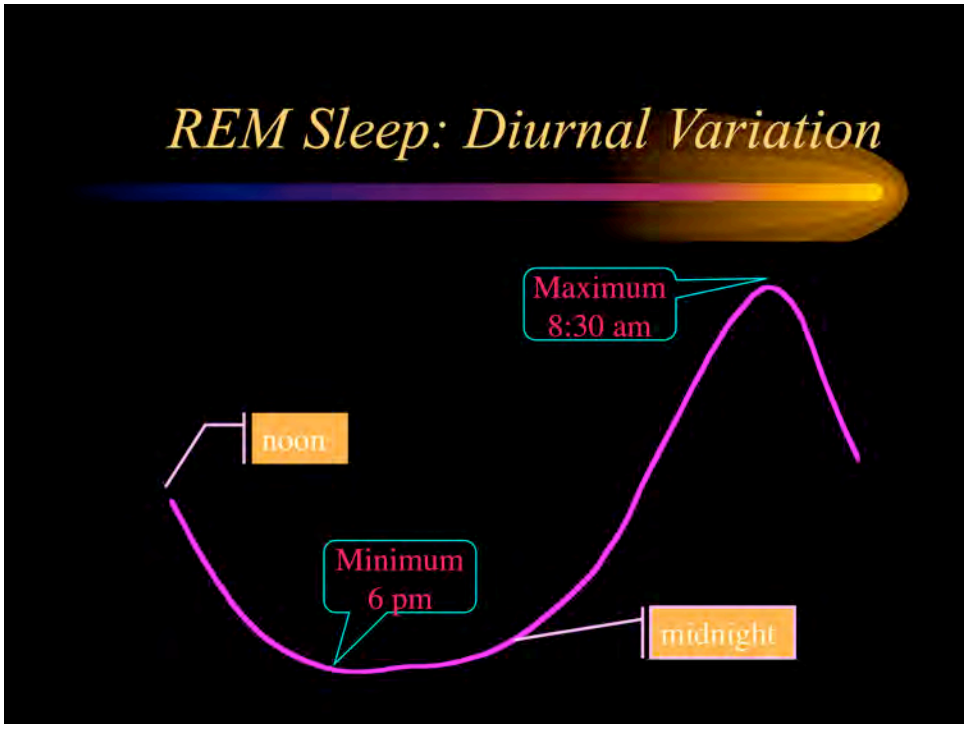
So, how can you get too much REM sleep? The easiest way would be to simply sleep more. However, this is often not as easy as it sounds. While some people are naturally long sleepers, most people who try to sleep longer, either by going to bed earlier, by getting up later, or by taking daytime naps, very 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.



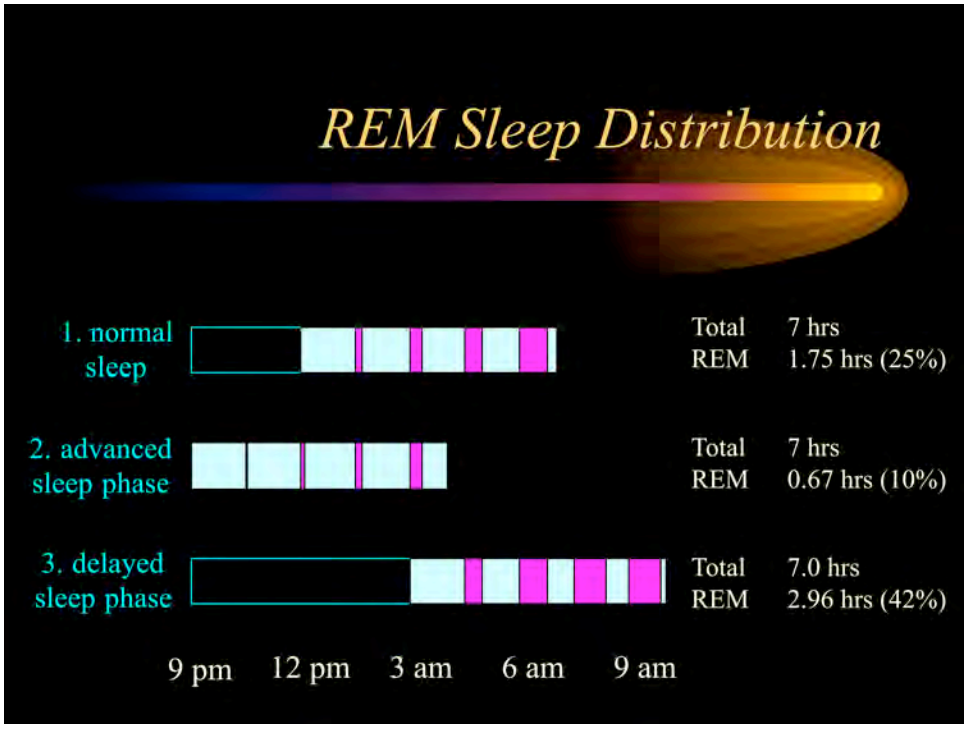
By far the easiest way of manipulating the amount of REM sleep is by varying the timing of our sleep, when we go to bed and when we get up.

On this slide, I've added a graph which shows the alternating pattern of REM sleep, shown in purple, with non-REM sleep, in pale turquoise. Compare this graph to the somnogram for young adults. The graph shows how REM sleep increases through the night, and peaks at perhaps 8:30 am, according to one study.



This graph illustrates the decrease in REM sleep propensity during the day, and the increase during the night. It seems to follow a typical diurnal variation, or circadian rhythm. This suggests that it may be controlled by the timing of sunrise, as we know that light is the most powerful trigger for circadian rhythms, both for plants and animals.

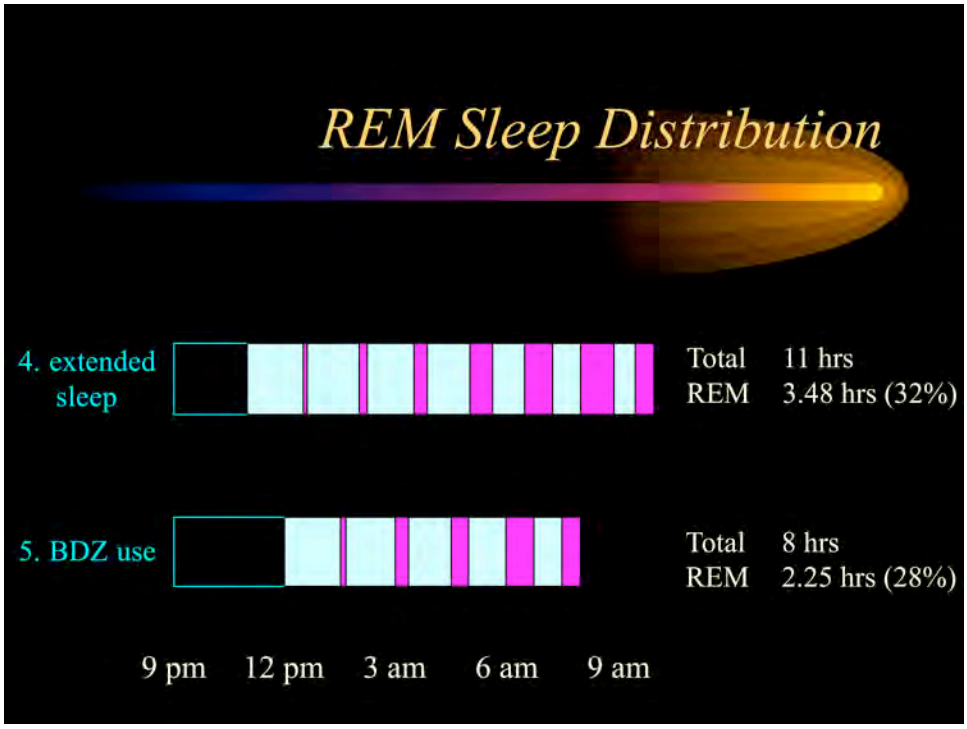
I used the curve shown on this slide to produce the graph on the previous slide, as well as the graphs on the next few slides. Keep in mind that this is not based on hard data; it is simply a thought experiment. I drew the curve based on a REM maximum at 8:30 am and a minimum at 6 pm, and so that for a typical sleep from midnight to 7 am, 25% would be REM sleep.



Here we have three graphs showing REM and non-REM sleep in three different conditions: normal sleep, ie seven hours between midnight and seven am; a condition called “advanced sleep phase” where the person goes to bed early and gets up early, in this case getting 7 hours of sleep but between 9 pm and 4 am; and at the bottom, “delayed sleep phase”, still 7 hours, but this time from 3 am until 10 am. As you can see, the width of each purple bar representing REM sleep increases through the night. The value for the amount of REM is just taken from the REM propensity curve you saw on the previous slide.

If you look at the total amount of REM sleep for each of the conditions, you will see that it ’s 1 and three-quarters hours out of 7 hours total sleep, or 25%, for the normal sleep condition. However, for the advanced sleep, the amount of REM drops to only two-thirds of an hour, a decrease of 62%. And for the delayed sleep phase condition, the amount of REM increases to just under 3 hours, an increase of 1.2 hours, or 69%, over normal sleep.

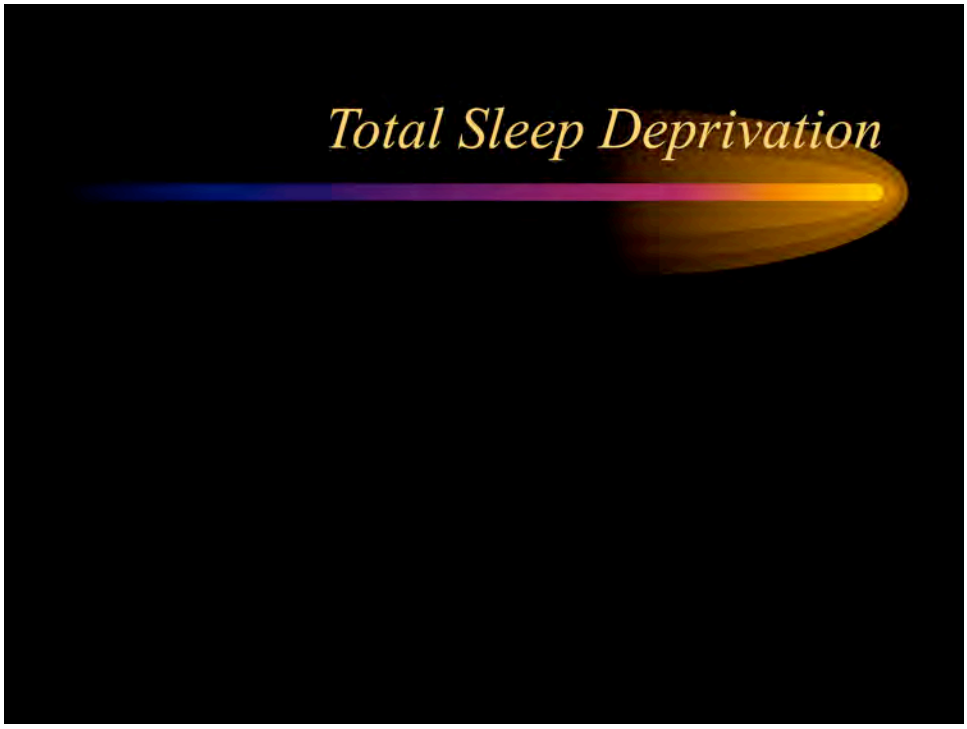
Would it surprise you to know that people with delayed sleep phase, the so-called “night owls”, are more likely to be young; and that as we get older, we tend to become ”morning people”, going to bed early and getting up early?



Now some peopletend to sleep longer than usual, a condition that almost doubles your risk of dying within the next 6 years (Kripke et al 1979). This graph shows what the sleep pattern might be for someone who sleeps from 11 pm until 10 the next morning, or 11 hours altogether. He or she will get 3 and a half hours of REM sleep, double the amount of the normal sleeper.

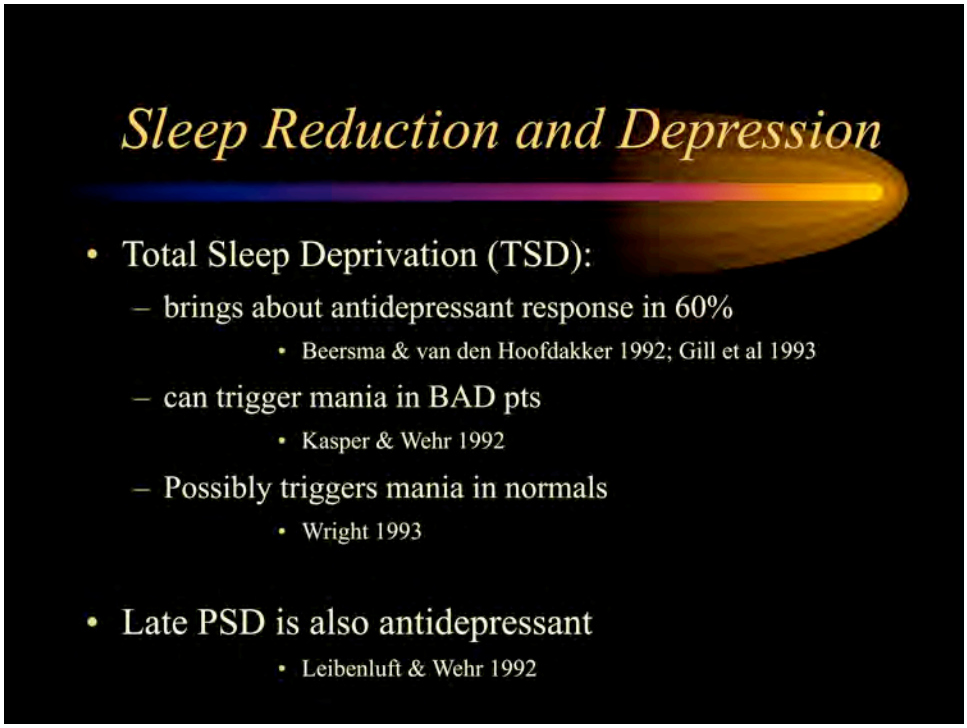
Now, 11 hours of sleep seems awfully long. However, someone with bipolar depression is likely to be hypersomnic, and could easily sleep 11 hours.

The lower graph shows what might happen if someone takes a benzodiazepine to help them sleep. Keep in mind that the relative risk of becoming depressed when you are started on a benzodiapine is more than four, if you get hospitalized on a medical or surgical floor (Patten et al 1996). The incidence jumps from 5.4% to 22.7%. If the benzodiazepine causes the person to sleep just one hour longer, the REM sleep jumps up to 2 and a quarter hours, an increase of a half hour, or 29%.



This slide has the graph for total sleep deprivation. Obviously, zero REM sleep.

Why is this important? It turns out that total sleep deprivation can be used as a treatment for depression.

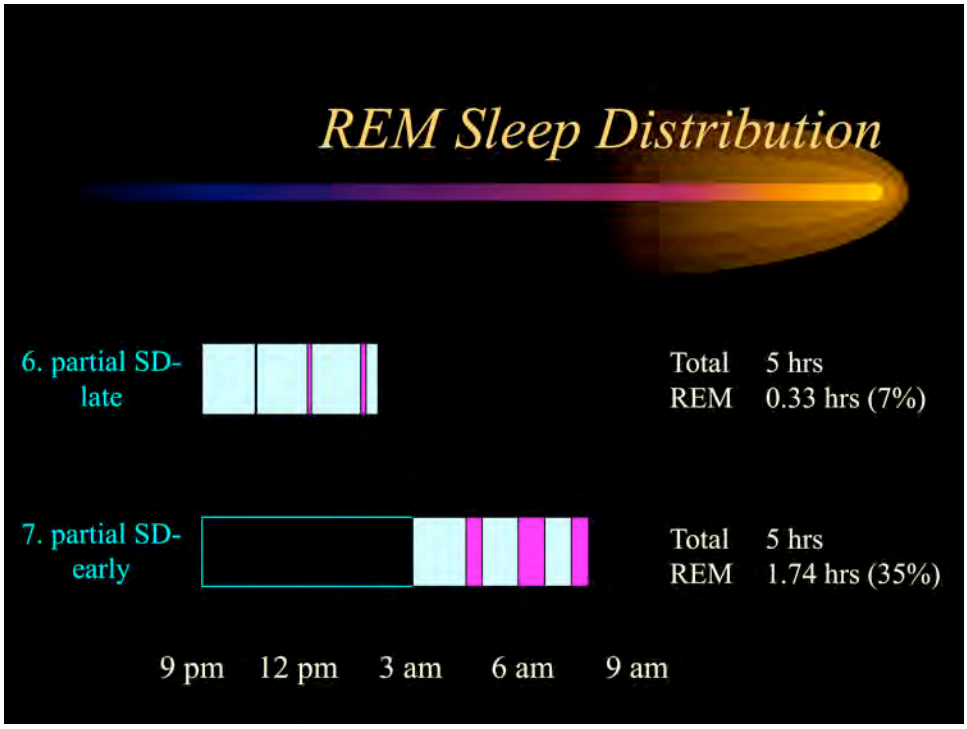


Total sleep deprivation leads to an immediate and substantial reduction of depressive symptoms in 60% to 70% of patients with major depression. This effect usually happens the same afternoon after only one night of no sleep. Considering that even the newer antidepressants are effective in the same percentage 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?

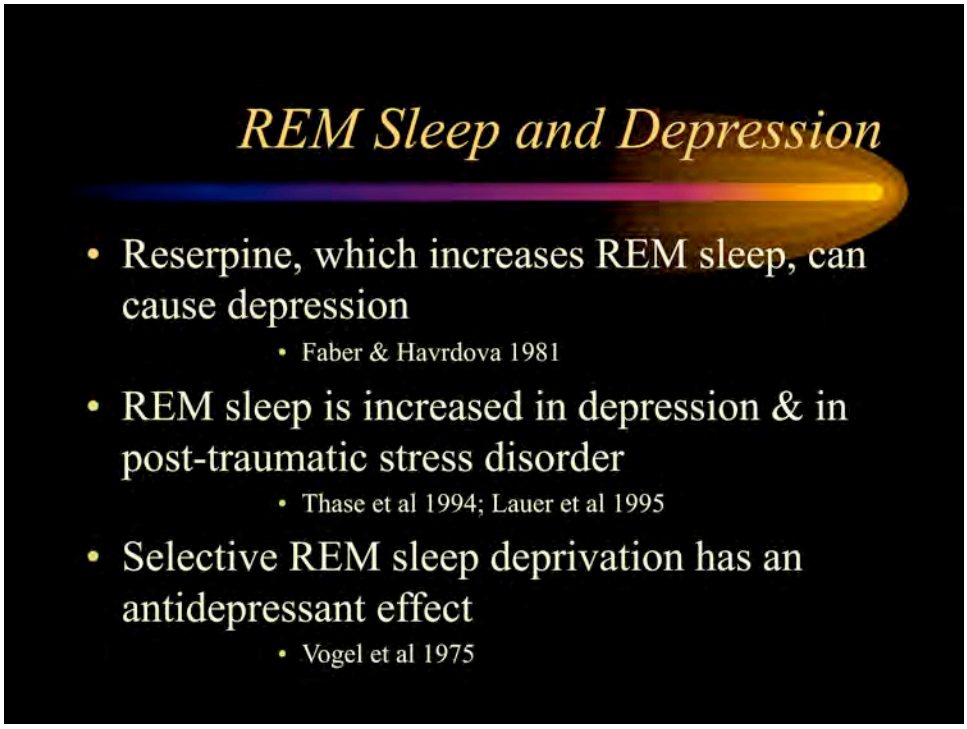
Unfortunately, the antidepressant effect is usually very short-lived. Long naps, on average 2 hours, caused a return of depressive symptoms. The presence of REM sleep during the nap was associated with this recurrence of depression.

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.



Partial sleep deprivation was studied by Sack and colleagues at the National Institutes of Health. When the person goes to sleep early and gets up very early, sleeping 5 hours from 9 pm until 2 am as in the top graph on this slide, the antidepressant effect is as good as for total sleep deprivation. In contrast, sleeping the same five hours, but this time from 3 am ' til 8 am, as in the lower graph, had no antidepressant effect. They noted that the reduction in depression was inversely correlated with the amount of REM sleep. Also, two nights of late partial sleep deprivation had a sustained antidepressant effect.



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

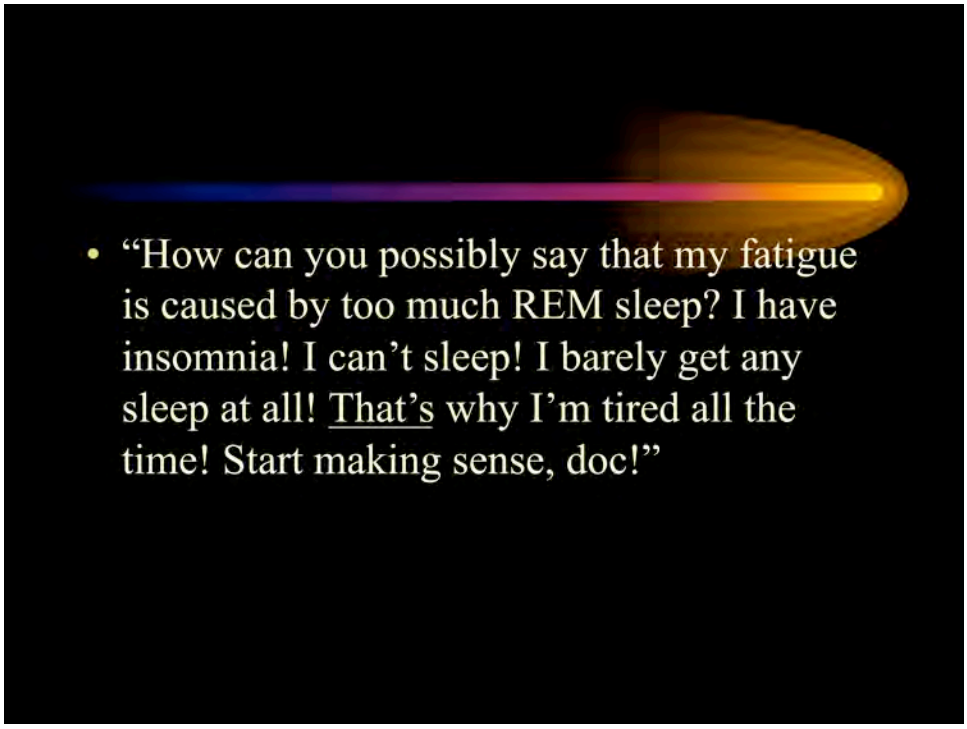
First, if you increase REM sleep, you can cause depression. For example, reserpine, a blood pressure medication which increases REM sleep, has depression as a side effect. Similarly, some beta-blockers, including timolol eye drops for glaucoma, can cause depression. These beta-blockers appear to also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

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

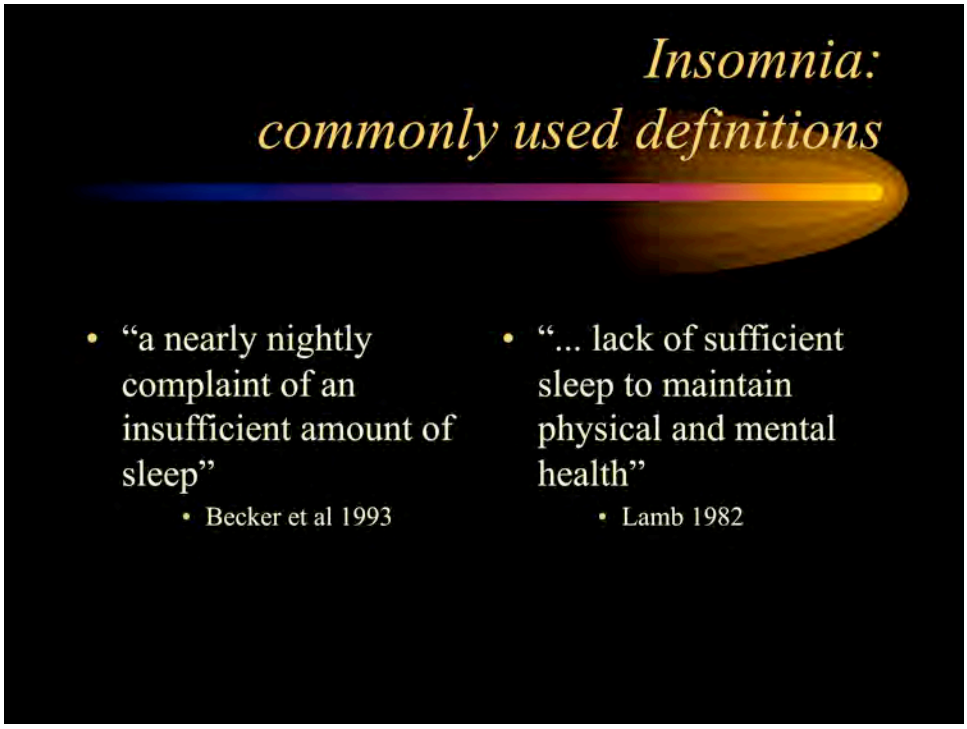
One notable exception is trazodone. But perhaps this explains why so many psychiatrists have given up on trazodone as not being a very effective antidepressant.



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.

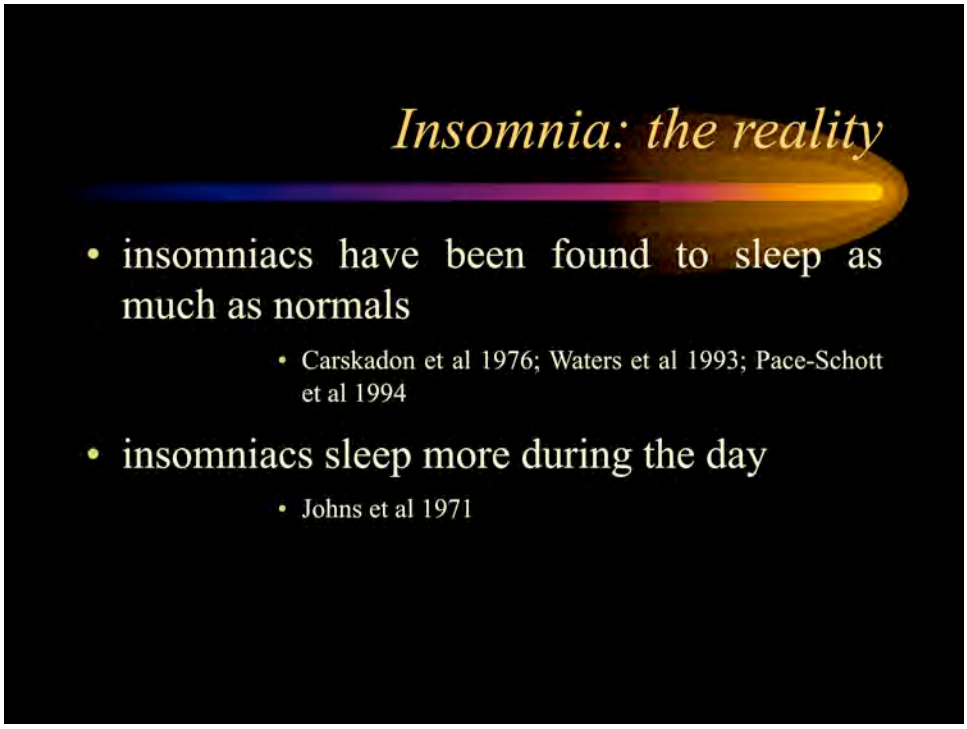
Well, you aren't any more skeptical than most of my patients when I suggest that their fatigue or their depression may be caused by too much REM sleep. The slide shows a typical reaction.

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.

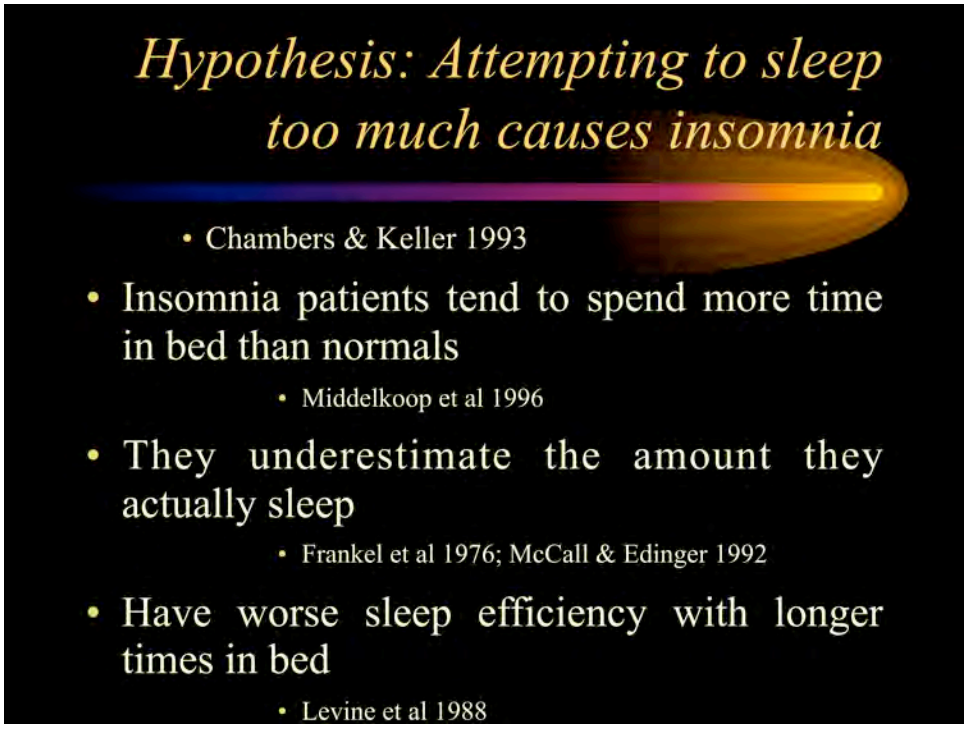


And most people, including sleep researchers, believe that insomnia means the person is not getting enough sleep. This slide quotes two typical definitions.

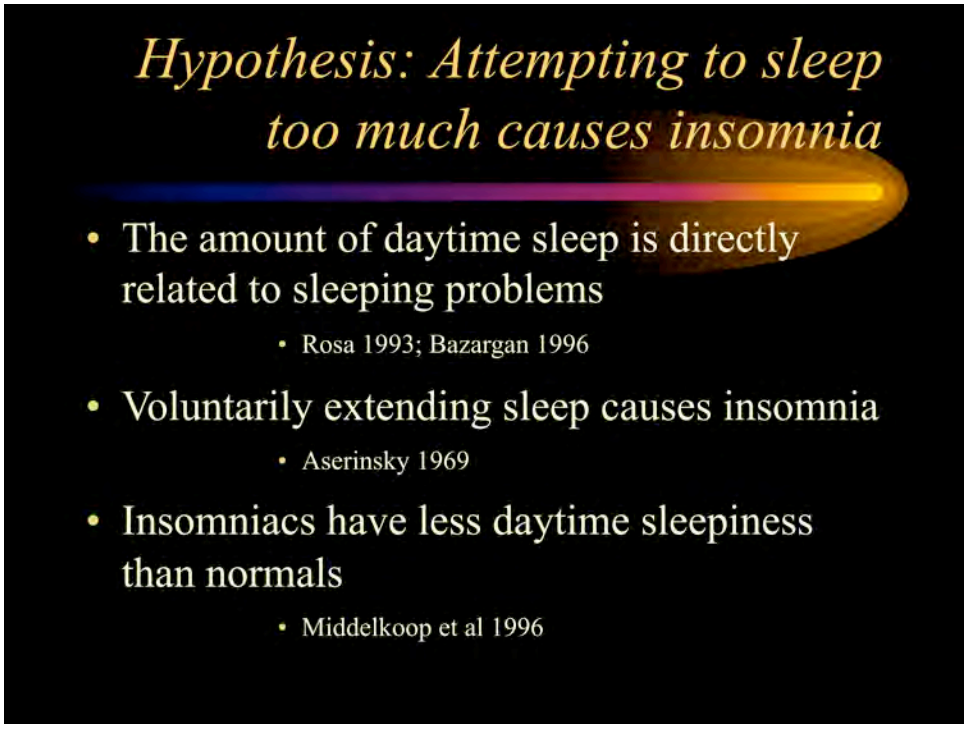
But is it really true that insomniacs are sleep deprived? Let's look at the research on insomnia.



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



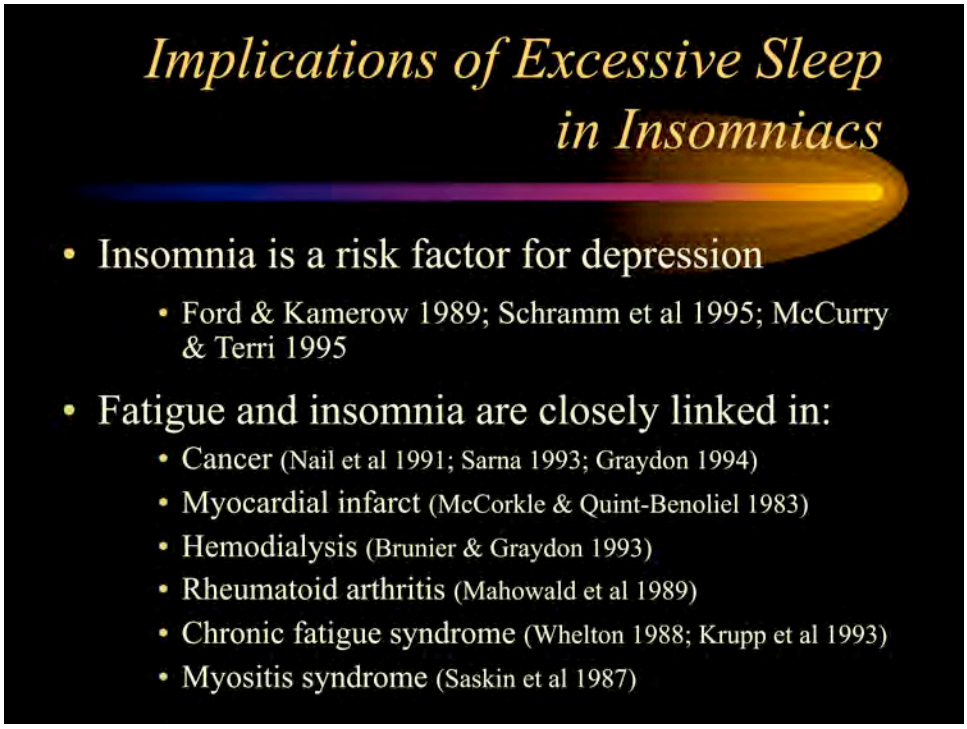
Chambers and Keller formulated the hypothesis that insomnia can be caused by attempting to sleep too much, that is, trying to get more sleep than one needs. We know that insomniacs spend more time in bed than normal people. They typically underestimate the amount they actually sleep, so they may believe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



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.

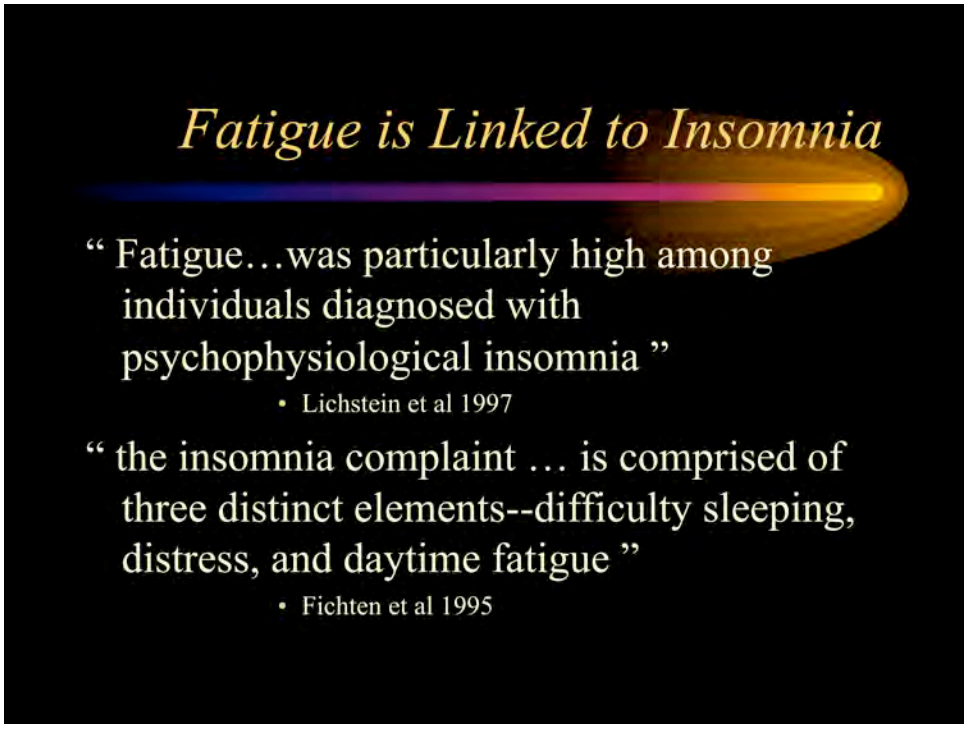


So if you accept this hypothesis, that symptoms of primary insomnia are caused by sleeping more than you need, then it is likely that these insomniacs are getting too much REM sleep, particularly since many insomniacs tend to sleep late, when REM sleep peaks. If they do get too much REM sleep, and too much REM sleep can 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.

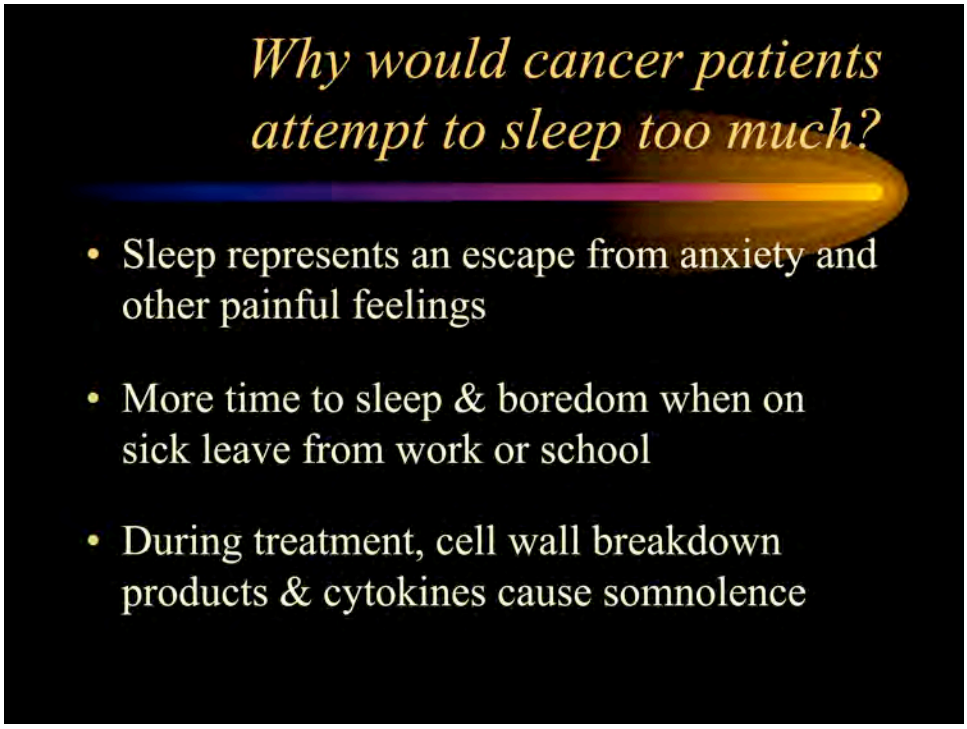
As for fatigue, I was unable to find direct evidence for the hypothesis that insomnia can cause fatigue, but there is lots of research demonstrating that fatigue and insomnia are closely linked in cancer and during cancer treatment. They are also Associated in people who have had heart attacks, who are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



It may be that you don't even need cancer or another serious illness to experience crippling fatigue; insomnia may be enough. It has been found that insomnia patients have the same levels of fatigue as fibrositis syndrome patients .

Ken Lichstein and his colleagues looked at fatigue in 206 persons who presented at a sleep disorders centre. They found high fatigue levels in a broad range of sleep disorders, but particularly high levels in patients with primary or psychophysiological insomnia.

Kathy Fichten and her coworkers, at the Institute of Community and Family Psychiatry of the Jewish General Hospital, looked at psychological adjustment and sleep parameters in 634 older community dwelling residents. I 've quoted their conclusion here.



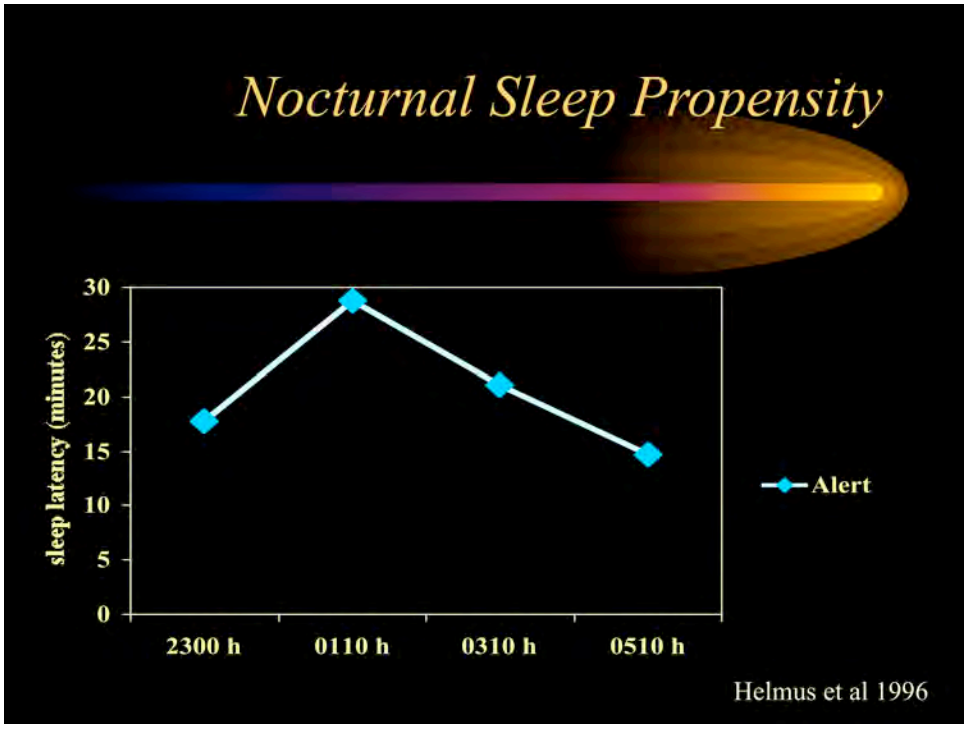
So let's go back to our cancer patients who are so distressed by fatigue, who have lots of insomnia, and who, I believe, are attempting to sleep more than they need.

This slide suggests some reasons why cancer patients may try to sleep more. The first two are self-explanatory. The third has to do with the acute phase inflammatory response, when cytokines, particularly the interleukins, which cause sleepiness, are present in large amounts. This may explain why a wounded animal will find a quiet place to curl up and go to sleep.

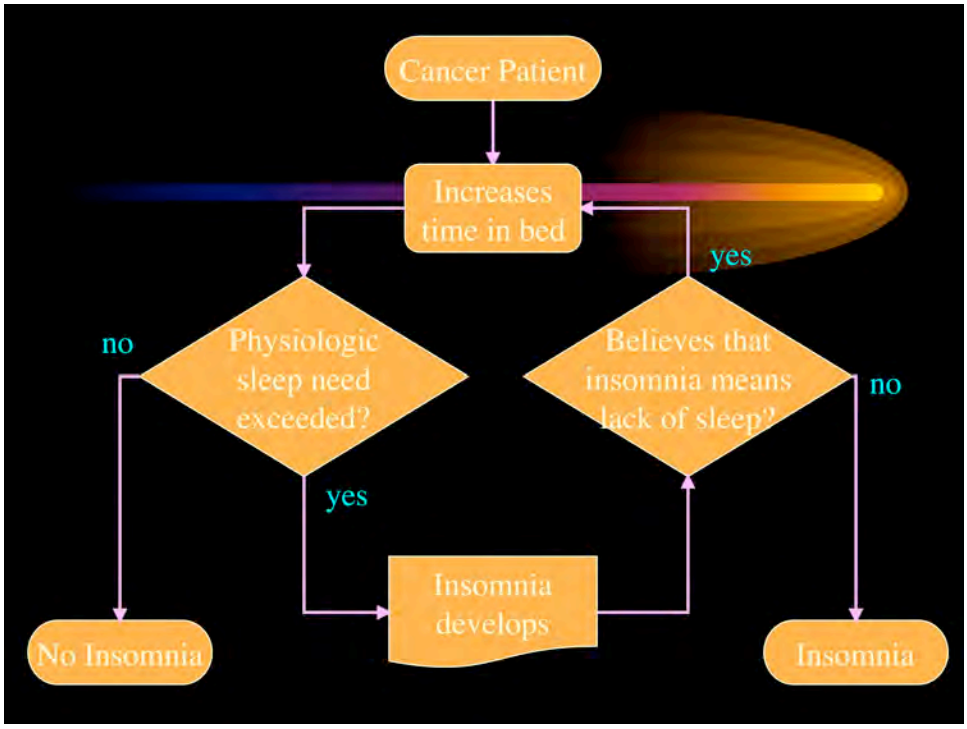
There are three ways in which cancer patients attempt to sleep more than they need. The first is to go to bed earlier. Second, get up later. Third, daytime naps. Some people use all three.

You've probably guessed, from the slides I showed earlier, that getting up late concerns me the most, because it can cause large increases in REM sleep. It turns out that sleeping late in the morning is also very easy to do, for almost everybody. I'll explain why.

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?

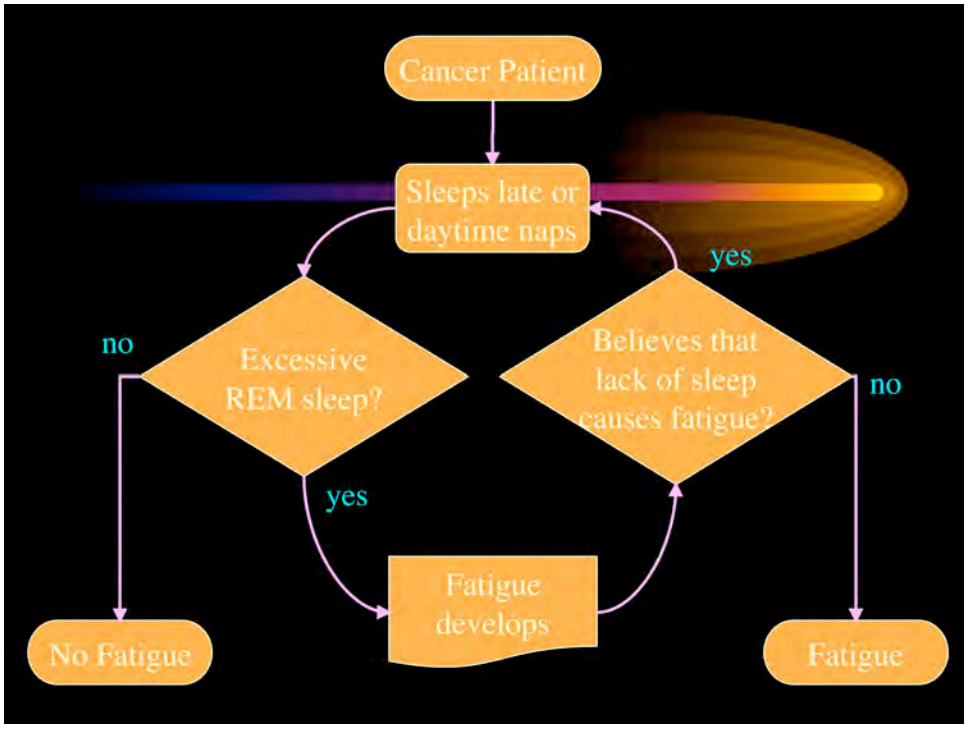


It turns out that people fall asleep quickest at 5 am, after having slept for 6 hours. This was true for normal people, normal people who were sleep-deprived for a whole night prior to the study night, and individuals who tended to be sleepy during the day. This finding suggests that, the more you sleep, 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.



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, the cancer patient increases time in bed, for the various reasons we've already talked about, escaping painful feelings, acute phase inflammatory response hormones, etc.

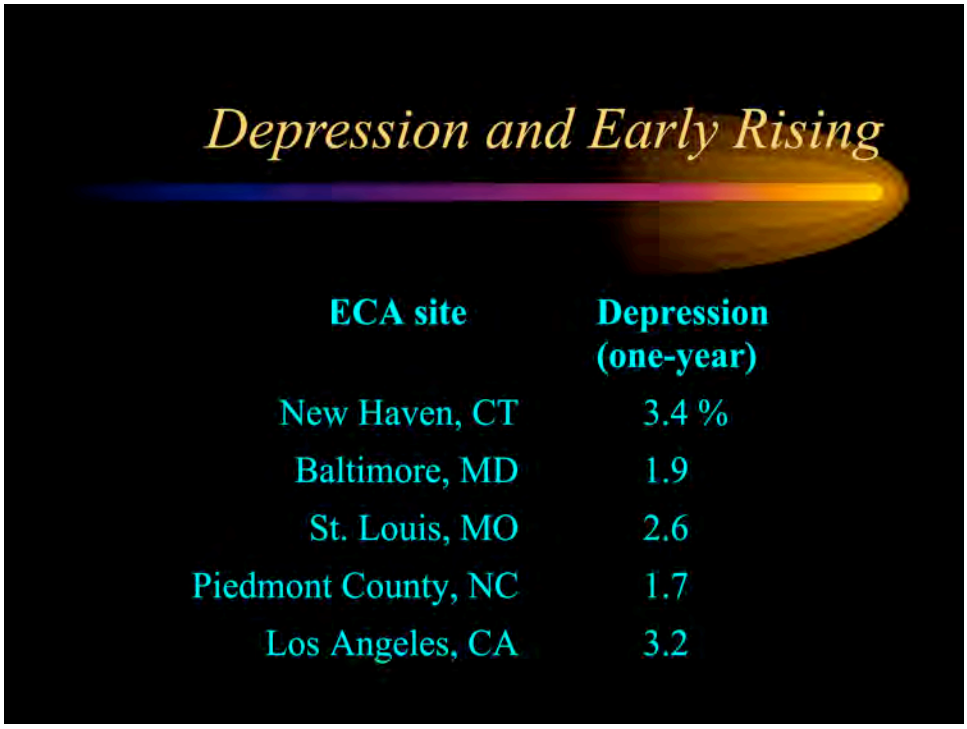
Following the arrow to the left, suppose the person's physiologic sleep need is now exceeded because of their increased time in bed. If so, insomnia develops. If the individual further believes that insomnia means that he or she's not getting enough sleep, then they are likely to try to sleep even more,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



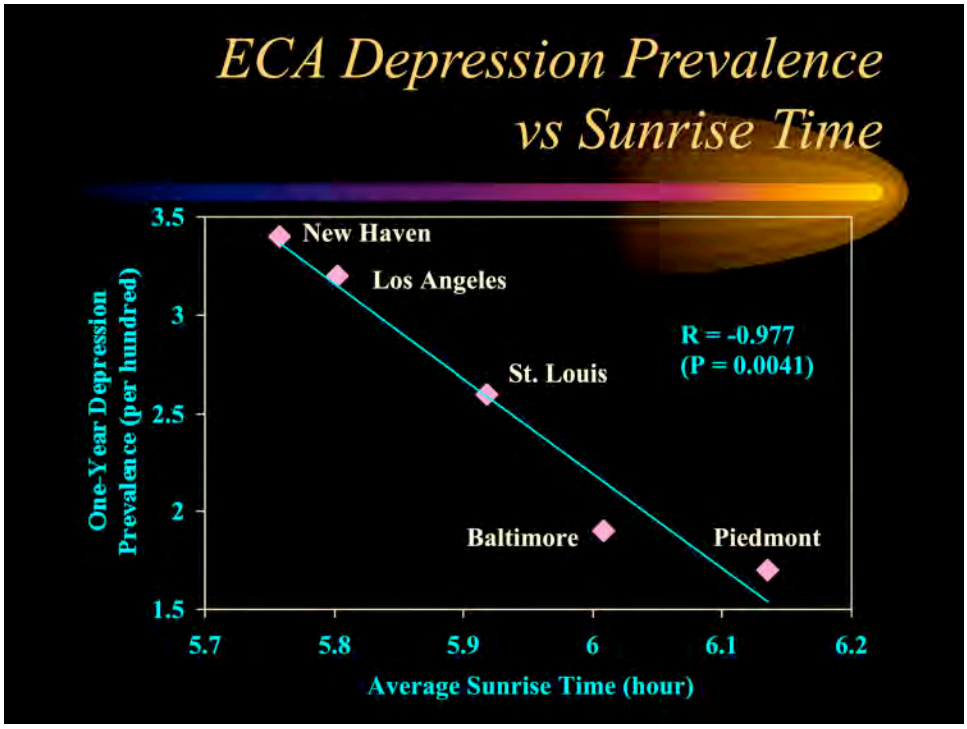
This slide illustrates a similar process, this time for fatigue. If the person with cancer sleeps later in the morning or begins to take daytime naps, thus increasing their REM sleep, at a certain point they will begin to have too much REM sleep. At this point, I believe, the majority will develop a minor depressive syndrome which we label fatigue, and a small percentage, those with a genetic predisposition, will develop a full-blown clinical depression.

If they also possess the belief that their fatigue is because of lack of sleep, and they try to compensate by sleeping more, either by getting up even later, or by taking more or longer daytime naps, they will get even more REM sleep, and be locked into this second vicious cycle.

Of course, both the insomnia vicious cycle from the previous slide, and this fatigue vicious cycle, may be operating simultaneously, and I think that in most cases they are, explaining the association between fatigue and insomnia, and between depression and insomnia.



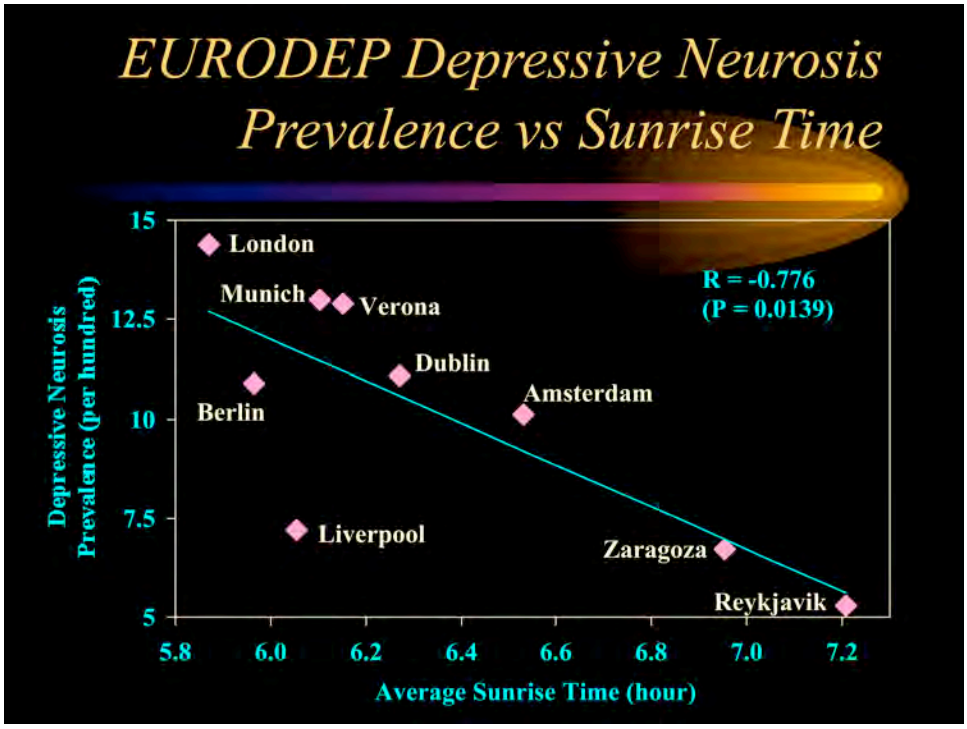
You know, there's nothing at all in the research literature that I could find on a connection between getting up early and preventing depression or fatigue. However, I did come across some numbers which I found very interesting. Back in the early 1980's the Epidemiologic Catchment Area Project was carried out in five communities in the United States to collect data on the prevalence of affective disorders. This study, sponsored by the National Institute of Mental Health, consisted of interviewing a probability sample of over 18,000 adults, using a structured questionnaire called the Diagnostic Interview Schedule. Over 200 papers have appeared in the literature looking at the data which resulted. I was not able to find any satisfactory explanation of why the prevalences varied so widely from one site to another. This slide shows, for example, the one-year prevalence for major depression, which was lowest in Piedmont County, but was twice as high in New Haven, Connecticut.



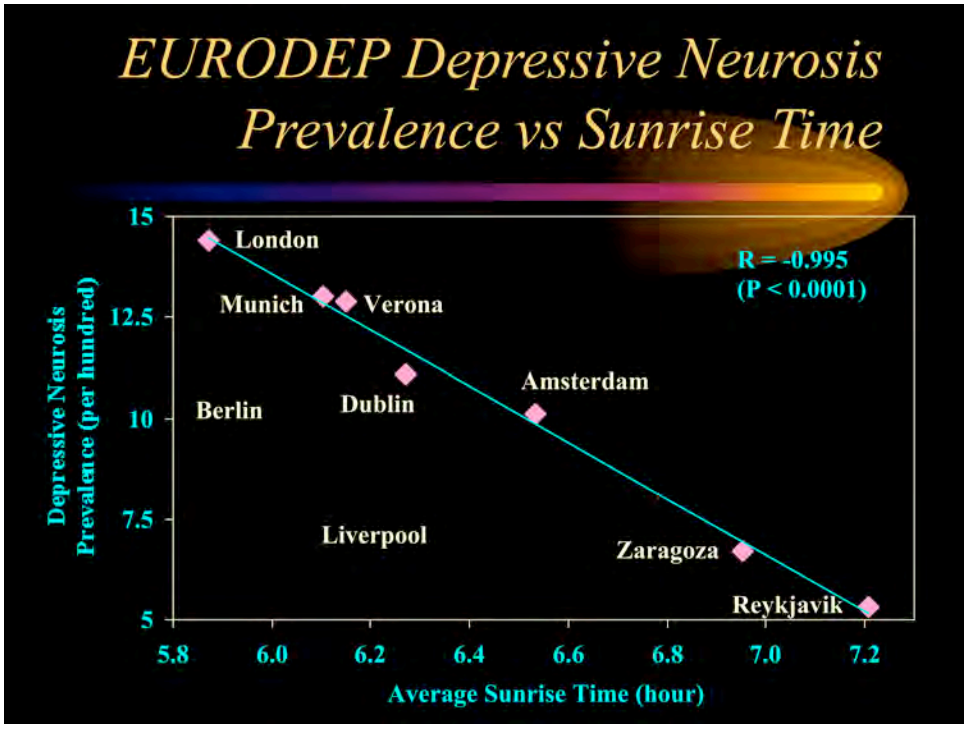
When I plotted these prevalence figures against the times for sunrise for the various communities, it looked like this. The sunrise times are averaged over the whole year. The Pearson correlation coefficient was -. 895.

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.

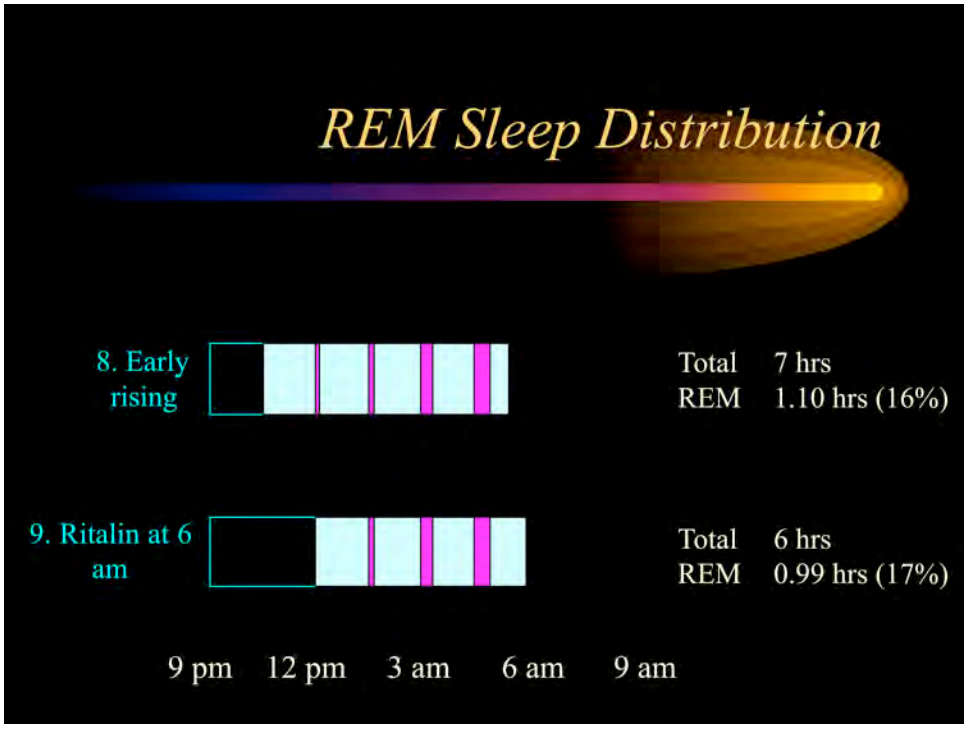


If this were the only study for which this relationship existed, it wouldn't mean much. But a study which was published this past April in the British Journal of Psychiatry, termed the EURODEP Programme, looked at the prevalence of affective disorder in the geriatric population in 9 European cities.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



When I take out the two outliers, Berlin and Liverpool, the regression line looks like this. The Pearson correlation coefficient now becomes -0.995, almost a perfect straight line correlation.

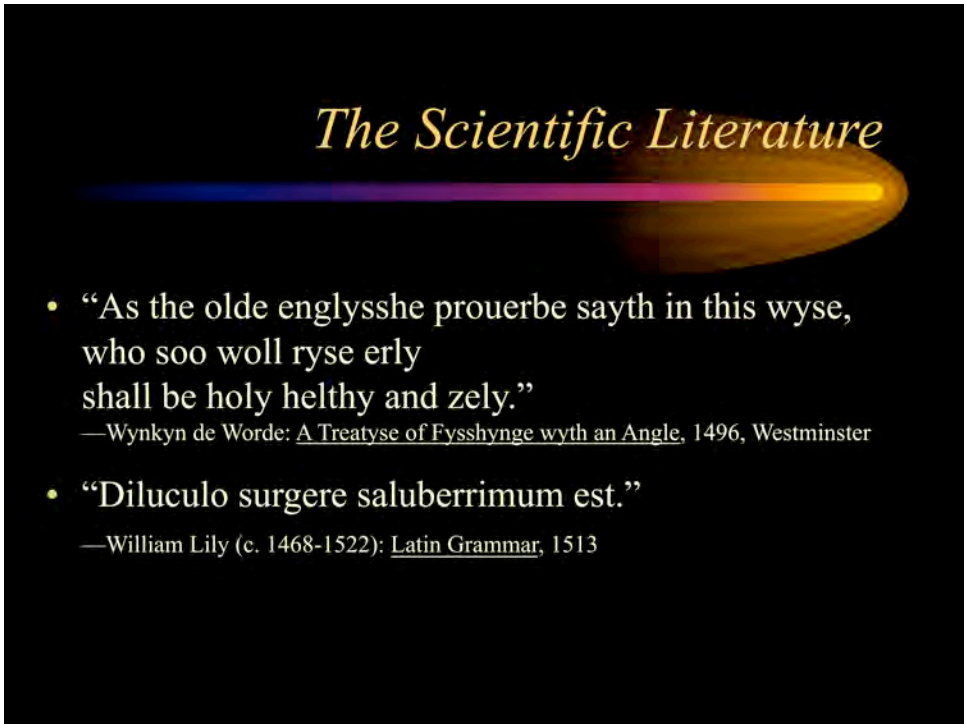
What determines when the sun rises for a given geographic location? The most important factor is the location of the city within its time zone: a city at the eastern edge of its time zone will have sunrise an hour earlier than a place at the western end of that time zone.
This has an important public health implication: if it were shown to be true that getting up early helps to prevent depression, then it would make sense to shift the borders of time zones, or, even easier, have daylight saving time all year round. This measure, which was applied in the U.S. during both world wars and again in 1973-74 as an energy saving measure, would cause the sun to rise 0.425 hours later on average. For the ECA study, this translates into a decrease in depression prevalence of about 2 people out of every hundred.
In the absence of such public health measures, individuals can always choose to get up earlier. This leads us to a treatment approach.



These two graphs reflect the approach I use with patients presenting with fatigue or depression, and on careful questioning give a history of sleeping late or taking daytime naps. If the individual is able and willing, I recommend early rising as in the upper graph. You can see that by going to bed at 10:30 pm and rising at 5:30 am, you will still get 7 hours of sleep, but only 1.1 hours of REM sleep, a reduction of 0.65 hours from what you get with even the normal sleep hours of midnight to 7 am. For elderly people who need less sleep, I might recommend just 6 hours in bed, from midnight to 6 am, as in the lower graph. This gives even less REM sleep.

In some situations where getting up early is problematic, for example patients who are non-ambulatory or for hospitalized patients, I prescribe a stimulant, methylphenidate, which you know by the trade name Ritalin, to be taken at 6 in the morning. Usual starting dose is 5 mg, going up to 10 mg after 2 or 3 days. Ritalin not only suppresses REM sleep, but helps people to stay awake, which of course suppresses REM sleep even more.

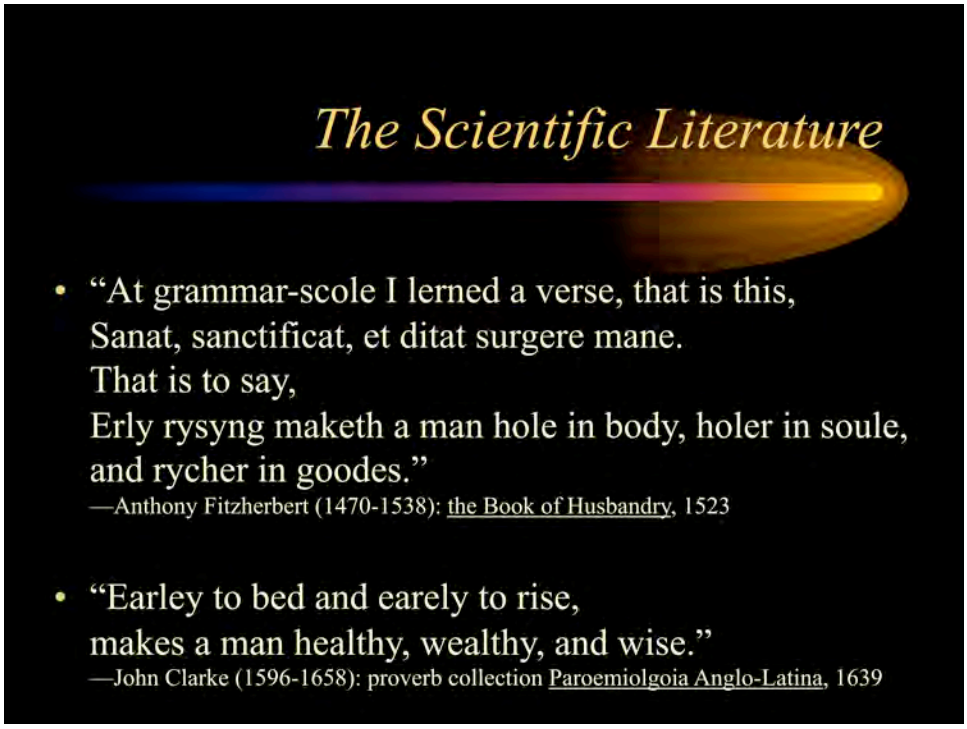
Clinically, I find that ritalin given at 6 am is effective much more often than if taken at the usual 8 or 9 am. I believe that this is because when given late, the REM peak will already have passed by the time the medication finds its way into the bloodstream.



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.

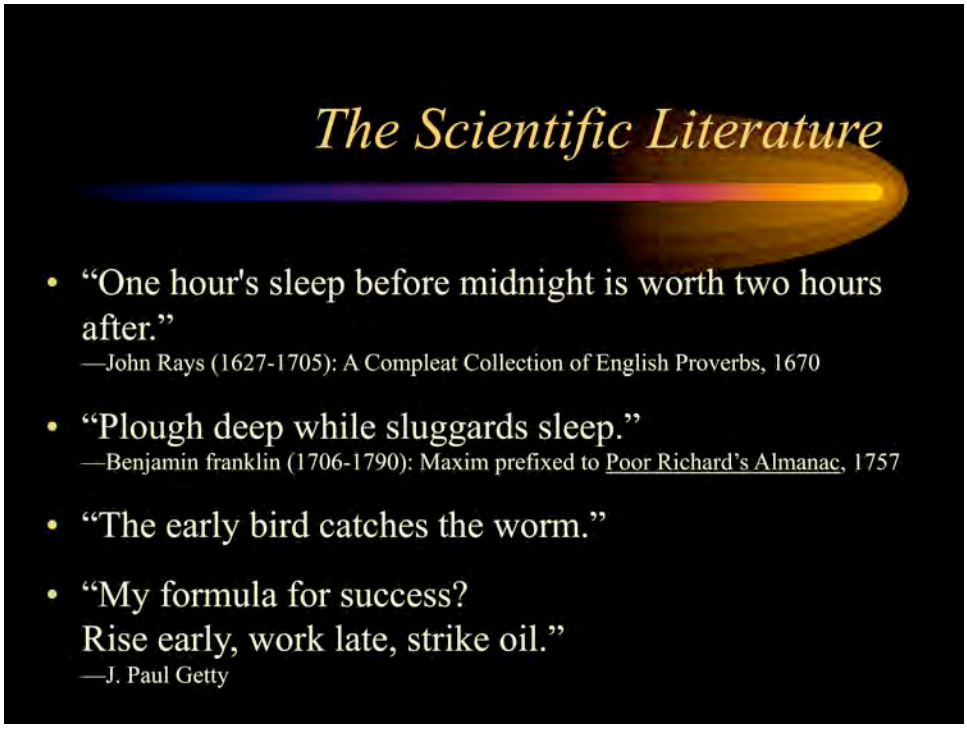
The earliest reference dates back to 1496, but it is clear that this proverb was already considered old at that time. The word "zely" means happy or fortunate.

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



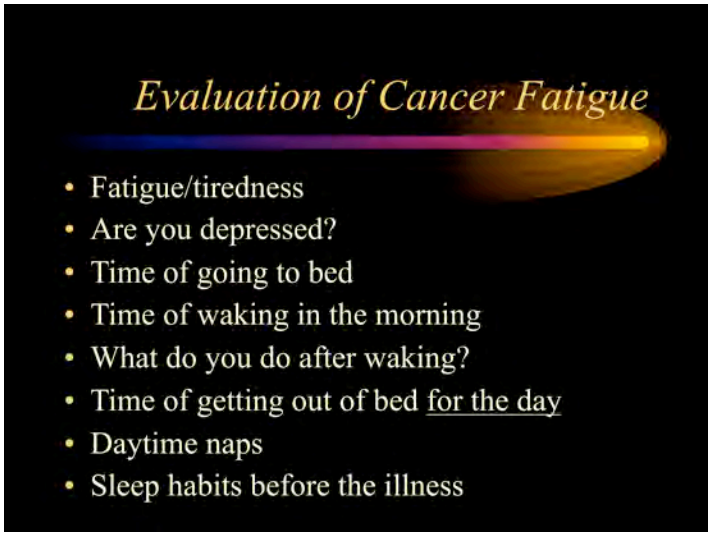
Here's another latin proverb.

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.



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

Thank you for being such a great audience!



Theories are all well and good, but what's the clinical implication? This slide shows the elements of history-taking which are important when evaluating a patient who presents with fatigue. First, clarify the presenting complaint: is it truly chronic fatigue, is it sleepiness, or is it acute fatigue occurring with exertion, possibly worsened by deconditioning and anemia? What time of day or evening is it worst? How distressing is it, and what impact does the fatigue have on the person's life (that is, how does it affect their work, their leisure activities, their relationships)?

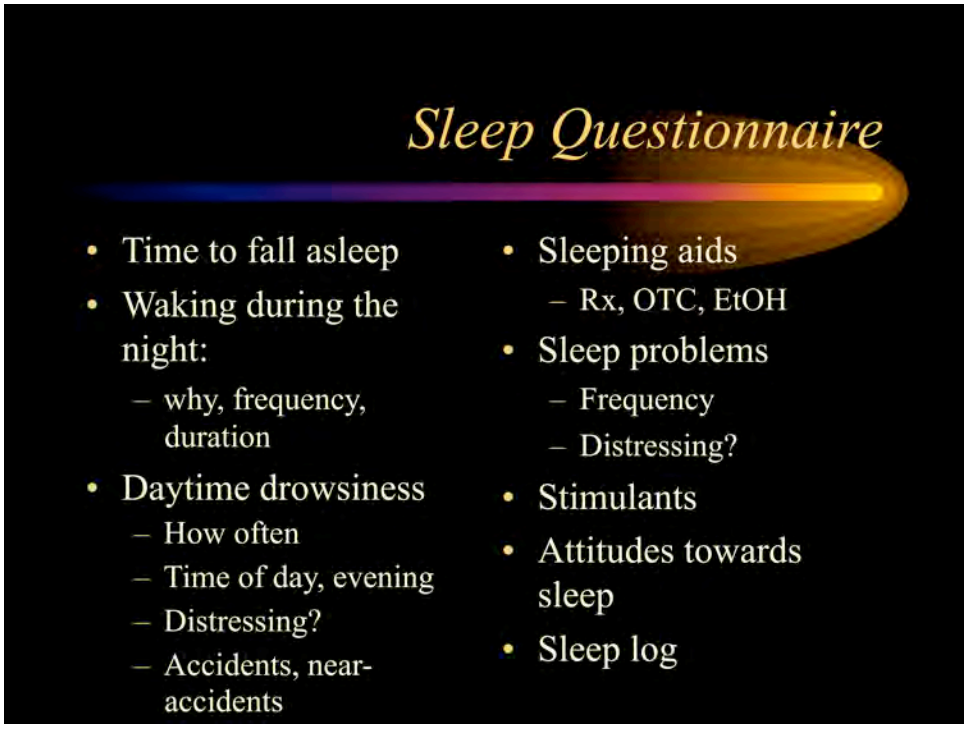
The single question, "Are you depressed?" has been shown to outperform the Beck Depression Inventory in correctly identifying persons with depression.

Time of going to bed, and time of waking are self-explanatory. I also ask, "What do you do after waking?" For example, do they stay in bed? Get up and have breakfast? Read the newspaper? Follow up with the question, "And what do you do after that?" I have been surprised frequently to find out that individuals often go back to bed after breakfast, or after getting the kids off to school.

If the person returns to bed, I ask what time they get up for the day.

Daytime naps should be explored: what time of day, how long, how often, and how long it takes to fall asleep.

An extremely useful question to ask is about sleep habits before the illness, when the person was working and doing well. This gives a baseline for the sleep duration and timing that works for that individual. An effective intervention might be to ask the person to go back to those earlier sleep habits.



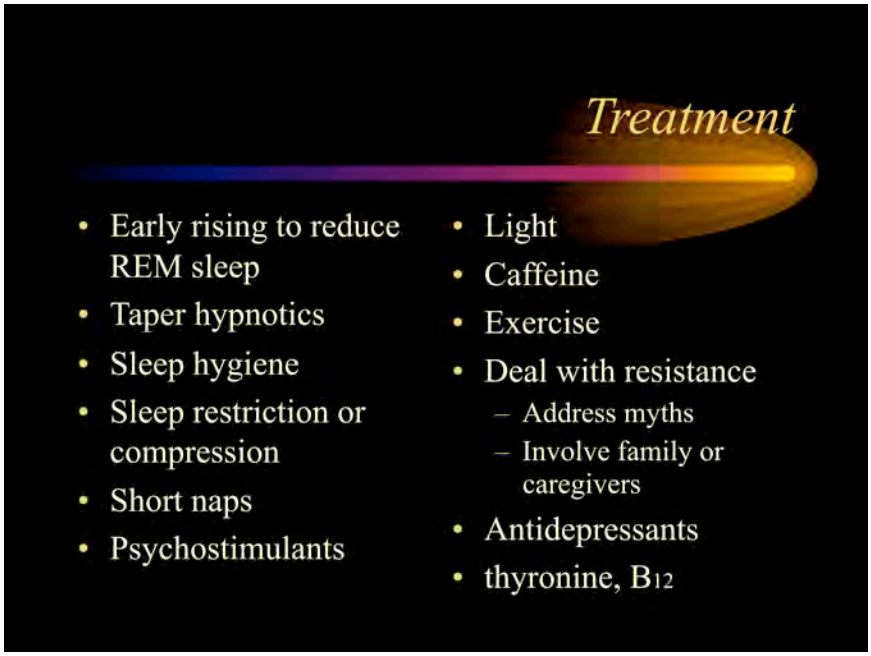
If the patient complains of a sleep disturbance, I ask about those aspects of sleep shown on this slide. I want to emphasize how important it is to correctly identify daytime drowsiness or sleepiness. If we fail to pick up on these cases and do not make the appropriate referrals, for example to a sleep 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.



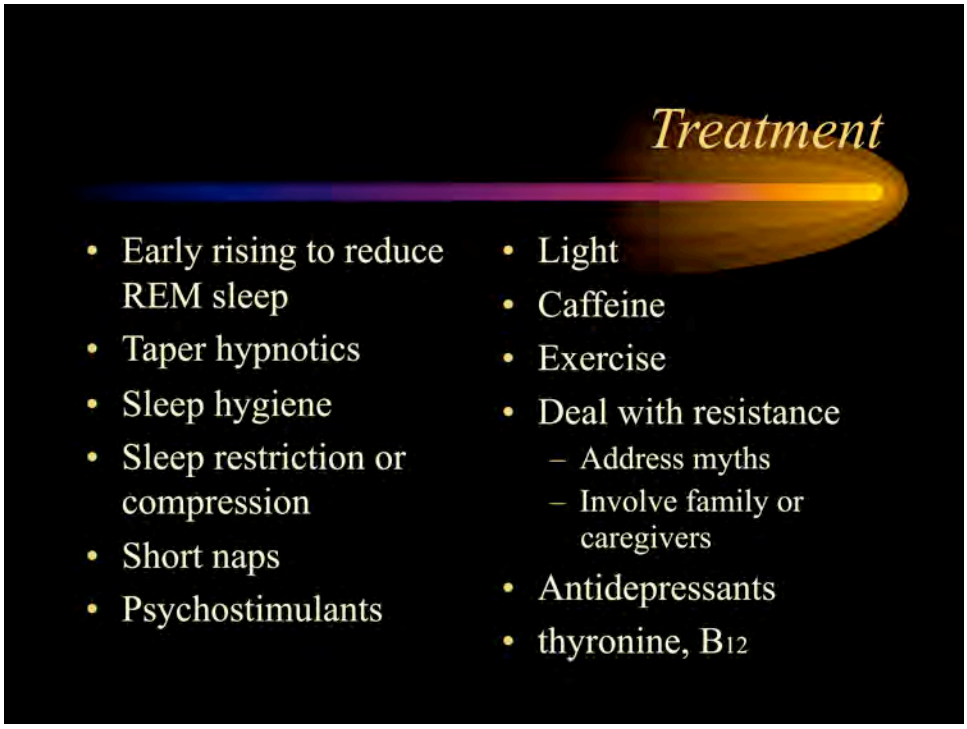
The most useful single intervention for many people with fatigue or other depressive symptoms is to counsel them to get up earlier, for example at 6 am, or simply to go back to the sleeping pattern they followed when well.

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.

DON'T CHANGE THE SLIDE!



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.

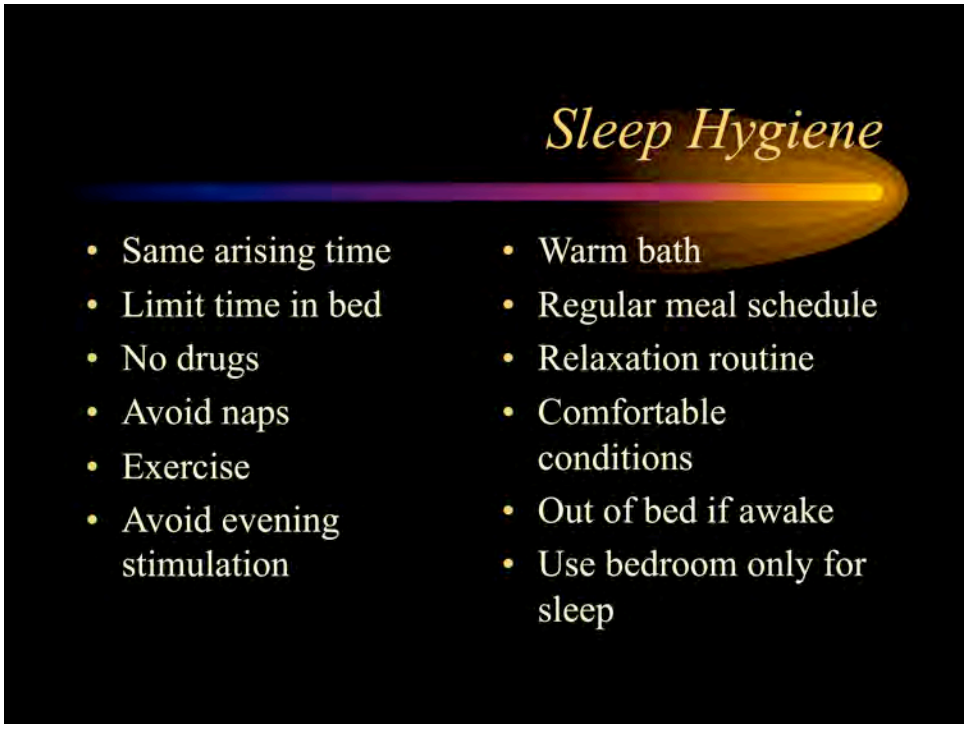
Caffeine acts as a mood elevator: women who drink no coffee commit suicide at 2.9 times the rate of those who drink 2 to 3 cups a day.

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.



These are typical sleep hygiene recommendations which I'm sure you've all heard or seen countless times.