



The Dark Side of Sleeping Pills

By Daniel F. Kripke, M.D.*



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IMPAIRMENT



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This little book explains risks of sleeping pills which you may not have heard about. It also describes better alternatives.

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People who take sleeping pills often hope that sleeping pills will increase their sleep enough to make them more energetic in the day. They may hope that sleeping pills will improve their long-term health. Sleeping pill effects are just the opposite of what people hope.

Because life and death are often our primary concern, I would like to first to discuss the darkest aspect of sleeping pills:

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

For over 30 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.

In the CPSI (this was the first of two large studies), in 1959-1960, American Cancer Society volunteers gave questionnaires to over 1 million Americans and then determining six years later (in over 98%) whether the participants had survived. **We found that 50% more of those who said that they "often" took sleeping pills had died, compared to participants of the same age, sex, and reported health status who "never" took sleeping pills** Note.

To re-examine these risks, the American Cancer Society agreed to ask new questions about sleeping pills to participants in a new study, called The Cancer Prevention Study II or CPSII. In 1982, American Cancer Society volunteers gave health questionnaires to 1.1 million new participants. The survival of these people was ascertained in 1988.



In the new study, we again found that people who said that they used sleeping pills had significantly higher mortality **Note**. Again, people who took sleeping pills had much higher mortality. Even when people were matched for age, sex, race, and education, and a total of 32 health risk factors, those who reported taking sleeping pills 30 or more times per month had 25% more mortality than those who said that they took no sleeping pills **Note**. However, we did not determine which particular sleeping pills were associated with this risk. The smaller risk of taking sleeping pills just a few times per month was 10-15% increased mortality, compared to those who took no sleeping pills. Sleeping pills appeared **unsafe in any amount**.

- 25% increased mortality among those taking sleeping pills nightly
- 10-15% increased mortality among those taking sleeping pills occasionally

To provide a perspective on this mortality risk, we noted that the risk of taking sleeping pills 30 or more times per month was not much less than the risk of smoking 1 pack of cigarettes a day, when the analyses were done in a similar manner.

One cause of death was especially increased. Among men, those who took sleeping pills 30 times a month had 7 times the risk of suicide! Women who took sleeping pills 30 times a month had 2 times the risk of suicide. Nevertheless, the suicides were only a small portion of deaths associated with using sleeping pills. Deaths from other common causes such as heart disease, cancer, and stroke were also increased among sleeping pill users.

As of 2008, fifteen epidemiologic studies from Scandinavia to Japan have found that use of sleeping pills predicted increased mortality risk. Three of these studies have specifically found that use of sleeping pills predicted increased risk of death from cancer. It is not that the other studies found no cancer risk. They probably were just too small to check on cancer as a specific cause of death. Incidentally, these studies mainly covered usage of the older sleeping pills such as barbiturates and benzodiazepines, e.g., flurazepam (Dalmane), triazolam (Halcion), and temazepam (Restoril).

1.A. New sleeping pills cause cancer in animals

Were the epidemiologic studies just statistical accidents, or do sleeping pills really cause cancer? Recently, 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](#).

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](#) seemed to say that animals given zolpidem developed three kinds of cancer, [the new labeling approved](#) 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 onto 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](#) 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, at least skin cancer. However, the data are not sufficient to prove that any specific sleeping pill or brand causes cancer, and more research is needed. **Note**

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 a new sleeping pill is likely to

be increasing his or her risk of getting cancer. I feel that my patients should be warned about this risk, even though the scientific evidence is not yet refined or fully conclusive.

How does the cancer risk of new sleeping pills and older sleeping pills compare? I know of more evidence from animal studies and randomizing clinical trials that the new sleeping pills cause cancer than with the older sleeping pills. This does not mean that the older sleeping pills were safer: just that I have found less information about their cancer risk from clinical trials and animal experiments. On the other hand, the epidemiologic trials showing higher mortality and higher cancer mortality were collected mainly with the older sleeping pills before any of the newer ones (except perhaps zolpidem) became available. In summary, we really do not know if the newer or older sleeping pills present more cancer risk.

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 **Note**. For the last 15 years, most new sleeping pills have been benzodiazepine agonists, which means that the chemical molecules are not classed as benzodiazepines but they act at the same receptors. All of these drugs seem to have less risk than barbiturates, but it is still possible that single doses of these newer sleeping pills are sometimes lethal.

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 **Note**. 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 **Note**. Of patients given Lunesta, 10% had accidents as compared to 6% given placebo in one study, and falls were specifically more common with Lunesta **Note**. Because several studies show that people who are responsible for automobile accidents are unusually likely to have sleeping pills in their blood **Note**, 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**.



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 **Note**. 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.

2.A. Sleeping pills impair daytime thinking.

The 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. 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. 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 **Note**. Ramelteon (Rozerem) produces no next-day impairment according to the manufacturer studies, but I have heard patients complain.



IMPAIRMENT As explained above, sleeping pills suppress the action potentials of a wide variety of our 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 **Note**. To summarize an extremely complex group of studies, 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.

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. 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 **Note**.

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 [Note](#). 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](#) that there were more accidents and more cancers among those receiving eszopiclone.

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

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 [Note](#). 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 [Note](#). 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 pill 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.

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 **Note**. 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 **Note** 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 **Note** Hallucinations have been reported with zolpidem, zaleplon, and eszopiclone. **Note** 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. **Note** 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).

Another side effect of sleeping pills is depression. The sleeping pill industry would like you to believe that insomnia leads to depression, implying 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. Perhaps the true mechanism is that insomnia leads to sleeping pill use, which in turn leads to depression.

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 **Note**. It is safe to assume that there often was no good medical justification. It has been the same in the hospitals where I teach. 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. Only a small percentage of patients given sleeping pill prescriptions receive any diagnosis related to sleep disorders **Note**. 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. 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.

2.E. The problem of addiction.

All prescription hypnotics (with the exception of ramelteon) 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 **Note**. 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 **Note**. 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 **Note**. 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 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.

About 2/3rds 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 drug 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. 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. 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.

CHAPTER 3 - GOOD SLEEP HABITS AND ATTITUDES

The 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 Note.

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 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! Certainly, if you get only 6.5 or 7 hours of sleep a night and feel rested, you do not have to sleep any more. 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!

- 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 little book *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 true that getting more sleep helps depression. Quite the opposite.

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.

Are you a Night Owl?

Do you go to bed late and get up late? For research, see the [UCSD Nightowl Web Site](#).



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, 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.

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 [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 Note.

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 little book [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.

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 sleeping pills are really much more important than the 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. 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.

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, 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 don't feel they are sleeping better, why buy the stuff? Most people would want to feel some benefit from a drug before taking any risk of increasing their chances of developing cancer.

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 **Note**, and in the triazolam-flurazepam study, the benefits were gone after 3 weeks as compared to placebo **Note**. 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 increases sleep even a little. One exception of the 8-week study of Morin **Note**. 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 do not receive it. Further, although we hear colleagues mention that perhaps a patient will be healthier if the patient sleeps better, certainly the CPSI and CPSII mortality data do not support any belief that sleeping pills are useful in the treatment of medical illnesses or in preserving health.

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 [Note](#). 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 [Note](#). 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 [Note](#). A new committee of the Institute of Medicine concluded in 1997 that the data only supported use of Halcion for two weeks [Note](#). In the summer of 2005, the National Institutes of Health had a [consensus conference](#) 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. 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. It would be nice to have a similar analysis for people under 60.

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 have reached the same conclusions:

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.

6. THE CHOICE OF HYPNOTICS

Patients and their doctors face a confusing array of prescription hypnotic drugs, with complex choices about which to select. An important limitation of our study of CPSII data is that it did not determine which of the hypnotic drugs have the most risk. Possibly some of these drugs (perhaps the barbiturates) produce the main mortality risk, and the other compounds might possibly be safer. Diazepam seems to be safe in terms of mortality--and different from at least some of the other drugs which are used as sleeping pills. Clearly, the public needs to know if the particular sleeping pills they are given are safe, but this will not be known until new long-term studies are done.

Since the 1979 Institute of Medicine report **Note**, most experts have agreed that the risks of barbiturates are greater than that of benzodiazepines and the effectiveness less, if anything. Tolerance (loss of effectiveness) is particularly prompt and well-documented with barbiturates, and the risk of physical addiction is familiar to the physicians who used these drugs. Barbiturates suppress rapid eye movement sleep, producing a rebound increase after withdrawal, which may cause nightmares to the patient withdrawing from barbiturates. Another problem is that barbiturates induce special liver enzymes which may severely alter the metabolism of other drugs, producing unpredictable drug interactions. Considering all these aspects, most experts would never choose a barbiturate for a sleeping pill. Drugs such as pentobarbital (Nembutal), secobarbital (Seconal), amobarbital (Amytal), and phenobarbital are considered obsolete as sleeping pills.

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The benzodiazepine drugs which came into use in the 1960's and 1970's were regarded as a marked improvement. Also, they are at least as effective as other hypnotics. Their tendency to produce tolerance, addiction, and withdrawal syndromes is usually not severe, and they suppress REM sleep only a little. Benzodiazepines are responsible for few metabolic drug interactions in the liver. There are situations today when a benzodiazepine may be the best available choice.

SUMMARY OF SLEEPING PILLS

DRUG	Brand Name	My Usual Preference	Possible Indications	I NEVER Recommend
zolpidem	Ambien	under 4 weeks (if at all)		

ramelteon	Rozerem		maybe for trouble falling asleep	
eszopiclone	Lunesta			Never
zaleplon	Sonata			Never
diazepam	Valium		under 4 weeks	
flurazepam	Dalmane		under 4 weeks	
quazepam	Doral		under 4 weeks	
estazolam	ProSom		under 4 weeks	
temazepam	Restoril		under 4 weeks	
pentobarbital	Nembutal			Never
secobarbital	Seconal			Never
amobarbital	Amytal			Never
methyprylon	Noludar			Never
methaqualone	Qualude			Never
chloral hydrate	Noctec			Never
glutethimide	Doriden			Never
ethchlorvynol	Placidyl			Never
triazolam	Halcion			Never
melatonin			maybe for delayed sleep phase syndrome	

Two benzodiazepines, flurazepam (Dalmane) and quazepam (Doral) are rapidly metabolized by the body to desmethylflurazepam, which is an active sleep-inducing compound. The half-life (time to be half-eliminated) for desmethylflurazepam in young adults is 3-4 days. In aging people, the half-life of desmethylflurazepam may be even a week or longer. Therefore, with dosage night after night, the blood concentrations of desmethylflurazepam increase day by day to concentrations as much as 5 times or more the concentration on the initial night of use. As a result, people who take flurazepam or quazepam sleep somewhat

better on the first night, but they may actually have somewhat more hypnotic effect on the second night, as the metabolite accumulates. Likewise, they are measurably sedated during the first day, and the daytime sedation may increase with nightly use. Fortunately, there seems to be tolerance to the daytime effects, so that as desmethylflurazepam concentrations increase, the daytime sedation may not be severe. However, repeated use of flurazepam and quazepam may produce insidious personality changes with nightly use, especially in elderly patients. In aging patients, the drug may accumulate for several weeks, sometimes leading to confusion or loss of memory, and it may be several weeks after the drug is withdrawn that the personality recovers. These long-acting drugs may also cause the worst problems with daytime weakness, falls, and automobile accidents. On the other hand, because they are self-tapering, these drugs have minimal withdrawal symptoms.

Among aging people, sleeping pills such as flurazepam and quazepam can produce gradually-developing weakness, confusion, and memory loss. Diazepam also has this danger.

Diazepam (Valium) is marketed as a tranquilizer and anticonvulsant, but many physicians prescribe diazepam as a sleeping pill. Diazepam is a relatively short-acting drug on the first night, because its metabolite desmethyldiazepam rapidly enters fat stores. After several days of usage, however, the concentrations of desmethyldiazepam may accumulate, producing accumulating daytime sedation and hangover. Thus, diazepam functions as a moderately-long-acting hypnotic with repeated use. When taken by elderly people, diazepam may accumulate for weeks and produce progressive confusion, memory loss, and weakness. Diazepam is one of the few benzodiazepines where controlled studies have demonstrated long-term effectiveness, albeit as an anti-anxiety agent and not as a hypnotic. In our CPSII analysis, people who said they took "Valium" 30 times or more per month had no increase in mortality risk, unlike those reporting regular "sleeping pill" use. This would be one argument for choosing diazepam.

Temazepam and estazolam have intermediate half-lives, which result in continuing effectiveness throughout the night and diminishing sedation during the day. They do not accumulate significantly with nightly use, at least, until aging increases the half-life. A problem with temazepam in formulations which have been sold in the U.S. is rather slow absorption, so that it is ineffective for decreasing time-to-fall-asleep unless it is taken 30-45 minutes before bedtime. Lorazepam (Ativan) and oxazepam (Serax) have many of the same disadvantages and advantages of temazepam, although they are not marketed specifically as sleeping pills.

Triazolam (Halcion), as mentioned, has a particularly short half-life, so it causes relatively little daytime hang-over. Triazolam is quite effective for helping people fall asleep, but as mentioned, for some patients it produces early awakening. Triazolam may also increase daytime anxiety, tension, and panic. Triazolam produces

particularly brisk withdrawal symptoms. Triazolam might be particularly prone to produce behavioral and memory abnormalities. Because of these side effects, many physicians have largely abandoned triazolam. I cannot imagine a patient for whom I would recommend triazolam.

I would never recommend zaleplon (Sonata), since it does not significantly increase sleep.

Incidentally, most experts would not recommend over-the-counter sleeping pills, although less is known about their effects. The suspicion is that the over-the-counter pills might be safer (at least in terms of addiction) but also even less effective. Most of the comments in this booklet refer to the prescription sleeping pills.

6.A. Zolpidem. The most popular option in the U.S. in 2000 - 2005 has been zolpidem (Ambien), which rapidly captured the majority of the U.S. market. Although zolpidem is not a benzodiazepine, it binds with benzodiazepine receptors and apparently acts like a benzodiazepine. However, zolpidem binds more specifically to some of the several kinds of benzodiazepine receptors, and for this reason, it possibly causes less anti-anxiety effect, less muscle weakness and less anti-epileptic effect than most benzodiazepines. It has been claimed that zolpidem distorts EEG sleep patterns less than other hypnotics and that it produces less withdrawal symptomatology. Because of its short half-life, zolpidem produces relatively little hangover but lacks effectiveness for treating early awakening. Zolpidem might increase daytime anxiety in some patients. It appears that zolpidem has little tendency to produce addiction, but addiction with zolpidem does occasionally occur. Ambien brand is extremely expensive compared to most hypnotics, and it is not recommended for long-term use, but inexpensive generic zolpidem may be available soon. Ambien CR is approved for long-term use. There is little evidence available as I write in May, 2006, but I believe Ambien CR (zolpidem tartrate extended release) will have more side effects than Ambien, though it will cause less early awakening. Weighing all factors, many physicians have concluded that zolpidem is the best available choice as a hypnotic for short-term use when early awakening and cost are not problems. I am inclined to agree.

6.B. A word about melatonin. Melatonin was first discovered because it blanches the skin of frogs. **Note.** Next it was learned that in small animals, melatonin can make the gonads atrophy **Note.** Indeed, there is evidence that melatonin interferes with gonadal functions in humans, so it is probably risky for sex and fertility. In some mammals, melatonin whitens the fur or promotes obesity **Note.** Considerable evidence indicates that melatonin might cause depression. Melatonin causes headache and nightmares. In animals, melatonin constricts brain blood vessels and affects the arteries of the heart. In humans, melatonin affects blood pressure. Melatonin is a hormone of darkness. I sometimes imagine that melatonin is recommended by the same sorcerers of darkness who mix owl eyes, newt ears, and wormwood to make magical concoctions. You might wonder why people think melatonin is such a great idea. So do I.

It has been claimed that melatonin is low among people with insomnia. Don't believe it. In our studies, there appears to be little or no relationship.

It has been claimed that melatonin is useful for treatment of

insomnia. In most studies, the sleep benefit is very weak or completely absent. Some meta-analyses have concluded that melatonin is ineffective as a sleeping pill. Melatonin is not primarily a sedative drug. For example, in rats, melatonin is highest when the animals are most alert. For the person whose sleep problem is awakening during the night or awakening too early in the morning, there is evidence that melatonin would do more harm than good. For common insomnia, I do not recommend melatonin.

Melatonin does have some effects on the body clock. There are some studies which suggest that melatonin helps with jet lag or night shift problems, and other studies which show no value in these situations. There has been insufficient testing. The only application where benefits of melatonin seem quite likely to outweigh risks is for the completely blind person who may have lost his or her eyeballs.

There is evidence that melatonin may be of some help for people with delayed sleep phase syndrome. I am not sure if it is of substantial use in the long run. When being used to make the body clock earlier (helping people fall asleep earlier and awaken earlier), melatonin should be taken about 6 hours before bedtime and in a very low dose, perhaps 0.1 to 0.5 mg only.

6.C. Ramelteon. Ramelteon (Rozerem) is a drug which is thought to work much like melatonin. It is not a benzodiazepine agonist. It stays in the blood much longer than melatonin and has some metabolites about which not much is known. As mentioned, by EEG, ramelteon helps insomniacs fall asleep only 7-16 minutes faster, and is virtually useless the rest of the night. Many patients experience no subjective benefit with ramelteon.

Although ramelteon has less risk of hangover and addiction than other sleeping pills, it is not without reported side effects. In part I.B., I have explained that ramelteon is one of the new hypnotics which (as a group) appear to cause cancer. All in all, I am skeptical that it is worth the risk, but ramelteon is so new that we need to learn more about it.

6.D. Eszopiclone. Eszopiclone (Lunesta) is the S-isomer of zopiclone. That is, zopiclone contains both eszopiclone and its mirror image. I don't know of any evidence that eszopiclone is more effective than zolpidem, certainly not as compared to Ambien CR, the extended release form of zolpidem. On the other hand, there is European evidence that zopiclone may cause more automobile accidents than zolpidem. There seems to be more evidence of cancer risk for zopiclone and eszopiclone than for zolpidem. Zopiclone and eszopiclone cause more hangover (daytime impairment) than zolpidem, though the comparison with the extended release form of zolpidem (Ambien CR) is unknown to me. Eszopiclone seems to cause viral infections and bitter taste in the mouth, side effects which do not seem common with zolpidem. All in all, I do not see any situation in which the benefits/risks ratio of eszopiclone would be as good as that of zolpidem. Therefore, eszopiclone is not a drug which I choose.

6.E. Quetiapine (Seroquel). Quetiapine is a powerful atypical antipsychotic drug which is indicated for treatment of schizophrenia and bipolar mania. It is not indicated for treatment of insomnia, though some physicians have been prescribing it as a sleeping pill. Quetiapine is a dangerous drug which frequently kills people when given to elderly patients with dementia. It has other

serious side effects such as neuroleptic malignant syndrome, tardive dyskinesia (permanent problems with movement), and diabetes. I would not ever advise quetiapine use simply as a sleeping pill.

7. HOW MUCH ARE SLEEPING PILLS USED IN THE UNITED STATES?

I 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 New York Times, data from IMS Health showed there were 43.1 million prescriptions for hypnotics in the U.S. in 2005 Note. I believe this may be an underestimate.

First, although the National Prescription Audit includes certain mail-order pharmacies and drugs distributed to private nursing homes as well as retail pharmacies, it does not monitor all medications distributed by health maintenance organizations, hospitals, or public clinics such as community mental health centers. Obviously, HMO's are becoming a growing part of the medical market. Also, it does not include drugs distributed by the Department of Veterans Affairs or Public Health Service and military hospitals, which provide a substantial portion of America's medical care. National hypnotic consumption figures based on the National Prescription Audit simply ignore numerous avenues of distribution.

This lack of monitoring might seem surprising, considering that the sleeping pills are addicting drugs governed by the narcotics laws, and everybody knows that they are occasionally drugs of abuse. Recently temazepam became popular among drug abusers in England. Rohypnol, the "date rape" benzodiazepine not sold legally in the United States, has obviously become widely available. Pharmacologically, Rohypnol is not distinct from other marketed benzodiazepine hypnotics. Who knows why drug abusers prefer "reds" (Seconal?) one year and Rohypnol another? In any case, the federal ostrich has its head in the sand.

Even given the likely underestimations of the National Prescription Audit data, I believe that the popular estimates of the percentage of Americans who use hypnotics must be incorrect. Consider, the National Prescription Audit reported 37,000,000 yearly prescriptions for hypnotics in 1970, with an average of about 40 pills per prescription, a total of perhaps 1,480,000,000 hypnotic pills. Yet the 37,000,000 prescriptions would have been sufficient to provide about 4,000,000 Americans with one pill per day, or 99,000,000 Americans could receive 15 pills per year. At that time, NIH scientists were estimating that only 3.5% of American adults were using any hypnotic pills per year Note. Something is terribly inconsistent about those survey estimates. In France and Germany, a much higher percentage of the population is said to take hypnotics, for the most part chronically. I wonder if the American figures aren't really closer to the European figures than our scientists have realized.

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.

8. WHY HAVEN'T YOU HEARD THIS OPINION OF SLEEPING PILLS FROM EVERY EXPERT?

The 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 **Note**.

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

9. NEEDS FOR HYPNOTICS RESEARCH

Today, nobody can be certain that any of the prescription sleeping pills is safe for long-term use or even that they help sleep with long-term use. Although the potential risk of intermittent use (a few times a month) seems to be less than the risk of nightly use, our CPSI and CPSII studies indicated that sleeping pills may be unsafe in any amount. It is important to recognize that both studies

were done before some of the drugs popular today came on the market. In particular, zolpidem, zaleplon, eszopiclone and ramelteon (the most popular U.S. sleeping pills in early 2006) were not tested. Different experts may have different opinions about the likelihood of long-term safety, but the fact is that nobody knows for sure about particular drugs. The only way to assure public safety is to do more long-term randomizing trials.

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 receive 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 addicting drugs.

You might expect that with the new evidence that new sleeping pills cause cancer, no company would want to do large long-term studies of their product which might demonstrate cancer risk. 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.

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 \$3 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.

10. ABOUT THIS WEB BOOK: PRINTING & COPYING

I wrote this little book and put it on a web page, so that people in need could learn about the dangers of sleeping pills and about alternative treatments. Much of this book 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.

You may make printed or electronic copies of this book for yourself or to give to family or friends without charge. I would be happy if this book can help lots of people. The materials are copyrighted, ©1997-2008 by Daniel F. Kripke, M.D., and may not be used commercially for sale without permission. It is possible to print the book from internet web pages or to download a [PDF version](#), which can be read by Adobe Acrobat Reader. A version printed by Acrobat Reader from the PDF file will print in a nice format, with all footnotes included.

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](#), the database provided by the U.S. National Library of Medicine. My most recent scientific writings about sleeping pills and more scientific references are found at [Note](#).

If you have depression or think you might benefit from bright light treatment, you may also be interested in [Brighten Your Life](#), which overlaps with some sections of this book.

11. ABOUT DR. KRIPKE

Daniel F. Kripke, M.D. is a licensed practicing physician certified by the American Board of Psychiatry and Neurology and a Professor of Psychiatry at the University of California, San Diego. Dr. Kripke was elected a Fellow of the American Psychiatric Association. Dr. Kripke has written 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.

You can contact Dr. Kripke at dkripke1@san.rr.com, but please do not write for personal medical advice. A physician should not give personal advice to a patient he does not know.

Acknowledgment: I have been fortunate that my research has been supported for over 30 years mainly by the U.S. National Institutes of Health (NIH) and the Department of Veterans Affairs. The Department of Psychiatry and the Sam and Rose Stein Institute for Research on Aging of the University of California, San Diego have also supported my research, as has the Weingart Foundation and the American Cancer Society. Recently, the Scripps Clinic Sleep Center has been supporting some of my research, with the help of generous gifts from private donors. Ambulatory Monitoring, Inc. (the manufacturer of the Actillum and other actigraphs) and Minimitter-Respiroics (makers of actigraphs), The Sunbox Company and Apollo Health (who make bright light boxes) have supported our research, mainly 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 do not accept 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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