

# THE DARK SIDE OF SLEEPING PILLS

## Mortality and Cancer Risks, Which Pills to Avoid & Better Alternatives

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# CHAPTER 1

## Sleeping Pills Could Shorten Your Life

**WARNING:** Sleeping pills are hazardous to your health and could cause death from cancer, heart disease, or other illnesses.

**F**or over 35 years I have worked to assess the risks of sleeping pills. I have learned that sleeping pills are associated with significantly increased mortality.

This means that people who take sleeping pills die sooner than people who do not use sleeping pills.

I first became interested when I saw the work of Dr. E. Cuyler Hammond at the American Cancer Society. In 1975, I went to visit The American Cancer Society, starting a collaboration which lasted for many years. American Cancer Society data from over 1 million people showed that use of sleeping pills was associated with more deaths within 6 years, but insomnia by itself was not associated with any death risk.

As of January, 2012, there were 24 published studies of the mortality risks of sleeping pills. Of the 22 studies which reported either greater or lesser mortality associated with sleeping pills, 21 studies showed that people taking sleeping pills died sooner. (The 22nd study found no mortality risk of sleeping pills but did find sleeping pill usage associated with increased cancer deaths.)



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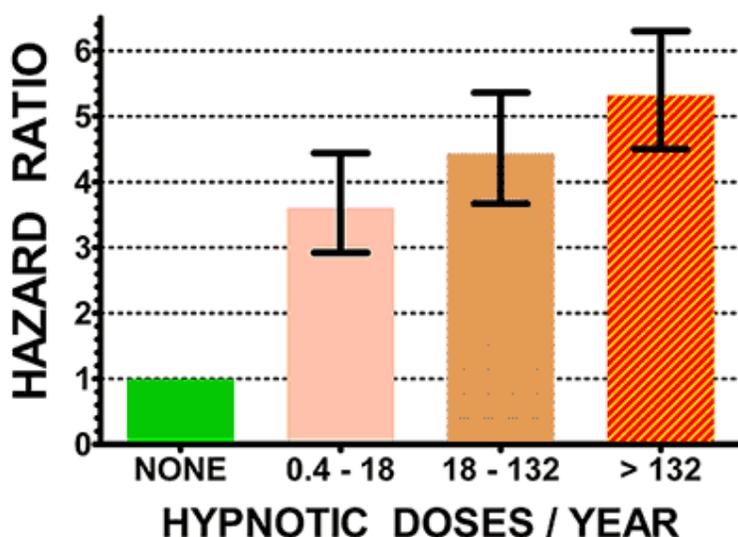
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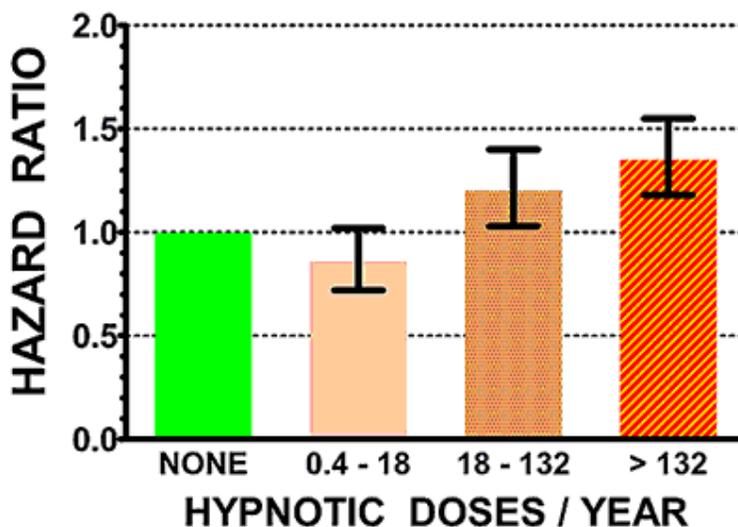
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We have now published a new study<sup>[1]</sup> of over 10,000 patients who took sleeping pills and over 20,000 matched patients who did not take sleeping pills. The patients who took sleeping pills died 4.6 times as often during follow-ups averaging 2.5 years. Patients who took higher doses (averaging over 132 pills per year) died 5.3 times as often. Even those patients who took fewer than 18 pills per year had very significantly elevated mortality, 3.6 times that of patients who took no hypnotics.

## MORTALITY with HYPNOTICS



## CANCER INCIDENCE



The illustrations above show the hazard ratios for mortality (above) and cancer incidence (below) for the control non-users of hypnotics (doses/year = NONE, in green) and for three groups of users of hypnotics with increasing numbers of doses/year prescribed. Hazard ratios above 1.0 are estimates of how many times

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the mortality or cancer incidence of hypnotics users exceeded that of controls. The heavy black bars show the statistical 95% confidence limits of the hazard estimates, that is, statistically the hazard ratio of the sample is 95% likely to be within the bars above and below the vertical black lines. However, unknown biases in the samples could produce true risks outside the confidence limits.

Patients who took sleeping pills died 4.6 times more often (on average) than patients who avoided sleeping pills.

It seems quite likely that the sleeping pills were causing early death for many of the patients. In addition, those who averaged over 132 sleeping pills per year **were 35% more likely to develop a new cancer.**

We went to great pains and effort to match the patients taking sleeping pills with those not taking sleeping pills for age, sex, smoking history, and various measures of poor health, so it seemed to be a fair comparison. Nevertheless, it is true that showing that sleeping pill use is associated with early death does not prove that the sleeping pills are causing the deaths. Theoretically, there could be confounding factors or biases in the selection of patients which caused these deaths without involving sleeping pills. We can only say that we found almost no evidence of such biases. Although there was certainly at least a small amount of confounding, it seemed to us unlikely that biases could entirely explain all of these excess deaths and cancers.

If sleeping pills cause even a small portion of the excess deaths and cancers associated with their use, they are too dangerous to use.

Some readers will remember when the cigarette companies claimed that the fact that cigarette smoking is associated with cancer and early death did not prove that cigarettes cause cancer. Cigarette manufacturers have by now given up on that argument. The risks are quite similar with sleeping pills. For absolute proof, we would need large randomized controlled trials of cigarettes or sleeping pills, but nobody is going to do such trials. If the cigarette companies believed that such trials would prove cigarettes were safe, they would have done such controlled trials decades ago. How about the sleeping pill companies? Of course, now that we know that particular sleeping pills are associated with excess mortality, it would probably be unethical to do such a controlled trial, so for those particular sleeping pills, we will probably never have absolute proof whether they cause mortality or not. The kind of data we gathered is probably about as good as one could get.

The particular sleeping pills we studied were zolpidem (e.g., Ambien), temazepam (e.g., Restoril), eszopiclone (e.g., Lunesta), zaleplon (e.g., Sonata), other benzodiazepines such as triazolam (e.g., Halcion) and flurazepam (e.g., Dalmane), barbiturates, and sedative antihistamines such as diphenhydramine (e.g., Benadryl). Most of the patients in this study were taking zolpidem or temazepam. We had only minimal data about the other drugs. However, all of the sleeping pills studied were significantly associated with excess mortality. Because

of the way the study was done and its limited size, we could not say that one sleeping pill is safer than another.

### Sleeping Pills Found To Have Significant Mortality Risk

Zolpidem  
Temazepam  
Eszopiclone  
Zaleplon  
Triazolam  
Flurazepam  
Estazolam  
Quazepam  
Barbiturates (esp. phenobarbital)  
Antihistamines, mainly diphenhydramine

These results do not necessarily apply to any sleeping pill which was not included in our study, except perhaps zopiclone (because zopiclone is half eszopiclone). Zopiclone is a sleeping pill popular outside the United States.

## 1.A. New sleeping pills cause cancer in animals

Were the epidemiologic studies just statistical accidents, or do sleeping pills really cause cancer? Several years ago, the Food and Drug Administration (FDA) started making available on the internet some of their documents about the review of those newer sleeping pills approved for marketing in the United States since 1998. You can find these documents yourself through the US Food & Drug Administration's Online Service, Drugs@FDA.[\[2\]](#)

To my great surprise, I learned that rats and mice given high doses of zaleplon (Sonata), eszopiclone (Lunesta) as part of zopiclone, and ramelteon (Rozerem) developed cancer. The information available was a little vague to be certain, but it seems that these new sleeping pills all caused cancer in animals. I am no expert on experiments of this type, but FDA reviewers thought some of the results were worrisome. One of the reasons I am not sure I understand these results is that I cannot find that the companies have ever published the details in the medical literature. It is conceivable that the manufacturers do not want these cancer experiments understood. These drugs also broke chromosomes, which is a well-known specific chemical mechanism by which drugs cause cancer.

There was also some older and confusing information about zolpidem (Ambien). Although one of the old records[\[3\]](#) seemed to say that animals given zolpidem developed three kinds of cancer, and FDA reviewers were concerned about these hints of carcinogenicity, the new labeling approved[\[4\]](#) for the extended release version of zolpidem (Ambien CR) says no evidence of carcinogenic potential was observed in either mice or rats. I would like to know how the company figures they do not owe people a warning.

## 1.B. Evidence that sleeping pills cause cancer in people

In 2005 and 2006, several new sleeping pills were introduced into the U.S. market. The industry was hoping to increase hypnotics sales by several billion dollars a year. Because the companies wanted Food and Drug Administration (FDA) approval to market their drugs for long-term consumption, they did larger studies of long-term use than ever had been done before. Summaries of the data from these randomizing controlled trials can be found at the FDA internet site<sup>[5]</sup> for zaleplon (Sonata), eszopiclone (Lunesta), and ramelteon (Rozerem). It turned out that because zaleplon was compared to zolpidem as well as to placebo, there was a bit of zolpidem data available also.

I have to admit that it is hard to understand the details of these controlled trials from the data which FDA has made available, but fortunately, I persuaded the FDA to review their files.

According to the FDA, there were 9 new skin cancers and four other cancers among study participants randomized to the

sleeping pills, but no new cancers among those who only received placebo. Even considering that there was over 2 times as much exposure to the sleeping pills, it looks like **this indicates that new sleeping pills caused cancer**. The best estimate would be that the cancer rate for participants randomized to sleeping pills was several times that of the luckier volunteers who received placebo. Because these data come from randomizing comparisons, they appear to be proof that new sleeping pills (as a group) cause cancer. However, the controlled trial data were not sufficient to prove that any specific sleeping pill or brand causes cancer.<sup>[6]</sup> Let's put together the epidemiologic data, the animal data, and the data from combining these controlled trials for 4 drugs. The evidence is that a patient who takes any of the sleeping pills listed in the [box above](#) is increasing his or her risk of getting cancer. I feel that my patients should be warned about this risk.

We do not have clear evidence that one sleeping pill has more cancer risk than another. In our epidemiologic study, we only demonstrated statistically significant cancer risks for zolpidem and temazepam, the most popular drugs in that study, but none of the drugs for which we had less data were clearly better or worse. For patients prescribed over 132 sleeping pills per year, there was a 35% increased risk of developing cancer within an average of 2.5 years.

A new study from Taiwan has appeared, based on a representative national health insurance data base.<sup>[7]</sup> These authors studied zolpidem, which was the most popular hypnotic in Taiwan, as zolpidem has also been for several years in the United States in both brand-name and generic versions. With over 8 years of follow-up, the Taiwan authors found a considerably larger mortality hazard associated with zolpidem than we had observed with shorter follow-up. There were also many differences in methodology of the Taiwan study compared to ours and the populations differed. The makers of zolpidem have been quoted in the *New York Times* as claiming that a longer study is better for cancer detection. There was also a bit of evidence that benzodiazepine use (e.g., temazepam) was associated with cancer, but this was not analyzed in detail. I expect that as time goes on, there will be several more studies confirming the conclusion of our study that mortality and cancer are associated with sleeping pills usage. So far, no information has appeared leading me to doubt any part of our study.

**The evidence is that a patient who takes any of the sleeping pills listed in the box above is increasing his or her risk of getting cancer.**

## 1.C. More lethal risks of sleeping pills

As a young medical student in my first year of training, one of the first things I learned in our student laboratory was that the kindest way to “put an animal to sleep” permanently was to administer a barbiturate such as pentobarbital. A bit later, I learned that pentobarbital was being prescribed almost automatically as a sleeping pill for patients in the hospital (in a sublethal dose, hopefully.) Related drugs are used to execute the death penalty. Any medical student knows that these drugs can kill.

Doctors have a wonderfully complete understanding of how sleeping pills such as pentobarbital kill animals. These drugs bind with protein molecules called GABA receptors on the surface of nerve cells. The same protein receptor molecules bind at the same time with a neurotransmitter chemical called GABA, which gives them their name. Barbiturates and other sleeping pills accentuate the action of GABA, which is to cause the receptor molecule to allow chloride ions to enter the nerve cells. Since the chloride ions are negatively charged, they make the inside the nerve cell more negatively polarized, which in turn, makes the nerve cells less likely to fire (to generate nerve activity). When the nerve cells which stimulate the muscles of breathing are inhibited from firing action potentials by GABA and by sleeping pills, the animal stops breathing. When breathing stops, the animal dies within a few minutes from lack of oxygen in the lungs. No doubt these same mechanisms explain how barbiturates kill people who take too high a dosage, either accidentally or with suicidal intention.

In the 1970's, a new group of sleeping pills became popular, molecules which chemically are named benzodiazepines. The first sold as tranquilizers were chlordiazepoxide (Librium) and diazepam (Valium). Soon, the benzodiazepine flurazepam (Dalmane) was marketed as a sleeping pill, and flurazepam soon dominated the market. The main advantage of benzodiazepines is that they are less likely to produce acute overdose deaths than barbiturates.<sup>[8]</sup> For the last 15 years, most new sleeping pills have been benzodiazepine agonists, which means that the chemical molecules may not be classed as benzodiazepines but they act at the same receptors. All of these newer drugs seem to have less overdose risk than barbiturates, but it is still possible that single doses of these newer sleeping pills are sometimes lethal. There is certainly evidence that large doses of these drugs by themselves or modest doses combined with alcohol and other drugs can be sometimes lethal.

There is an age-old belief that sleeping pills might help depressed people, but sleeping pill manufacturers' controlled trials prove that sleeping pills can cause depression.<sup>[9]</sup> In fact, the sleeping pills examined in one study seemed to double the rate of new depressions.

Suicide, accidental overdose and cancer are probably not the most common ways in which sleeping pills kill, but the other ways are more poorly understood and less well documented. Here are some of the other possible mechanisms.

All of the sleeping pills can cause “hangover,” that is, they not only reduce the action potentials of our brain cells during sleep, but they can also reduce brain cell activity during the day.<sup>[10]</sup> This can make us sleepy, less alert, confused, and weak during the day. We will discuss psychological consequences of this hangover later, but here I mention the impairments of survival. Falls are much more common among elderly people who are taking hypnotics.<sup>[11]</sup> Of patients given Lunesta, 10% had accidents as compared to 6% given placebo in one study, and falls were

specifically more common with Lunesta.[12] Because several studies show that people who are responsible for automobile accidents are unusually likely to have sleeping pills in their blood[13], it is thought that hangover may often cause automobile accidents, as well as other fatal accidents. The recent publicity about Ambien zombies driving like sleep walkers provides some extremely vivid examples.[14]

In the last 20 years, physicians have become concerned about sleep apnea, a condition where there are pauses of breathing during sleep. Physicians suspect that sleep apnea can cause deaths during sleep. Not all studies are in agreement, but several studies have found that when a person with sleep apnea

takes sleeping pills, there are more pauses in breathing and the pauses last longer, which could be dangerous. I was surprised to learn in the FDA data how well-documented it is that zolpidem makes sleep apnea worse. Because sleeping pills risk making apnea worse, many experts recommend that people with apnea should not be given sleeping pills. The problem is that almost everybody above age 40 has some sleep apnea, and the majority of people over 65 would meet commonly-used criteria for a diagnosis of sleep apnea.[15] Therefore, a large proportion of people taking sleeping pills must be making their apnea worse. Over a period of many years, anything which makes sleep apnea worse would be expected to cause high blood pressure, and therefore, to increase the risk of heart attacks, heart failure, and strokes.

A final concern in regard to mortality is how people care for themselves. Because sleeping pills, like tranquilizers, reduce worry about possible threats and risks in our lives, it is possible that the hangover effects of sleeping pills would reduce people's attentiveness in taking care of themselves.

**Because sleeping pills risk making apnea worse, many experts recommend that people with apnea should not be given sleeping pills.**

## CHAPTER 2

### Other Risks of Sleeping Pills

#### 2.A. Sleeping pills impair daytime thinking.

**T**he side effects of the prescription sleeping pills are much like their benefits. At night, we want our brain cells to stop working (unless we need to get up in the middle of the night), so sleeping pills make the brain less active. If the sleeping pill is in the blood during the day, it will make the daytime brain less active and less functional. The problem is that no sleeping pill remains in the blood all night, impairing consciousness, and then suddenly evaporates at the moment of awakening. Besides, a large percentage of people who take sleeping pills do often get up at night, at a time when the sleeping pill could cause falls or confusion. Most of the marketed prescription hypnotics, when taken at bedtime, will remain in the

blood with at least half strength when morning comes.

Only a few prescription hypnotics marketed in the U.S. leave the blood fast enough to be largely gone from the blood by morning: these include zolpidem (Ambien), zaleplon (Sonata), and triazolam (Halcion). Even these drugs may be found in the morning blood if they are taken in the middle of the night. Ambien CR may sometimes affect people the next morning, and eszopiclone (Lunesta) is likely to produce a few hours of morning impairment, particularly among people over age 60. On January 10, 2013, the FDA issued a warning recommending that the usual dose of zolpidem (Ambien) be no more than 6.25 mg for women. The FDA had finally discovered that a percentage of patients have enough zolpidem in the blood the next morning to impair performance such as driving. Oddly enough, despite the brief half-life (time to be half-dissipated) of zolpidem, zaleplon, and triazolam, there is fragmentary evidence that these short-acting hypnotics produce impairments lasting after their disappearance from the blood.[\[16\]](#) Perhaps this is because a percentage of people have genetic variations in their metabolism of sleeping pills which may cause dangerous concentrations to linger. Ramelteon (Rozerem) produces no next-day impairment according to the manufacturer studies, but one well-controlled independent European study showed impairment in driving performance.

As explained above, sleeping pills suppress the action potentials of a wide variety of brain cells. The psychological effects are to make us sleepy, reduce alertness and vigilance, slow reaction times and judgment, and impair aspects of intelligence and memory. Literally hundreds of studies have been done concerning the psychological effects of sleeping pills, both within a few hours after ingestion and then during the day following taking a sleeping pill at bedtime.[\[17\]](#) To summarize an extremely complex group of studies, almost all sleeping pills produce immediate impairments of memory and performance. Further, there is extensive evidence that sleeping pills on average impair performance and memory on the following day.

**The psychological effects are to make us sleepy, reduce alertness and vigilance, slow reaction times and judgment, and impair aspects of intelligence and memory.**

Sleeping pills generally make function WORSE the next day.

To view sleeping pill advertising, you might imagine sleeping pills help you to work better, think better, or function better the next day. This is deceptive. With very few exceptions, controlled studies supported by the manufacturers show that sleeping pills make test performance WORSE on the following day, or have no effect on performance. Look through the FDA files for Ambien, Lunesta, Sonata, and Rozerem, at the FDA website.[\[18\]](#) See if you can find any evidence that these drugs improved next-day performance for people with insomnia.

The problem of daytime impairment is more severe with the longer-acting drugs such as flurazepam (Dalmane) and quazepam (Doral), because the active by-products of these drugs remain in the blood day after day following only a single

dose. When one of the long-acting drugs is taken every night, the blood concentrations accumulate day by day, increasing for up to 10-20 days, reaching much higher concentrations than after the initial dose. Therefore, with flurazepam (Dalmane) and quazepam (Doral), and also with diazepam (Valium) and chlordiazepoxide (Librium) when they are taken nightly as sleeping pills, daytime impairment accumulates after consecutive days of use.[\[19\]](#)

Remarkably there has been only a smattering of evidence in special conditions that any sleeping pill ever improves daytime performance. Even when it is possible to show that sleeping pills increase sleep (a little) and even though the short-acting drugs are gone by morning, sleeping pills generally do not improve people's ability to function in their lives. The few experiments where sleeping pills seemed to produce transient improvements in performance often involved models of jet lag and shift work, not the common problem of the aging person with insomnia. In the hundreds of studies where the pharmaceutical industry has studied hypnotic effects on waking function, the emphasis has been on trying to reduce impairments caused by these products, not on assisting people's ability to carry on their lives. A person's hope and belief that a prescription sleeping pill will improve the person's function on the next day is consistently betrayed. It simply does not work.

I admit there might be at least one exception, a study of eszopiclone, which claimed that people given the drug reported better function in the long term.[\[20\]](#) I must say that I have trouble believing that is correct. Those subjective reports did not seem consistent with the company's own objective studies of how eszopiclone impairs performance. This same study reported more severe adverse effects with eszopiclone than with placebo. We find from the FDA records of this study[\[21\]](#) that there were more accidents and more cancers among those receiving eszopiclone. A new study by a different manufacturer showed conclusively that eszopiclone can impair many kinds of performance on the morning after taking a bedtime dose, even in healthy young adults.

To repeat, as a generalization, taking sleeping pills at bedtime impairs how people perform on the following day.[\[22\]](#)

## 2.B. A telling study.

Some years ago, I was privileged to participate with a group of sleep experts from different medical schools in a study sponsored by Hoffmann-La Roche, the makers of Dalmane (flurazepam). Concerned about the impairments of driving and other performance caused by Dalmane, the manufacturer wanted to see if a very-short-acting benzodiazepine would improve performance. The short-acting drug tested was midazolam, which is sold as a hypnotic in Europe, though in the U.S. it is marketed only as a short-acting anesthetic. Many experiments on hypnotic effects on performance had used young healthy volunteers, who had little room for improvement in their sleep. We thought that healthy volunteers might benefit less than insomniacs who really had disturbed sleep. Perhaps the people who benefit most might be a special group. Therefore, we recruited a group of chronic insomniacs who said they had had insomnia and had taken benzodiazepines successfully for an average of over 13 years.[\[23\]](#) Moreover, we selected volunteers in whom we could verify with EEG-sleep recording that their sleep really was disturbed at night, and then we withdrew these people from their sleeping pills for at least 4 weeks. Once withdrawn from whatever they had been taking, they were studied for two baseline nights while receiving a placebo pill. Then, the volunteers were randomly assigned to receive Dalmane, to receive midazolam, or to continue

receiving inactive placebo pills.

As expected, these chronic insomniacs slept about 20-27 min. more for the first two days they were given Dalmane or midazolam than when given the placebo.<sup>[24]</sup> That was not a big improvement. Remarkably, after 9 or 14 days of administration, there was no statistically-reliable increase at all in the sleep of the volunteers taking Dalmane or midazolam as compared to those receiving placebo. The volunteers had become tolerant to the sleeping pills, which had lost their effect. Part of the reason that the sleeping pills showed no significant benefit after 14 days was that the placebo group had improved. Perhaps regular sleep habits and the belief that they were being helped had produced this improvement, and possibly, placebo patients improved because they had been two weeks longer off the benzodiazepines they had been previously taking, which might have been making them worse. This is an important point, because the fact that a person taking a sleeping pills is sleeping more than at an experimental baseline does not mean that the pill is working, a point confused in many of the most-quoted studies. In any case, after two weeks, the groups receiving Dalmane and midazolam were not significantly improved compared to placebo patients.

The hope that these powerful hypnotics would increase sleep in these chronic insomniacs (for even 2 weeks) was disappointed.

The small increase in sleep which Dalmane and midazolam produced on the first two nights of administration was not sufficient to produce any improvement in performance, which was measured the following mornings with a variety of sophisticated testing methods. Moreover, by 14 days, both drugs were making performance significantly worse. On tests reflecting driving performance, **these sleeping pills would have made the patients less safe drivers.**

This study yielded a very interesting observation in these chronic insomniacs who for years had believed in sleeping pills. The volunteers themselves said that they thought the research sleeping pill was good and that it was helping them, even when objective tests and at times, their own family observed that the hypnotics were making them worse. Even the group receiving placebo said that placebo was a good sleeping pill which they would like to use again. That is a lesson in the **misperception of sleeping pill users**. The group receiving either Dalmane or midazolam liked their pill a bit more than the placebo was liked, even although the active drugs were worse for the patients than placebo. These patients were self-deceived about the value of the medication, almost deluded, thinking the medicines made them better when they actually made them worse.

**These patients were self-deceived about the value of the medication, almost deluded, thinking the medicines made them better when they actually made them worse.**

A rather similar study of chronic insomniacs receiving flurazepam (Dalmane) or triazolam (Halcion) also showed that after several weeks of use, the drugs were no

better than placebo.[25] This study was interesting because it studied the period of withdrawal after the research drugs were stopped. Even though the volunteers receiving triazolam were no longer sleeping better than those given placebo at the end of 5 weeks, when the drugs were stopped, those who had received triazolam developed a drug-withdrawal insomnia which made them worse than those who had taken placebo. This study implied that after several weeks of use, people may take sleeping pills not because they continue to benefit in any way, but because their sleep becomes so much worse when they withdraw. It hurts too much to stop. In effect, they have become habituated or addicted to sleeping pills.

Because these two studies were focused on the kinds of people who are actually chronic users of sleeping pills, it was particularly disturbing that the active drugs did not produce long-term benefit (only deleterious effects). It was particularly revealing that the volunteers thought they were benefitting from the drugs (even placebo), when that certainly was not the case.

Testing intermittent use (3 times a week), a recent study showed a similar result with zolpidem (Ambien). After several weeks of use, those taking this sleeping pill were sleeping better when they took the drug but then worse when they skipped it.[26] Overall, after several weeks of use, their sleep was averaging no better than a group taking inactive placebo.

The manufacturers now admit that both zolpidem (Ambien) and eszopiclone (Lunesta) cause withdrawal insomnia on the night after you stop the pill. Anxiety may also occur as a withdrawal symptom. People become habituated to these drugs because they experience such anxiety and poor sleep, whenever they try to stop. If they stayed off the drug for a few days, they might sleep just as well without the medication.

## 2.C. Disastrous side effects.

We now realize that sleeping pills can cause some very strange and disastrous side effects. Because sleeping pills turn off our brain cells – not always in all parts of the brain to an equal extent – they can make people do some mighty strange things. For example, having taken Ambien, people can act like somnambulists or sleep walkers. In the more amusing examples, they may sleep-walk to the refrigerator and stuff themselves with strange foods that they would not normally eat in such quantity. Of course, this is not amusing if it leads to obesity, which can be a life-threatening condition, or if they eat something unhealthy. Unfortunately, the behavior of the so-called Ambien Zombies is not always harmless. In a few reported cases, people intoxicated with Ambien have climbed into their cars and engaged in sleep driving. Some of the accidents were bad, and the police did not like how the zombies behaved.[27] Hallucinations have been reported with zolpidem, zaleplon, and eszopiclone.[28] At other times, people receiving sleeping pills have become confused or disoriented. Another odd symptom is complete amnesia for events, even during the day. For example, a successful businessman told me that while taking Ambien, he might have absolutely no recollection of a conference which his own notes showed that he had attended. From viewing various reports, I now realize that these terrible side effects may develop in about 1% of users of sleeping pills.

I do not think that these strange symptoms are unique to the new non-benzodiazepine hypnotics such as zolpidem, though in 2006, Ambien was getting most of the bad publicity. Similar lapses in memory and strange behaviors were

reported frequently when triazolam was the most popular sleeping pill.[29] A lawyer once asked me to consult with her client in the jail, where he was awaiting trial for having **murdered his sister**. The lawyer said her client thought that the Halcion (triazolam) he had been taking had caused him to commit this irrational crime, because otherwise he had no idea why he had done it. There would be no way of knowing for certain if Halcion was the explanation, but I wouldn't be surprised if the murderer had been a Halcion Zombie. One wonders if these reports have been most common with Halcion and Ambien because they were the market leaders, but it is interesting that both drugs are absorbed and removed from blood at about the same speed. I am inclined to think that these disastrous side effects are not so uncommon and can occur with any prescription sleeping pill (though we do not know yet about ramelteon or doxepin).

**Another side effect of sleeping pills is depression.** The sleeping pill industry would like you to believe that insomnia leads to depression, which might be true some of the time. They imply that sleeping pills might prevent depression. It isn't so. The controlled trials of zaleplon, zolpidem, eszopiclone, and ramelteon mentioned in the FDA NDA documents show a higher rate of developing depression among those given the sleeping pills as compared to those given placebo. This means that sleeping pills cause people to have more depression. Perhaps the common mechanism is that insomnia leads to sleeping pill use, which in turn leads to depression. It has been proven very clearly that sleeping pill use is associated with very high suicide rates, but as yet, the evidence that sleeping pills **cause** increased suicide is based on the strong evidence that the pills cause depression, as well as very high rates of suicide observed among those known to have taken sleeping pills.

## 2.D. Lollipops, not sleeping pills.

The motivations of physicians to give patients sleeping pills have not been studied extensively, but there is some interesting evidence. Physicians routinely explain their medical thinking in their medical records. Even in the medical records of a distinguished teaching hospital, not one of 331 charts of patients receiving sleeping pills had a proper record of why the pill was given.[30] It is safe to assume that there often was no good medical justification. It has been the same in the hospitals where I taught. In the hospital, however, the staff motivations are not hard to understand.

Everyone has heard the stories of nurses awakening patients to give them sleeping pills. When I was a medical student, I learned that nurses like to keep their patients quiet for the night. Physicians routinely write sleeping pill orders in the hospital, because they hate for nurses to call at night and wake the doctor up to get a sleeping pill order. As a medical student, I was instructed that if I wanted to sleep at night, I had better routinely prescribe a sleeping pill for every patient. If we train young doctors this way in hospitals, the habits will carry over to outpatient practice.

When I was a child, my pediatrician would give me a lollipop at every visit to compensate for the pain of the injections I was likely to receive. Unfortunately, physicians don't give lollipops to adult patients. They give sleeping pills instead, when a big lemon sucker might do less harm. Giving sleeping pills is often a gift-giving behavior which is part of the "bedside manner." When a distinguished group of physicians from our national Institute of Medicine were asked which times they would give a patient a sleeping pill, they said it was when they knew the patient

well. The decision had to do with the doctor-patient relationship, not with any particular complaint or medical diagnosis.

In the CPSI study, about 1/3 of people who said that they took sleeping pills “often” said that they never had insomnia. Before doctors were required to write in a diagnosis justifying every prescription, only a small percentage of patients given sleeping pill prescriptions received any diagnosis related to sleep disorders.[31] Even if we include all diagnoses related to emotional problems and nervousness, most patients given sleeping pills were not given any diagnosis suggesting a genuine medical reason for the prescription. This suggests that gift-giving explains much hypnotic prescribing.

I don’t want to blame the physicians alone. Patients like to receive gifts! They like to feel that they are taking something which might help, even if there is no scientific evidence. In fact, patients often insist that they need sleeping pills, and may become quite irate if a doctor does not want to provide what the patient wants. When I talk to physicians about sleeping pills, they tell me these stories again and again. I am certain that most physicians try to be ethical about sleeping pills, but they also realize that the patient given a sleeping pill is likely to return for a renewal prescription, whereas the patient refused a sleeping pill may look for another doctor. Doctors are fond of their patients and like to keep them. In fee-for-service medicine, it is also quite clear where the doctor’s financial interest lies.

**Even if we include all diagnoses related to emotional problems and nervousness, most patients given sleeping pills are not given any diagnosis suggesting a genuine medical reason for the prescription.**

## 2.E. The problem of addiction.

All prescription hypnotics (with the exception of ramelteon and the new drug Silenor) may be physically addicting drugs, and all are sometimes attractive to drug addicts. By addicting, we mean that these drugs have two properties. First, when we take addicting drug such as narcotics or barbiturates, we develop tolerance so that a given dosage has less and less effect or “stops working.” People who develop tolerance are prone to increase their dosage more and more. I frequently see this problem with long-term users of sleeping pills. Second, addicting drugs cause physical withdrawal symptoms when they are stopped abruptly. The withdrawal symptoms of hypnotics such as barbiturates and benzodiazepines are very well known.[32] They include shakiness and tremor, nervousness and anxiety, panic, hyperactivity and increased reflexes, rapid heart rate, and epileptic seizures and death in the most severe cases. In one sense, the withdrawal syndrome with hypnotics can be worse than withdrawal from heroin, because while the heroin addict experiences withdrawal as a terrible anguish, it is rare that addicts do not survive even the most severe heroin withdrawal. Severe withdrawal of sleeping pills can produce death. The risk of seizures and death is probably more severe with withdrawal of barbiturates than with benzodiazepines. On the other hand, zolpidem (Ambien) seems less prone to cause withdrawal symptoms than the barbiturates or benzodiazepines. As compared to heroin, the withdrawal syndrome

may be more lasting with the hypnotics, perhaps more than a month in some cases, though too little controlled experimentation has been done to be really sure.

The addicting properties of hypnotics manifest themselves in several ways. Triazolam (Halcion) is such a short-acting drug that many people used to take bedtime doses which (for the first hour) were much stronger than the initial dose of a drug such as flurazepam or temazepam. But because triazolam disappears from blood largely with 2-3 hours, some people find themselves in triazolam-withdrawal before morning. As a consequence, people taking triazolam may experience increased early awakening.<sup>[33]</sup> I suspect that zaleplon (Sonata) may be similar to Halcion in this regard, since it scarcely increases total sleep time. The manufacturers have admitted that zolpidem (Ambien) and eszopiclone (Lunesta) can also cause this early awakening. Although the problem may be less with Ambien CR, it is not entirely eliminated.

Next, by wake-up time, the person taking zaleplon or triazolam or zolpidem will certainly be approaching withdrawal. The result, in at least some patients, may be increased tension and anxiety during the day.<sup>[34]</sup> Such anxiety symptoms might develop somewhat later in the day with temazepam (Restoril) or estazolam (ProSom), because of the longer half-life. I have seen two patients who developed daytime panic attacks for the first time while taking triazolam. After withdrawing from this sleeping pill, the panic attacks of these patients disappeared.

Almost any patient discontinuing any of the short-acting benzodiazepines might experience some sense of anxiety and some withdrawal insomnia after discontinuation. Doctors argue whether the withdrawal syndrome universally leaves patients worse than they would be without the drug, but I suspect it often does. This makes it very difficult for patients to stop using these drugs once they have become habituated to them, and sometimes very long-term usage results, because the patient finds too much difficulty withdrawing.

If you listen to the drug companies and many experts who receive research grants from drug manufacturers, they would emphasize that most people who take sleeping pills use them for less than 15 doses in a year and do not become habituated. While this is true, it is likewise true that a small percentage do get into the habit of taking one or more hypnotic pills every night.

Because these long-term users take so many pills (365 or more per year), it turns out that most of the hypnotic prescriptions sold go to these chronic users. For example, in our CPSII data, 65% of the sleeping pills reported taken in the past month were taken by people reporting that they took at least 30 doses per month, and these patients reported taking sleeping pills for an average of 5 years. It gives quite a different picture of the sleeping pill industry, when we realize that they are profiting primarily from chronic users who have become habituated or physically addicted to these medicines.

**It gives quite a different picture of the sleeping pill industry, when we realize that they are profiting primarily from chronic users who have become habituated or physically addicted to these medicines.**

About two-thirds of

sleeping pills are taken by people who use them chronically for several years.

Studies of barbiturate addicts showed that while taking huge doses of these sleeping pills, many addicts slept very little. In some cases, after a long and unpleasant withdrawal, the abstinent addict found himself sleeping more than he had been while taking high sleeping pill doses. It seemed that long-term usage of the barbiturates had actually decreased sleep. Whether a similar phenomenon occurs with the benzodiazepines is uncertain, but it is a possibility. Certainly, the CPSII study and similar studies show that people who use sleeping pills often sleep less than people who do not use them, although that relationship does not distinguish which is cause and which effect. It appears that patients who stop chronic sleeping pill use may find that their sleep actually improves. Maybe it becomes a circular process, where people take sleeping pills because of poor sleep, but sleeping pills cause poor sleep. The situation may be similar to that with alcohol, which can be a sleep-inducing drug with a very short half-life. I know of little study of how much alcoholics sleep while they are drinking, but after abstinence, it is clear that abstinent alcoholics sleep very poorly, and they are unable to obtain a normal sleep duration. It appears that in the long run, chronic usage of alcohol damages the sleep system.

One advantage of some over-the-counter sleeping pills is that there is less evidence that they cause habituation and addiction.

## 2.F. Strange sensations of benefit.

Studies of sleeping pill effects on insomniacs show that they often describe a greater improvement in their sleep than EEG recordings measure. Although the hypnotic medication may hasten sleep onset rather little and decrease awakenings only modestly, the patient feels that the benefit is greater. It often appears based on objective recording that insomniacs are mistaken in their estimate of whether the sleeping pills are helping with sleep. An example was the Dalmane-midazolam study, where the insomniacs said that the drug was helping, even when after 14 days, there was no benefit either by EEG measurement or even by their own estimates of how long they had slept.

Another element may be that the sleeping pills simply make insomniacs forget how much they are awake at night. In the past, many of the over-the-counter sleeping pills contained scopolamine, an anticholinergic drug which causes amnesia but has no substantial sleep-inducing effect. Presumably, scopolamine affected the memory of insomnia rather than its actuality. It just helped people forget how poorly they might be sleeping.

It appears that benzodiazepines may make people less aware of their awakenings or less disturbed by them, because the drug may produce a sense of well-being. Indeed, any number of studies have documented that patients like how they feel when they take sleeping pills. To give perspective, let me mention that people also like how they feel when they take heroin. A good feeling does not mean that taking the drug is wise. I am not insensitive to the idea that some dying people at the end of their lives should receive medications to ease their pain when they want them, even if it shortens their lives. Most people who take sleeping pills are a long way from being ready to die. I do not think that relief of distress justifies

a drugs which may shorten life for most people who take sleeping pills. Regardless of whether or not you agree with assisted suicide, most patients who seek sleeping pills are not ready for this assistance.

## 2.G. Disinhibition of punished behaviors and the dark side of tranquilization.

To understand why people continue taking benzodiazepine hypnotics when experiments show they improve sleep so little and impair performance, it may be helpful to discuss some affects of these drugs on behavior. In experiments where a laboratory rat will receive an unpleasant shock when it presses a lever, an animal given a benzodiazepine will be more likely to press the lever than an animal given placebo. Scientists say that benzodiazepines disinhibit punished behavior, which means that the animals become more likely to hurt themselves or to behave in a way in which they will be hurt. Another way of saying this is that benzodiazepines disinhibit aversive behaviors. There is a human analogy.

In humans, the action of benzodiazepines is to reduce fears of being harmed, which we may call being tranquilized. People very much like this feeling of reduced fear, and there is no doubt that many people like how they feel when taking benzodiazepines. The manufacturers could not sell as many as 100,000,000 benzodiazepine prescriptions in

the U.S. yearly if people did not like them. Unfortunately, this tranquilization effect includes the risk of reducing a person healthy fear of self-destructive actions. For example, a person driving 80 mph down the highway approaching a curve ought to slow down for the curve, but taking a benzodiazepine might make the driver less likely to slow down. In some studies, benzodiazepines make people more likely to be aggressive. This blunted fear of harmful behaviors or blunted anxiousness to protect oneself may be one way in which sleeping pills shorten people's lives.

There is another curious twist to this idea. When we consider that benzodiazepines increase people's tendency to act in a self-harmful way, it is logical that taking harmful sleeping pills may be one of the harmful behaviors which benzodiazepines tend to increase.

## 2.H. Infection.

A strange new finding we have obtained with colleagues at Scripps Clinic is that people who take sleeping pills such as eszopiclone, zaleplon, and zolpidem have about a 44% higher risk of developing infections such as sinusitis, pharyngitis, upper respiratory tract infections, influenza, herpes, and so forth.<sup>[35]</sup> There has been essentially no discussion of this risk in the medical literature, but it is statistically extremely convincing, based on studies which the manufacturers submitted to the FDA and some of their published controlled trials. One mechanism is that zolpidem (and probably other sleeping pills) relax the stomach sphincter and cause gastro-esophageal regurgitation. The acid irritation may lead to infection.

**This blunted fear of harmful behaviors or blunted anxiousness to protect oneself may be one way in which sleeping pills shorten people's lives.**

Incidentally, acid regurgitation may also lead to esophageal cancer, which is one of the cancers most greatly increased among sleeping pill users. At present, we do not know why these infections occur, but it does seem that they would be sometimes annoying, sometimes painful, and sometimes frankly dangerous. It is not clear if ramelteon has the same risks, but there is one table in FDA data which suggests that it might. We could not find adequate information concerning the older sleeping pills. A new study from Great Britain showed that use of benzodiazepines (including popular sleeping pills) was associated with a 50% increase in hospitalizations for pneumonia and about a 30% increase in subsequent mortality.

## CHAPTER 3

### Good Sleep Habits and Attitudes

**T**he alternative to sleeping pills is to develop good sleep habits and good sleep attitudes. Good sleep habits and attitude are the best approach for a long-term sleep problem, and they produce surprising improvement.[\[36\]](#)

First, remember that most people do not need 8 hours of sleep per night. That old idea just is not so. In our studies in San Diego, the average adult is actually asleep only between 6 and 6.5 hours a night. National polls give similar results. Moreover, in the recent Cancer Prevention Study II results, people who said they slept 6.5 to 7.5 hours lived a bit longer than people who slept 8 hours or more. The shorter sleepers lived longer! Even people who said that they slept as little as 3.5 hours lived longer than those who slept 8 hours or more! In a group of women over age 65 who volunteered for the Women's Health Initiative, wrist recording indicated that they actually slept about an hour less than they thought they slept. According to the recordings, those who slept 5.0-6.5 hours had the lowest mortality.[\[37\]](#) If you feel you sleep 5 to 7 hours a night and feel rested, there is no evidence that you have to sleep any more as far as life expectancy is concerned. Incidentally, controlling for other illnesses, age, and so forth, people who said that they had insomnia lived a little longer than those who did not have insomnia! Therefore, do not worry about insomnia!

**If you feel you sleep 5 to 7 hours a night and feel rested, there is no evidence that you have to sleep any more as far as life expectancy is concerned.**

- People who said that they slept as little as 3.5 hours lived longer than those who slept 8 hours or more.
- People who said that they had insomnia lived a little longer than those who

did not have insomnia.

Short sleep is associated with good health as well as long life. Studies show that in the range that most Americans sleep (which is 6, 7, or 8 hours or so), there are few discernable differences between people. This may surprise you, but people who sleep 6 hours seem to be at least as happy as people who sleep 8 hours. Moreover, people who sleep 6 hours get just as much work done and are just as rich as people who sleep 8 hours. There may be some tendency for people with the shortest sleep times (5 or 6 hours) to be outgoing and energetic, whereas people with the longest sleep times (9 or 10 hours) seem to be more introverted, imaginative, or perhaps a bit depressed. Notice the surprise! People who sleep less are less depressed!

Indeed, hospital studies of depressed patients show something very surprising. When depressed patients are kept awake all night (or at least for the second half of the night, e.g., after 2 AM), they actually feel less depressed the following day. The sleep loss actually helps depressed mood. Moreover, after the wake therapy, taking a nap makes depressive symptoms recur. Wake therapy would be a very popular treatment for depression except for one problem: people with depression who stay up at night do get sleepy, and after they sleep soundly the next night, the low mood relapses. In my ebook [Brighten Your Life](#), I explain how this relapse can be avoided with bright light. Evidently, although it is true that people who are getting depressed have poor sleep, it is not proven that getting more sleep helps depression. It may be quite the opposite. In fact, it has now been proven that cognitive-behavioral therapy which restricts sleep improves the mood of patients with insomnia. Less time in bed can lessen depression.

For these reasons, depressed people should not struggle to get more sleep, and should certainly avoid sleeping pills, which tend to cause depression.

People may actually improve their moods by getting up a bit earlier.

There is another factor. Spending too long in bed – as you might expect – causes people trouble with falling asleep and makes them more likely to awaken while in bed. Sometimes, the frustration of lying in bed awake adds to the problem, and it builds on itself, getting worse and worse. The more time the person spends in bed trying to get more sleep, the more trouble develops in falling asleep and the more the person awakens in the night. Surprisingly, it seems that spending too long in bed might be a major cause of sleep trouble among both elderly and depressed people. Fortunately, there is an easy solution.

**People who are spending a lot of time in bed lying awake should spend less time in bed.** This means either going to bed later or getting up earlier. Getting up by a regular time seems to be important, so trouble falling asleep should not persuade you to sleep late. The less time you spend in bed, the more sleepy you will be the next evening. Think about it. If you spend less time in bed, you will surely tend to fall asleep more easily and sleep more soundly in the future. Moreover, the less time you spend in bed, the more you will restore the habit of falling asleep quickly after going to bed, and the more you improve the habit of sleeping soundly. Some doctors would recommend that you should not spend more time in bed than you actually sleep. If you think you only sleep 5 hours a night, spend only 5 hours in bed until you are sleeping all 5 hours. Then you can try increasing time-in-bed about 15 min., e.g., to 5 hours and 15 minutes. You can

gradually increase your time in bed on a weekly basis until you are no longer sleepy enough to sleep at least 85% of your time in bed. Once you are sleeping only 85%, that is the longest bed time which you should allow yourself.

Most sleep experts also recommend that whatever bedtime you allow yourself, **you should not go to bed if you do not feel sleepy**. Moreover, if you awaken at night and no longer feel sleepy, get out of bed, and do not go back until you are sleepy again and expect to fall asleep. Even after being up during the night, you should get out of bed by your regular awakening time, because sleeping late tends to make the problem worse. Getting out of bed when you are not sleepy makes you sleepier the next night and helps maintain good sleep habits.

Almost all of us have stayed up entirely for a night or two, so we know that nothing terrible happens to us. Many of the patients I talk to say that they have slept only a few hours a night for years, and yet they are somehow afraid that losing sleep will hurt them. Probably not. Remember that if anything, people who sleep a bit less than average tend to live longer and be less depressed. If you are willing to stay out of bed and amuse yourself somewhere else when you are not sleepy, soon you will stop worrying about sleep. If you lose a whole night's sleep or part of a night, so what? It will not be so bad, as long as you do not worry about it. When you do go to bed (because you are finally sleepy), you will have restored your confidence that you are likely to fall asleep, so the long-term problem resolves.

If you do begin to worry about how a bad night of sleep will affect you the next day, remember that there is no reason to take a sleeping pill. The sleeping pill is likely to make your performance worse the next day, and very unlikely to help.

Experts also advise that you avoid worrying in bed, watching TV (especially those scary late-night movies), reading scary mysteries, and doing other things besides sleep and sex in bed. The idea is not to make a habit of being worried or alerted in bed. If you are a person who worries, select a place to worry (such as a chair in another room), and sit down to worry there. When you are tired of worrying, then go to bed.

Good sleep habits also require avoiding coffee or anything else with caffeine within 6 hours of bedtime. Alcohol is sometimes a cause of sleep trouble, because although it relaxes us at first, it leads to insomnia as soon as the blood alcohol level falls. Drinking early in the evening may cause trouble falling asleep. Drinking at bedtime may cause midsleep awakenings and early awakening.

**Alcohol is sometimes a cause of sleep trouble, because although it relaxes us at first, it leads to insomnia as soon as the blood alcohol level falls.**

People say that exercise helps sleep, but I think the benefit is minimal. Probably it is being outdoors in daylight, which is often where people exercise, which is helpful. We have found that people who are outdoors more have fewer sleep problems. For more information about this, see my online ebook, [Brighten Your Life](#).

Controlled scientific studies show that adopting good sleep habits and attitudes is extremely effective in solving long-term sleep problems. It is more effective than

sleeping pills.[38]

If good sleep habits and good attitudes do not solve your problem, there is a good chance that you are suffering from depression. You should consult your doctor. You can read more about treatment of depression in my online ebook, [Brighten Your Life](#). You might also consult a sleep specialist at a sleep clinic. You might have a problem with your body clock (which I describe in [Brighten Your Life](#)) or another sleep disorder which could benefit from specific treatment. For a chronic problem, I do not advise that you ask a doctor for sleeping pills. It is the wrong approach.

For help with insomnia by changing habits and attitudes, try **Cognitive-Behavioral Therapy** or **CBT**. If you can't find a CBT therapist in your community, there are several helpful commercial web sites which cost less than a single therapist visit, e.g., [CBTforInsomnia.com](#).[39] Two other CBT web sites are B-Med Interactive[40] and the University of Virginia's Sleep Healthy Using the Internet (SHUTi) program[41], but I have no experience with either of them.

**CBT is better than sleeping pills and safer.**

## CHAPTER 4

### The Benefits of Hypnotics

I have written of the dark side of hypnotics and described the alternative treatment of habits and attitudes, because these are the most important points about sleeping pills. I did not describe benefits until this Chapter 4, because in my view, the risks of death, cancer, depression, and infection with sleeping pills, besides the behavioral impairments, are much more important than any small benefits.

A laborious and somewhat misplaced effort has occupied sleep laboratories over the years to measure the small amount by which sleeping pills increase sleep. I will not bore you with the details. The effort is misplaced, in the sense that the prescription sleeping pills increase sleep only a little, so that the exact size of

the tiny benefit may be trivial.[42] In most sleep laboratory studies, sleeping pills given to insomniacs increase the duration of sleep only 20-40 min. or even less. This is only a small increase, when we consider that many people who sleep only 5 hours do not complain of insomnia, whereas there are people who sleep 9 hours or more who feel their insomnia is severe. As I have mentioned above, although 20 min. increases in sleep may be statistically significant (which means statistically reliable), they are not functionally significant, since sleeping pills usually produce no measurable improvements in daytime performance.

**In most sleep laboratory studies, sleeping pills given to insomniacs increase the duration of sleep only 20-40 min. or even less.**

Zaleplon (Sonata) is an especially unfortunate pill. The official information on this drug stated, "a significant difference from placebo on sleep duration was not demonstrated," which means that zaleplon generally did not help people sleep more than a dummy pill. Does it make sense to take a hypnotic which does not substantially increase nocturnal sleep? Although this drug might help a person fall asleep 10 minutes faster, possibly it makes sleep worse later the same night, so that total sleep time does not significantly improve.

Zaleplon (Sonata) may NOT significantly increase nightly sleep.

Ramelteon (Rozerem) may offer little risk (we did not have enough data in our epidemiologic study for ramelteon), but it also offers little benefit. According to the NDA data at the FDA web sites, in many of the company studies, patients who received Rozerem did not think they were sleeping better than those receiving placebo. Rozerem produces a small decrease of time to objective EEG sleep of 7 to 16 minutes, which is trivial. However, if many patients taking ramelteon do not feel they are sleeping better, why buy the stuff? I have found that many patients do not like it. We do not know about mortality, but some indications suggest that ramelteon might cause depression, infection and cancer.

"The European Committee for Medicinal Products for Human Use (CHMP) has issued a negative opinion on the use of the melatonin receptor agonist ramelteon in insomnia, due to its unfavourable risk-benefit balance."<sup>[43]</sup> They thought melatonin itself might have a better benefits/risk ratio for treating insomnia.

I agree with the European opinion.

Whereas most sleeping pills increase sleep a few minutes for the first few nights of use, it is unclear how long the benefits last with continuous nightly usage. In our Dalmane-midazolam study, the benefits were gone in less than 7 days as compared to placebo,<sup>[44]</sup> and in the triazolam-flurazepam study, the benefits were gone after 3 weeks as compared to placebo.<sup>[45]</sup> Unfortunately, the majority of laboratory studies have used placebo baseline recordings as the control, without counterbalancing the order of placebo and hypnotic. The studies where hypnotic and placebo are given in parallel (at the same time to randomly-assigned volunteers) suggest that participation in laboratory experiments (and spontaneous recovery) lead to improvements in sleep. After 2-4 weeks, the improvement seen in a drug-treated group as compared to baseline may be due to the time-related improvement rather than due to drug benefit.

When we go beyond 4 weeks, there are few properly controlled experiments which show that any sleeping pill objectively increases sleep even a little. One exception was the 8-week study of Morin.<sup>[46]</sup> Morin's study, however, showed that behavioral treatment was as effective as temazepam and more lasting in its benefit. When we ask whether hypnotic drugs work when taken nightly for years, there really is no scientifically convincing evidence of efficacy or benefit.

Again, I wish to emphasize that in general, hypnotics do not improve daytime function. Patients often seek this benefit, but they usually do not receive it. Further, although we hear colleagues mention that perhaps a patient will be healthier if the patient sleeps better, our research found that patients taking sleeping pills were more likely to develop new medical disorders than matched control patients who avoided sleeping pills.

# CHAPTER 5

## Recommendations of Experts

In 1979, a distinguished committee of our national Institute of Medicine considered the risks and benefits of hypnotics. Noting concern with the side effects and risks of sleeping pills balanced by the lack of evidence for long-term benefit, this distinguished committee recommended that hypnotics generally be limited to short-term use.<sup>[47]</sup> In 1983, a Consensus Conference held by the National Institutes of Health on the treatment of insomnia. This group recommended that sleeping pills be used mainly for up to 3 weeks, not chronically.<sup>[48]</sup> Another consensus conference was held in 1990 to discuss problems of sleep in aging. Complaints of insomnia are much more common among people above age 60 years, and 40-50% of all sleeping pills are taken in the U.S. by people older than 60. This consensus group also recommended only short-term use of sleeping pills.<sup>[49]</sup> A new committee of the Institute of Medicine concluded in 1997 that the data only supported use of Halcion for two weeks.<sup>[50]</sup> In the summer of 2005, the National Institutes of Health had a consensus conference<sup>[51]</sup> about insomnia, which emphasized how little we understand about chronic insomnia. This group of experts concluded that the evidence for CBT therapy for chronic insomnia was better than evidence for long-term use of sleeping pills, though this group of experts did not frankly condemn long-term sleeping pill use. In summary, there is expert consensus that the medical evidence does not support chronic use of sleeping pills.

Most recently, a meta-analysis (combined analysis) of a large number of sleeping pill trials was published in the *British Medical Journal*, one of the most authoritative medical journals.<sup>[52]</sup> This analysis, focusing on studies of people with insomnia over 60 years of age, concluded that long-term use of sleeping pills more often does harm than good. This conclusion was reached without considering risks of mortality and cancer, which further tip the likelihood towards harm.

In conclusion, despite the enormous propaganda which results from over half a billion dollars a year spent on sleeping pill marketing, most expert opinion recommends against long-term use of sleeping pills. The opinions voiced in this web book may not be marketed, but most experts without financial ties to the sleeping pill industry had reached the same conclusions even before seeing our 2012 data about mortality and cancer.

Experts have repeatedly concluded that long-term use of sleeping pills is not advisable.

There is no convincing

scientific evidence that taking any sleeping pill for years benefits sleep even a little.

# CHAPTER 6

## Getting Off Sleeping Pills

**A**s I have explained, because of mortality, cancer, depression, infection, and behavioral risks, I cannot recommend circumstances when anybody should continue taking zolpidem, eszopiclone, zaleplon, temazepam, triazolam, flurazepam, estazolam, quazepam, barbiturates, or diphenhydramine as hypnotics.

The manufacturers generally claim that a person taking only the recommended dosage each night should safely be able to stop the pill immediately. Actually, patients who have been taking higher doses or a regular dosage for a long time may need to slowly taper off the medication, reducing their dosage by a small portion every week or two.

Withdrawal from sleeping pills can cause at least a few nights of insomnia, anxiety (both day and night), tremulousness, and other symptoms. People will have much less difficulty withdrawing from sleeping pills if they first begin CBT treatment as described in [Chapter 3](#) above, or obtain CBT from a therapist or web site.

**Withdrawal from sleeping pills can cause at least a few nights of insomnia, anxiety (both day and night), tremulousness, and other symptoms.**

It is always recommended that a patient consult the prescribing doctor before discontinuing a prescribed sleeping pill.

For most patients, it will not be necessary to replace a sleeping pill with any other drug merely for treatment of insomnia. If related illnesses such as depression, anxiety, etc. are involved, an approved medication for those conditions may be needed.

Even people with no intrinsic depression or anxiety are likely to become anxious when withdrawing from a sleeping pill. It helps to understand that this anxiety and fear of insomnia is probably a drug withdrawal reaction which will go away in time, often within a day or two, so starting a replacement drug may not be advisable. People withdrawing from sleeping pills may become filled with the idea that they can never do without their pill, when a few days later, they do perfectly well without

it.

There are some drugs which could be substituted for the sleeping pills which I have recommended discontinuing because of mortality and cancer risks. I do not say that I recommend such substitution. Certainly I would not recommend substituting in ordinary circumstances, but I recognize that physicians will encounter some patients for whom at least short-term substitution seems a good idea. I do not think that the possible substitutes have been shown to be associated with mortality or human cancer.

The most reasonable substitute drugs might be trazodone, Silenor (doxepin 3 or 6 mg.) and melatonin, but I say this without recommending substitution. Trazodone and melatonin are not FDA-approved as hypnotics as of February, 2012.

Trazodone has been shown to be somewhat effective as a hypnotic in low doses (in higher doses, it is an effective antidepressant), but trazodone has a number of side effects. Trazodone has recently been very popular in the United States for off-label use as a hypnotic, which seems to indicate that patients and doctors like it. I have seen good results myself, but I have also seen some bad side effects such as falls and excessive daytime sedation. Use of trazodone as a hypnotic is not FDA-approved, and little is known about its long-term safety.

Silenor in early reports seems to be somewhat effective for maintaining sleep, though of less use for helping people fall asleep. I am not convinced that we have enough experience with use of Silenor to be sure of its safety, and I have not personally seen patients who are doing well with Silenor. It is claimed that Silenor is lacking in significant side effects at doses of 6 mg. and below, which might be believable, since we formerly prescribed up to 300 mg. of doxepin to treat depression. Time will tell. Silenor is currently FDA-approved as a hypnotic.

Melatonin in an immediate release form sometimes has a benefit in reducing the time to fall asleep, but it is less effective or ineffective in prolonging sleep later in the night, so its benefits for total sleep time are often weak or absent. Melatonin may accelerate sleep onset, but it is a timing drug, not a hypnotic as such. Rodents have the highest melatonin blood concentrations when they are wide awake. There is evidence that melatonin has a variety of minor side effects such as headache and nightmares, and some effects on the reproductive endocrine system, but little or no evidence of serious side effects. A sustained release melatonin preparation (Circadin) has been approved as a sleeping pill in Europe. Initial published reports suggest that Circadin has a favorable benefits/risks ratio. However, there seems to have been a trend to leave the less favorable studies of sustained release melatonin unpublished.[\[53\]](#) I confess I am skeptical of drugs whose manufacturers tend not to publish the less favorable studies, although it is a common failing of pharmaceutical manufacturers. As of this writing, sustained release melatonin is not yet FDA approved in the U.S. Our research suggested a trend for older women who secreted more natural melatonin to have higher mortality, but this trend was not statistically significant.[\[54\]](#) I think we need more long-term studies of melatonin safety.

There is a specific use for melatonin for people with delayed sleep phase disorder (nightowls who have trouble falling asleep and trouble getting up in the morning). There is considerable evidence that very low doses of melatonin (50-500 micrograms) may be useful for these patients. The recommended dosage is much lower than the 1-5 mg. (1000-5000 micrograms) usually sold over the counter. As I have mentioned, I agree with the European Committee for Medicinal Products for Human Use (CHMP), which thought that melatonin would have a better

benefits/risks ratio than ramelteon.

## CHAPTER 7

### How Much Are Sleeping Pills Used In the United States?

**do not think anybody has reliable information** on how much Americans take sleeping pills. Most scientific discussion cites data from the National Prescription Audit, a survey system conducted by IMS America, Ltd. Their survey methods are proprietary, and I do not know in detail what they are, but they involve computerized monitoring of retail pharmacy sales. According to the *Wall Street Journal*, IMS Health data showed about 60 million prescriptions for hypnotics in the U.S. in 2010.<sup>[55]</sup> I believe this may be an underestimate.

The U.S. Government seems to have no clear data about the use of sleeping pills, even although most are addicting drugs regulated by the Drug Enforcement Agency under the narcotics laws. It is known that some sleeping pills become drugs of abuse.

**It is known that some sleeping pills become drugs of abuse.**

At some personal expense, I filed Freedom of Information requests, asking the FDA, the Drug Enforcement Administration, and Customs what the sales of hypnotics were in the United States. Under penalty of law, the government agencies stalled, but once threatened with legal action, these government agencies stated that they did not have the information. I believe it. I believe that the U.S. government does not know how many sleeping pills Americans use and what percentage of Americans use them. Considering that the hypnotics are addicting drugs and drugs of abuse, I think our government ought to pay better attention.

Considering both United Nations data<sup>[56]</sup> and the newspaper reports of IMS data, I have estimated that about 10% of U.S. adults were probably taking sleeping pills in 2010.

## CHAPTER 8

### Why Haven't You Heard This Opinion of Sleeping Pills From Every Expert?

**T**he idea that sleeping pills have a dark side is nothing new. Indeed, generations of physicians have shared my opinion, based on their own clinical experiences. Probably, the majority today agree. They are a silent majority, with little to be gained by making their opinions public.

*“The treatment of insomnia by drugs is always to be avoided as much as possible.” - H.C. Woods, 1893*

The sleeping pills industry has over two billion dollars of yearly sales, and it has thought of many subtle ways of keeping its products popular. To be frank, the manufacturers of sleeping pills have often given the leaders of sleep research large monetary grants to test their products. These colleagues are very nice people who are not the sort to bite the hand which feeds them. Some of the most prominent leaders of sleep research have been supported mainly by drug company grants. The drug companies have used many subtle free offers and not-so-subtle methods of influencing the wider group of sleep clinicians to mute their critical attitude towards sleeping pills.

For example, a few years ago, manufacturers offered free chocolate cream pie at a national sleep meeting for attendees to watch a bizarre comic session in which leaders of the sleep community mocked the Food and Drug Administration for its efforts to regulate sleeping pills. I suppose a good deal of money was spent for those free chocolate cream pies and the advertising of that clowning.

For several years, the National Sleep Foundation has launched a yearly publicity campaign about the dangers of insomnia, encouraging everybody to sleep 8 hours. Scientific evidence to support 8 hours sleep is almost nonexistent: for example, people live longer who sleep less (see above). Could this campaign be influenced by the fact that much of its money comes from sleeping pill manufacturers? The public relations firm for Ambien bragged that National Sleep Foundation publicity was effective in increasing sleeping pill sales.[\[57\]](#)

**The public relations firm for Ambien bragged that National Sleep Foundation publicity was effective in increasing sleeping pill sales.**

Unfortunately, nobody advertises for behavioral treatments, or for hypnotic abstinence. The advertising for bright light treatment is minuscule compared to pharmaceutical advertising.

## **8.A. Why haven't you heard from the FDA?**

When we reported that people who took sleeping pills died 4.6 times faster and suffered more cancer,[\[58\]](#) I thought the FDA would ban the drugs studied or warn people. Forgive my naivety. Ignoring, now, 21 studies showing that people who take sleeping pills die sooner or suffer more cancer, and might be as dangerous as cigarettes, the FDA still claimed (in August, 2012) that sleeping pills are safe and effective. I had made quite certain that the FDA had reviewed the new studies, but the FDA decided to require no black box warnings about these risks and to require no further studies to confirm whether the mortality and cancer risks are so serious.

Look at the spring, 2012 product labeling for Ambien CR (zolpidem), for example. You will find no warning that Ambien is associated with excess deaths. No

studies reporting excess human cancer risk are mentioned. The word cancer does not appear, despite some euphemisms. Similarly, the Lunesta labeling in the spring of 2012 does not disclose that some FDA scientists thought that Lunesta had so much cancer risk in animals that it should not be sold. Incidentally, Lunesta labeling did not disclose the new British study showing clearly that Lunesta impairs next-day performance even in young adults.

Perhaps we should not have expected the FDA to protect the public. A 2009 report of the Congressional Government Accountability Office questioned the FDA's ability to protect Americans from unsafe medical products.<sup>[59]</sup> A 2012 National Institute of Medicine report found that the FDA's current oversight was not adequately assuring the safety of marketed drugs.<sup>[60]</sup> The FDA Amendments Act of 2007 gave the FDA authority to require additional safety studies on marketed drugs when needed. The Act provided authority to require risk evaluation and mitigation strategies, but the FDA disclosed no such strategy to deal with cancer and mortality risks of sleeping pills. In July, 2012 we learned that not only had the FDA fired scientists for trying to protect the public from health risks, but FDA allegedly invaded the computer systems of Congressional offices to catch whistleblower leaks about the risks of industry products. In a September, 2012 law suit and press release, Public Citizen alleged that the FDA was acting unlawfully in failing to protect the public from an Alzheimer's Disease drug, because it had "chosen to support the profit interests of a large pharmaceutical company."<sup>[61]</sup>

Given their health impact, the National Institutes of Health (NIH) should clarify the risks of sleeping pills (see [Chapter 9](#)). NIH has made no effort. With planned budget cuts, one cannot anticipate that NIH sleeping pill research will expand. The medical insurance companies can tell from their own medical data bases whether hypnotic users are developing more cancers or dying sooner. Medical insurance companies and Medicaid might ask themselves why they are paying for sleeping pills which are increasing medical costs. They might warn their clients. Unfortunately, private insurance companies have a conflict of interest. The higher medical costs become, the more profits these companies can make. Oddly, drugs which shorten life span might decrease Medicare and Department of Veterans Affairs costs. Medicare and the VA also fail to warn.

## 8.B. What if your family was injured?

If somebody in your family died or developed cancer after taking sleeping pills, you may have an entitlement to reimbursement for injury, but equally important, perhaps injured families could spread the warnings. When the medical community was no match for the cigarette companies, lawyers and law suits helped disclose cigarette risks. We may now need law suits for failure to disclose sleeping pill risks. If your family member died while regularly taking sleeping pills, and the risk was not disclosed, consult your attorney. If your family member developed a cancer while taking sleeping pills, especially esophageal or lung cancers or lymphoma, and the risk was not disclosed, consult your attorney. In *Wyeth v. Levine*<sup>[62]</sup>, the U.S. Supreme Court ruled that drug manufacturers are liable if failing to warn patients, even when the FDA has not required a warning in the labeling. If the drug companies, the many doctors taking gifts and money from drug companies, the FDA, and the insurance systems will not alert the public to the risks of sleeping pills, injured families might have to give the warnings with legal assistance. You may contribute to better warnings if injured patient families and whistle blowers file enough law suits, recovering damages like the \$4.85 billion which one company paid to settle Vioxx claims.<sup>[63]</sup> You might help save hundreds of thousands of lives.

# CHAPTER 9

## Needs For Hypnotics Research

**T**here is a preponderance of evidence that the sleeping pills I have listed in [Chapter 1](#) above are so risky that they should not be used. We do not need more research before we stop using these pills for sleep.

Today, nobody can be certain that any of the prescription sleeping pills (or melatonin) is safe for long-term use or even that they help sleep with long-term use (meaning several years).

There must be quite a few billionaires who have seen family members develop cancer or die after taking sleeping pills. One would think that charitable donors would want clear information about when sleeping pills are safe and whether any sleeping pills are worth the risks. A few tens of millions of dollars donated to universities or private foundations could advance medical research about sleeping pill safety a long way.

It is not a unique idea that long-term studies should be done. The National Institutes of Health (NIH) are doing long-term studies of diet and exercise, hormone replacement and vitamins, cholesterol-lowering drugs and aspirin. Of the psychoactive drugs, long-term studies have been supported for

anti-depressant and anti-psychotic drugs, mood stabilizers (such as lithium), tranquilizers, narcotic agonists and antagonists, and stimulants for treatment of hyperactive kids. Truthfully, hypnotics are the only class of psychotropic drugs for which long-term studies have not been supported by the NIH. In a 1997 search of the CRISP list of NIH-supported projects, I found about 140 clinical studies of other psychotropic drugs, but none on sleeping pills. This is neglectful, considering the proportion of total psychotropic drug sales which the sleeping pill market occupies.

Although I have received generous grant funding in other areas of sleep research, the federal agencies have never been willing to support any studies of sleeping pills which I have proposed. I do not take it personally, since I know other investigators have the same problem. There is a mind set against funding studies of sleeping pills and a lot of passing the buck among different NIH Institutes. You could count on one hand (and have fingers left) the total number of clinical trials of hypnotic drugs funded by NIH in its entire half-century history. Of the few funded, the purpose was usually to compare some other treatment with sleeping pills, not directly to test sleeping pills.

Lack of government curiosity about sleeping pill prescribing is exceptional. As mentioned above, government agencies denied that they had data on overall U.S. consumption of sleeping pills. They are certainly more careful in studying other

**Truthfully, hypnotics are the only class of psychotropic drugs for which long-term studies have not been supported by the NIH.**

addicting drugs.

You might expect that with increasing evidence that sleeping pills cause cancer and excess mortality, the manufacturers might not wish to do long-term studies of their products which would prove the cancer and mortality risks. On the other hand, a company which really believed their product was safe should do such trials to prove it. If they are not doing the trials, you can assume that they themselves are not sure their product is safe.

Before I denounce the drug companies excessively, let me mention that the same heavy prescribing of hypnotics existed in Communist countries before the dissolution of the Soviet block, and there was a similar lack of studies behind the Iron Curtain. One should not ascribe the scientific neglect of sleeping pills entirely to the profit motive.

I think there is enough evidence now to stop using the drugs I have described as dangerous above in [Chapter 1](#) for sleep. Moreover, I expect that many similar studies of electronic records will confirm the associations with mortality and cancer for those drugs. Additional studies can add to the accuracy of our risk estimates and perhaps explain some of the pathologic mechanisms, but we already know that the risks are too high. It would be scientifically more definitive to have controlled trials of these risk-associated drugs to confirm whether or not they cause mortality and cancer, but as I have mentioned, I do not think think controlled trials of those drugs to assess lethality and cancer will ever be done.

For potential substitute drugs such as trazodone, doxepin, and melatonin, we do not have equivalent electronic records studies, nor for the still-newer drugs in the development pipeline. Perhaps electronic records studies of the current substitute drugs will eventually reflect on their association (if any) with mortality and cancer. Nevertheless, for any sleeping pill kept in use or for any newer drug, we ought to have long-term controlled trials of sufficient size to determine if the drugs do or do not cause excess mortality, cancer, depression, infection, and other serious adverse effects.

The cost of studies which would establish the long-term benefits/risks ratios of the most popular hypnotics would probably be \$10-20 million for a period of several years. This would mean devoting less than 1% of sleeping pill costs for long-term research, in a sleeping-pill-giving industry which grosses over 2 billion dollars a year. The retail costs of the hypnotics drugs themselves may surpass two billion, and in addition, the fees of the prescribing doctors, the necessary laboratory tests, etc. amplify the total cost. Compare this with other areas of drug research, where the research costs may reach 25% of sales, or aircraft, computer and defense industries, where the R&D costs may reach 50% of total costs.

The Congress would have several choices for how to finance this research. It could require the manufacturers by law to perform the needed research. It could impose a user-fee on hypnotics (either at the retail level or the manufacturer level) to do the studies. A cost of a nickel a pill added to pills which cost as much as \$8-\$10 each would be a trivial cost to the consumer and well worth while in keeping consumers safe. To the extent that this small cost might discourage people from using sleeping pills, it would be doing them a favor. Such a user-fee might be regarded like the levies on other addicting substances such as cigarettes and alcohol. Congress could take the money out of the overall appropriations for health services research or for the National Institutes of Health, or it could conceivably appropriate new funds from general revenues. It is for the Congress to decide from where the money should come, but one way or another, the studies should be

done.

There is a new genetic analysis technique which may make it possible to explore whether particular sleeping pills cause death and cancer without expensive and risky controlled clinical trials. This research approach relies on Mendelian randomization, the random process by which we are born with various genetic differences, to assess the causal role of various risk factors. Because Mendelian randomization studies might be possible with genetic testing and clinical records already collected for other purposes, these studies might only require more analysis of existing data. With its authority under the 2007 FDA Amendments Act, the FDA should require the manufacturers of the common sleeping pills to perform these studies. In addition, the NIH, which has banked much suitable data, should urgently support the analyses.

## CHAPTER 10

### About This eBook

I **wrote these little books** – both this title and [Brighten Your Life](#) – and put the books on the web, so that people in need could learn about the dangers of sleeping pills and about alternative treatments. Much of the two books is written in the same tone and language with which I explain about sleeping pills to my patients. I offer opinions and guidance even where the scientific proof is incomplete. People want a doctor's best advice, even when we are not certain of everything.

This is not intended to be a scientific article, but it may be useful to physicians who want to learn more about hypnotic drugs. For physicians and others who want more scientific facts, I have included several scientific references without attempting to document every opinion. This is my advice, so not every doctor will agree with everything. You can find many of the articles at a medical library or by searching the web through PubMed[\[64\]](#), the database provided by the U.S. National Library of Medicine.

## CHAPTER 11

### About Dr. Kripke

**Daniel F. Kripke, M.D.** is a licensed physician certified by the American Board of Psychiatry and Neurology and an Emeritus Professor of Psychiatry at the University of California, San Diego. He also does some research with the Scripps Clinic Viterbi Family Sleep Center. Dr. Kripke was elected a Fellow of the American Psychiatric Association. Dr. Kripke has co-authored hundreds of medical articles and has given invited lectures in 18 countries.

In 1973, Dr. Kripke established one of the first sleep clinics in the United States. He has been treating patients with sleep disorders and doing research on sleep ever since.

Please do not contact Dr. Kripke for personal advice. Dr. Kripke is no longer seeing patients, and the California Medical Board thinks it is unethical for a physician to give advice to a patient he has not personally examined. You could make an appointment for a personal consultation with physicians at the Scripps Clinic Viterbi Family Sleep Center<sup>[65]</sup> or look for other sleep physicians at numerous web sites such as those sponsored by the American Academy of Sleep Medicine (AASM).<sup>[66]</sup>

**Acknowledgment:** I have been fortunate that my research has been supported for over 35 years mainly by the U.S. National Institutes of Health (NIH) and the Department of Veterans Affairs. The Department of Psychiatry, the Sam and Rose Stein Institute for Research on Aging, and the Center for Chronobiology of the University of California, San Diego have also supported my research, as has the Weingart Foundation and the American Cancer Society. Some years ago my laboratory received research grants from the agencies of the U.S. Army and the Navy, and from 1966-1968, I was a US Air Force sleep researcher. Recently, the Scripps Clinic Viterbi Family Sleep Center has been supporting some of my research, particularly the most recent study of mortality associated with hypnotics, assisted by the help of generous gifts from private donors. Ambulatory Monitoring, Inc. (the manufacturer of the Actillum and other actigraphs) and Minimitter-Respironics (makers of actigraphs), The Sunbox Company, Apollo Health (now part of Phillips), and Enviro-Med (which make bright light boxes) have supported our research, partly through joint research projects funded by the National Institutes of Health. In the 1970's and 1980's, I did sleeping pill studies with Hoffmann-La Roche and Upjohn and once consulted with Schering, but for years I have avoided accepting any fee from pharmaceutical manufacturers, so that I would be free to report this information. I also stopped accepting fees from tort lawyers or class-action attorneys. It is important that readers understand for whom an author works. Being supported largely by public funds, I am able to speak out for public interests. I appreciate this opportunity.

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63. See Wikipedia's summary of the Vioxx case history, as part of its article on Merck and Co., Inc., available online at [en.wikipedia.org/wiki/Merck\\_%26\\_Co.#Vioxx](http://en.wikipedia.org/wiki/Merck_%26_Co.#Vioxx) . [\[return\]](#)

64. PubMed.gov is a free resource that is developed and maintained by the National Center for Biotechnology Information (NCBI), at the U.S. National Library of Medicine (NLM), located at the National Institutes of Health (NIH). Available online at [www.ncbi.nlm.nih.gov/pubmed](http://www.ncbi.nlm.nih.gov/pubmed) . [\[return\]](#)

65. More information about Scripps Clinic Viterbi Family Sleep Center in La Jolla, California, is available online, [www.scripps.org/locations/scripps-clinic/services/sleep-medicine](http://www.scripps.org/locations/scripps-clinic/services/sleep-medicine) , or by phoning (858) 554-8845. [\[\[return\]](#)

66. The American Academy of Sleep Medicine (AASM), a national accrediting body for sleep disorders centers and laboratories, lists more than 2,000 of its accredited centers and labs at its website [sleepcenters.org](http://sleepcenters.org) , and provides patient education at its website [yoursleep.aasmnet.org](http://yoursleep.aasmnet.org) . [\[return\]](#)

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