




2009

## Insomnia: Its Causes, Its Consequences, and Its Cures

Shoshana Fried  
*Touro College*

Follow this and additional works at: <https://touro scholar.touro.edu/sjlcas>

 Part of the [Biology Commons](#), and the [Pharmacology, Toxicology and Environmental Health Commons](#)

---

### Recommended Citation

Fried, S. (2009). Insomnia: Its Causes, Its Consequences, and Its Cures. *The Science Journal of the Lander College of Arts and Sciences*, 2(1), 53-69. Retrieved from <https://touro scholar.touro.edu/sjlcas/vol2/iss1/6>

This Article is brought to you for free and open access by the Lander College of Arts and Sciences at Touro Scholar. It has been accepted for inclusion in The Science Journal of the Lander College of Arts and Sciences by an authorized editor of Touro Scholar. For more information, please contact [touro.scholar@touro.edu](mailto:touro.scholar@touro.edu).

## **Insomnia: Its Causes, Its Consequences, and Its Cures**

*Shoshana Fried*

### **ABSTRACT**

Insomnia is a complaint that affects almost all Americans at some point throughout their lives. However, only chronic insomnia is truly a disorder. This type of insomnia can be caused by various reasons, whether physiological, molecular, or psychological. This paper will elaborate on a number of possible causes for insomnia. Furthermore, this paper will present some of the many adverse effects that are caused by the sleep deprivation resulting from chronic insomnia. There are many possible treatments available to help against insomnia. This paper will explain

some of the behavioral methods. In addition, it will discuss the many different medications that have been used or are still used to treat insomnia, including chloral hydrate, barbiturates, antihistamines, and antidepressants. This paper will show the benefits and risks of benzodiazepines, a class of drugs used to treat insomnia, as well as the benefits and risks of the benzodiazepine-like agents BZRAs. This paper will also mention the new EVT 201 drug for insomnia that is currently undergoing testing for its efficacy and safety. In conclusion, this paper will show that each case of insomnia is unique and different, from its cause to its ramifications. Each case must be dealt with and treated individually.

Most people spend about a quarter of their lives sleeping. That's about forty-two hours a week, ninety-one days per year, and, in a lifetime of ninety years, over twenty of them will be spent asleep. Many think of this as wasted time; we cannot accomplish many things on our "To Do" lists while snoozing. However, sleep is an important and essential need of the body, and in fact one could not live long without it. Many restorative and healthy benefits take place during those hours of sleep, making sleep quite necessary for life.

Various parts of the brain are responsible for or involved in sleep, and a few theories exist as to how we fall asleep. The generally accepted view today is that several parts of the brain are involved in sleep regulation. In some areas of the brain, neurotransmitters such as serotonin and norepinephrine are produced by neurons in the brainstem and act on different groups of neurons. Whether we are asleep or awake depends on which neurons receive the signals. In other cases, neurons begin to signal only once we fall asleep. These activated neurons are believed to switch off the signals and keep us awake (NINDS '04). One area of the brain involved in sleep regulation is the raphe nuclei which are located in a thin strip down the midline of the caudal reticular formation. It is believed that these nuclei promote sleep (Pinel '03). The basal forebrain region and the nearby anterior hypothalamus are also thought to be instrumental in promoting sleep (Pinel '03). Sites throughout the caudal reticular formation are thought to be responsible for controlling the major indices of REM sleep, the stage of sleep most physiologically similar to wakefulness. Different sites control different features of REM sleep, such as core muscle relaxation, cardiorespiratory changes, and rapid eye movements.

*Shoshana Fried, B.S. 2008, majored in Biology. She is currently studying for her PharmD at Touro College School of Pharmacy.*

These sites communicate through cholinergic and monoaminergic neurons located in the caudal reticular formation. If all these areas work together, REM sleep is induced (Pinel '03).

Why do we sleep? What do we gain? According to many studies done on both animals and humans, much. Sleep is necessary for survival. According to the recuperation theories of sleep, the body's homeostasis is disrupted while one is awake. Sleep restores the body to homeostasis, for example restoring the body's energy levels. These theories imply that when a great deviation from homeostasis results after a period of wakefulness, sleepiness is triggered and the person will go to sleep. Once homeostasis is reestablished, the person wakes up (Pinel '03).

Another theory proposed is that sleep is necessary for our nervous system to properly function. Sleep gives regularly active neurons a chance to rest and repair themselves while using

other groups of neurons during sleep. Without sleep, daytime neurons would become energy depleted or so clogged up with metabolic byproducts that they would malfunction (NINDS '04). Sleep also allows for certain neuronal connections that do not regularly occur during wakefulness, which otherwise might degenerate from misuse (NINDS '04).

Additionally, many cells in the body show higher rates of protein production during sleep. These proteins are necessary for cell growth and repair. In children and young adults, release of growth hormone occurs during deep sleep (NINDS '04). When a person's body has an infection, he or she sleeps more due to the increased levels of cytokines, which are powerful sleep-inducing chemicals. This indicates that sleep may help conserve energy and other resources that the immune system can now use to attack the source of infection (Dunn '04).

The benefits of sleep are many, indicating that sleep is extremely significant. Not only is sleep relaxing and restorative, it is also actively beneficial. Sleep helps the body maintain its normal metabolism and activity, and that is why a deficit of sleep is so detrimental.

Insomnia is defined as "the sensation of daytime fatigue and impaired performance caused by insufficient sleep" (A.D.A.M. '03). Insomnia is divided into three categories, based on its duration. Transient insomnia, which is experienced by 35% of Americans (Caldwell '03), is the inability to fall asleep for a few nights. Short-term insomnia lasts for up to three weeks. Chronic insomnia, which is the truly problematic type, is defined when a person finds it difficult to fall asleep or maintain sleep or he feels his sleep is nonrestorative for at least three nights a week for a month or more (A.D.A.M. '03). The patient also must be in distress and believe that his or her normal daily functioning is suffering from the sleep loss (A.D.A.M. '03).

Transient and short-term insomnia can have many causes. These types of insomnia can often be a response to a change or a stress, such as travel, an acute illness, a job change, or even an exam. These symptoms are minor and only last for a short while; when the stress is removed or the person adjusts to the change, the insomnia stops and normal sleep returns. Transient or short-term insomnia can often occur in females due to fluctuations in hormones, such as during menstruation or pregnancy. Changes in the amount of light to which a person is exposed can influence his or her ability to fall asleep, along with noise, uncomfortable temperatures, or other environmental disruptions (A.D.A.M. '03). Increases muscle tension, caused by daily stress, will not allow a person to fall asleep easily (Caldwell '03). Ingesting certain substances, such as caffeine or nicotine, can disrupt sleep and generate insomnia. Many medications include insomnia as a side effect, especially those containing caffeine (A.D.A.M. '03). However, in all these cases, unless the insomnia persists for more than a few weeks, no treatment is necessary.

Chronic insomnia, however, is more significant. Chronic insomnia is usually caused by a collaboration of different psychological and physical conditions. One important kind of insomnia is psychophysiological insomnia which is caused by initial transient insomnia. After experiencing difficulty falling asleep for a few nights, the patient begins to associate the bed with a struggle to sleep. This causes even more difficulty in falling asleep. Eventually the patient begins to worry excessively about sleep loss and continually experiences anxiety at bedtime. This cycle continues over a long period and the insomnia becomes chronic (A.D.A.M. '03).

Chronic insomnia can also be caused by pain or discomfort. Leg disorders especially, such as restless leg syndrome or leg cramps, are often a cause of insomnia. Other medical problems that can cause insomnia include arthritis, heart disease, asthma, Attention Deficit

Hyperactivity Disorder (ADHD), and cancer. Many medications as well induce insomnia. These medications include beta-blockers, certain antidepressants, beta-agonists, and many more. When taken over a long period of time, they can produce chronic insomnia. Substance abuse, especially overuse of alcohol or cocaine, can also play a major role in causing insomnia (A.D.A.M. '03).

Very often insomnia has an underlying psychological cause. Certain emotional disorders often cause insomnia, especially anxiety, bipolar disorder, and depression. These emotional disorders prevent the relaxation necessary for sleep onset (Caldwell '03). They also often cause repeated awakenings during the night and the inability to return to sleep after awakening (A.D.A.M. '03).

Insomnia can be annoying. Lying in bed for hours waiting to fall asleep can be frustrating, and waking up repeatedly throughout the night can be exasperating. However, the effects of sleep deprivation are much more significant and detrimental than that.

Sleep deprivation can cause a decline in certain cognitive abilities. The National Sleep Foundation (NSF) lists a number of consequences of inadequate sleep, including slow thinking or reacting and frequent mistakes. They also include difficulty focusing, a narrowing of attention, difficulty following directions, difficulty remembering information, and poor judgment regarding complex situations (A.D.A.M. '03). Sleep deprivation can also cause impairment of higher neurological functions. Awareness and perception decline, and vision difficulties often occur. Difficulty with coordination and fine motor skills is also quite common (Caldwell '03). General performance declines and simple tasks become more difficult or even impossible.

Even more unsettling are the emotional problems caused by inadequate sleep. Sleep deprivation often has an adverse effect on mood or temperament. The NSF includes in its list impatience and quick anger, as well as depression or negative mood. [j] Insomnia can interfere with the activity of hormones and pathways that deal with emotion, so that even minimal sleep deprivation can greatly effect one's mood (A.D.A.M. '03).

When one has had inadequate sleep, one is more likely to feel forlorn, depressed, or hopeless. Lack of sleep also causes motivation to diminish. In addition to the actual decline in cognitive abilities due to his sleep deprivation, insomnia also causes a person's desire and interests to lessen. He would much rather rest than do a math problem or solve a puzzle. Perhaps this is what account for the great disparity in performance when one is sleep deprived (Caldwell '03). The negative repercussions that result from sleep deprivation can decrease the quality of life as much as living with a chronic condition like heart failure (A.D.A.M. '03).

During periods of inadequate sleep, many abnormal physiological conditions are observed. A study done in 1991 found that after a single night of three hours of sleep, during submaximal exercise maximum oxygen consumption significantly decreased while heart rate and ventilation significantly increased. A 1993 study investigating the endocrinological effects of sleep deprivation found that TSH, thyroid hormones, estradiol, and LH levels went up, while prolactin levels decreased (Walsh and Lindholm '97). Although the reasons for these changes are unclear, their message is not: Sleep deprivation causes many changes in the body's metabolism, and most of them are evidently not very beneficial.

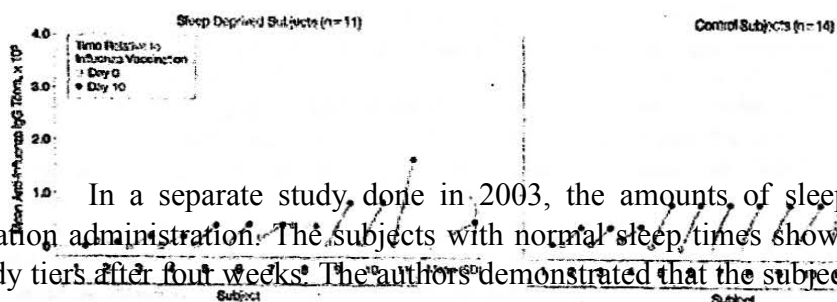
Chronic sleep loss adversely affects metabolic functions, in particular carbohydrate metabolism. A study done at the University of Chicago in 1999 found that after a period of sleep deprivation, glucose conditions were higher than they were after a period of adequate rest (Van

Cauter '99). These variations in glucose metabolism resembled those in patients with type-2 diabetes (The University of Chicago Medical Center '99). A subsequent study was conducted in 2006 by the same author. The HbA1c, glycosylated hemoglobin which reflects the average blood glucose blood level over the previous three months, was measured in various patients already diagnosed with diabetes. They found that higher HbA1c results were closely associated with inadequate or poor quality sleep. This study showed that insufficient proper sleep is related to increased blood glucose levels in patients with diabetes (The University of Chicago Medical Center '06).

The 1999 study concluded that the reduction of metabolic function capacity due to chronic sleep loss is devastating. The metabolic and endocrine changes that result “mimic many of the hallmarks of aging”. Cutting back on sleep “produced striking changes in glucose tolerance and endocrine function-changes that resembled the effects of advanced age or the early stages of diabetes.” These results occurred after less than a week of sleep deficiency! This study showed that chronic sleep loss can “hasten the onset but could also increase the severity of age-related ailments such as diabetes, hypertension, obesity and memory loss” (The University of Chicago Medical Center '06).

Besides altering endocrine and metabolic functions, sleep deprivation can also have an adverse effect on the immune system. In a study done in 2002, influenza vaccinations were given to two groups of people. One group had been restricted to four hours of sleep for the previous four nights, while the other group had maintained their usual bedtimes before receiving the vaccination. It was found that those in the group of decreased sleep had mean antibody titers less than half of those in the group with normal sleep times. The authors concluded that “the response to influenza vaccination may be impaired in individuals with chronic partial sleep restriction” (Lurie 2002).

#### Antibody Titers at Baseline and 10 Days Following Influenza Vaccination



In a separate study, done in 2003, the amounts of sleep were altered *after* the vaccination administration. The subjects with normal sleep times showed almost twice as great antibody tiers after four weeks. The authors demonstrated that the subjects with sleep deprivation did not produce antibodies as efficiently as those with adequate sleep (Lange et al. '03). This weakened immune system makes people deprived of sleep more vulnerable to diseases and infections (Dunn '04). In a study done by the American Cancer Society, they found that men who slept for less than four hours a night had mortality rates ten times greater than those who slept seven to eight hours a night. Perhaps that is why the National Center for Health Service Research in the United States considers proper amount of sleep one of the six most important factors affecting illness and death rates (Caldwell '03).

Insomnia is not a disease but a symptom (Caldwell '03). However, insomnia can be cured- not only by taking care of the underlying cause but also by treating the insomnia itself. There are many behavioral therapies and other treatments to stop insomnia that do not involve medications. In addition, hypnotic drugs, which are the class of drugs that can bring on sleep, lengthen sleep time, or improve it in any way (Caldwell '03).

Behavioral techniques are often favored over medications for many reasons. Using drugs always introduces side effects, interactions, and other restrictions, while making adjustments in behavioral often does not. Behavioral methods can be used by all insomniacs, including those already taking an incompatible medication or elderly patients. Additionally, although medications are equally or even more effective, behavioral techniques often work faster (A.D.A.M. '03).

There are a number of behavioral approaches for treating insomnia. The first step usually recommended is to check for proper sleep hygiene. This term is used "to describe simple behaviors that may help improve sleep" (Bootzin and Rider '97). Behaviors that constitute improper sleep hygiene are identified and stopped. These include spending too much time in bed, using substances like caffeine or nicotine that interfere with sleep, attempting to sleep in a poor sleep environment, napping in the late afternoon or evening, and engaging in extremely stressful or exciting activities close to bedtime (Bootzin and Rider '97). Instead, proper sleep behaviors are set. These behaviors may include establishing a fixed time for going to bed and getting up, taking a hot bath about one and a half to two hours before bedtime, or doing something relaxing such as reading or meditating half an hour before bedtime (A.D.A.M. '03). Proper sleep hygiene education has proven quite effective, often even after only one or two sessions of evaluation and recommendations (Bootzin and Rider '97).

One suggestion made to improve sleep hygiene is to exercise in the early evening. A few hours after exercise, a low point in energy is experienced, and this can help the person to fall asleep more easily (A.D.A.M. '03). Engaging in moderate to heavy exercise causes one to fall asleep more quickly, wake up less often throughout the night, and experience increased amounts of deep sleep (Caldwell '03).

Another behavioral treatment used for insomnia is stimulus control instructions. These are a set of instructions that focus primarily on helping the patient associate the bed with falling asleep quickly. Some of the instructions include going to bed only when ready for sleep, as well as getting out of bed and leaving the bedroom if unable to fall asleep within ten minutes. Studies have found stimulus control to be one of the most effective therapies for treating insomnia (Bootzin and Rider '97).

There are other behavioral techniques that can be used in the treatment of insomnia. Some of these techniques are light therapy, progressive muscle relaxation, and cognitive behavior therapy (A.D.A.M. '03). However, the value of these methods is not so certain and many do not provide conclusive evidence as to their effectiveness. Experts are still studying the benefits and helpfulness of each, and studies are still being conducted to find more ways to help in the treatment of insomnia.

Sometimes, however, behavioral methods are not enough. Each individual's patient's case of insomnia is unique, and the treatment provided must match in each case. Sometimes the behavioral techniques do not work well enough, and other proven methods must be used.

Medications can also be helpful in the treatment of insomnia. Some over-the-counter drugs and even drugs regularly given to treat a different symptoms- can be helpful, and sometimes doctors might prescribe a specific medication to treat insomnia.

One drug that was formerly very common as a remedy for insomnia is chloral hydrate. It has been in use for more than one hundred fifty years (A.D.A.M. '03). Chloral hydrate works quickly, reaching peak blood levels within an hour (Caldwell '03). It has a fairly short half-life so does not usually produce a hangover after awakening. However, its popularity as a treatment for insomnia has gone down, due to the many adverse side effects and risks it involves. As a direct brain-cell depressant, chloral hydrate can interfere with brain functions and cause confusion and drowsiness (Caldwell '03). It can also cause inflammation of the skin or irritation of the stomach (A.D.A.M. '03). Because it is metabolized in the liver and excreted in urine, patients with liver or kidney disorders should not use it (Caldwell '03). Chloral hydrate also has carcinogenic properties and may damage genetic material. Additionally, the lethal dose of chloral hydrate is very close to the therapeutic dose, and even a slight overdose can be fatal (Pagel and Parnes '01). Because of all the risks it incurs, chloral hydrate is no longer regularly used in the treatment of insomnia.

Barbiturates is another class of drugs that can be used to treat insomnia. Barbiturates were used as the standard sleeping medication in the years before the 1960's (Pagel and Parnes '01). However, addiction and abuse of barbiturates were quite common (A.D.A.M. '03). They also have a high danger of overdose and have caused the deaths of many, including some famous celebrities like Elvis Presley and Marilyn Monroe (Pagel and Parnes '01). Presently, due to their potential for abuse and overdoses, these drugs are rarely or never prescribed to treat insomnia (A.D.A.M. '03).

Antihistamines are another type of drug used in the treatment of insomnia. Antihistamines are regularly prescribed to unclog congestion from a common cold or to stop allergic reaction that might become dangerous. A very prominent side effect of antihistamines is sedation. Everyone knows that taking Sudafed or Benadryl will cause one to fall asleep. For certain antihistamines, this side effect is so pronounced that it was decided to market the drugs for insomnia. These antihistamines include diphenhydramine, the one ingredient in the most over-the-counter "sleeping pills," diphenhydramine, promethazine, and meclizine. However, in most antihistamines leave patients feeling drowsy the next day (A.D.A.M. '03). They also cause some other adverse side effects, such as dizziness, blurred vision, increased heart rate, and weight gain (Caldwell '03).

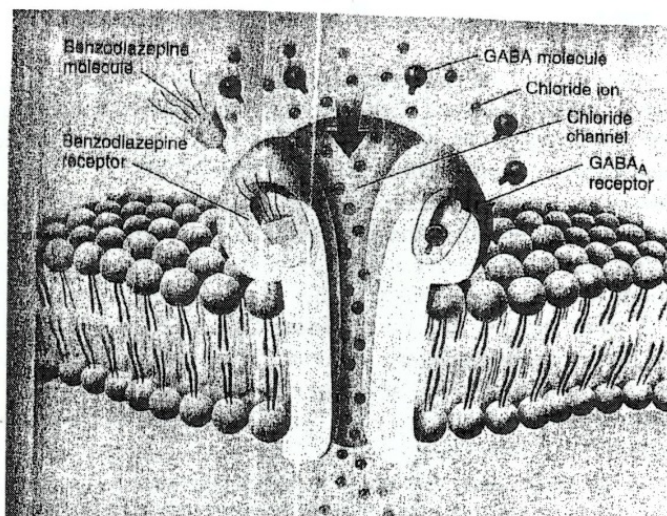
Over-the-counter sleeping pills are used by 3/1% of adults in the United States (Pagel and Parnes '01). These antihistamines are quick acting and cause quick onset of their hypnotic effects. The effects generally last for six to eight hours (Caldwell '03). However, many sleeping pills work differently for different people. Sleeping pills often cause daytime sleepiness and cognitive impairment. These side effects often remain until the next day, interfering with daytime performance (Pagel and Parnes '01). Sleeping pills can also have a diminishing effect on brain function. This dangerous symptom is exacerbated if the antihistamine is reaching with another drug substance that causes sedations (Caldwell '03). They should be taken with caution and used only as a last resort.



A class of drugs used quite frequently in the treatment of insomnia is sedating antidepressants. Many patients with insomnia also suffer from depressive symptoms, and sometimes the depression is a direct result of the insomnia (Pagel and Parnes '01). One group of antidepressants used are the tricyclic antidepressants. Tricyclics are absorbed quickly and reach peak blood levels in two to four hours. Tricyclics can increase deep sleep and decrease the number of awakenings during the night (A.D.A.M. '03). In addition, they cause a gradual improvement in the depressed patient's mood, although this effect only starts two to three weeks after starting regular dosage (Tyrer '93).

The required dose to treat insomnia is smaller than the dose used to treat depression, an amount that often causes many negative side effects. However, even the small dose does cause a few minor side effects such as weight gain, increased heart rate, dry mouth, and constipation. It can also cause daytime sleepiness and hangover or even weakness and fainting spells (Caldwell '03). Tricyclics also have a high danger of overdose (Pagel and Parnes '01). Additionally, if a patient is taking antidepressants, especially a large dose, and abruptly withdraws, he can suffer symptoms of severe anxiety and perhaps even panic. However, withdrawing gradually by slowly reducing the dose over a period of four weeks can usually help circumvent this effect (Tyrer '93).

The main class of drugs used today in the treatment of insomnia is benzodiazepines. Benzodiazepines act as GABA receptor agonists in the nervous system. GABA (gamma-aminobutyric acid) is the chief inhibitory transmitter in the central nervous system (Pinel '03). There are three types of receptors for GABA in the CNS; one type is GABA<sub>A</sub> receptors. The GABA<sub>A</sub> receptor controls the direction and magnitude of the ionic currents of the neuronal ion channels. When GABA binds to the GABA<sub>A</sub> receptors, it triggers the opening of a chloride ion pore. This inhibits the firing of new action potentials. Benzodiazepines act by binding to a different site on the GABA<sub>A</sub> receptor and thereby increasing the binding of GABA molecules to the receptor (Pinel '03). This increases the inhibitory effects and slows down the flow of chemical information from one neuron to another (Caldwell '03). This is what causes the relaxation and sedation that aid in reducing insomnia.



Since they were developed in the 1960's, benzodiazepines have proven their effectiveness. Today benzodiazepines are the drugs of choice in the treatment of insomnia, since they have the highest benefit and the lowest risk of other sleep-enhancing medications (NSF '02). As with most sleep-promoting drugs, benzodiazepines have proven effective for decreasing the time it takes to fall asleep, increasing total sleep time, minimizing the number of awakenings during the night, and improving the quality of sleep (A.D.A.M. '03). Benzodiazepines, though, are less likely to lose efficiency after a few months (A.D.A.M. '03), while many other drugs require higher and higher doses to continue to work against the insomnia. In addition, benzodiazepines have a much smaller abuse potential and overdose danger (Pagel and Parnes '01). The therapeutic index, or the relationship between the effective dose and the lethal dose, is about one hundred for benzodiazepines, while it is a mere two to four for drugs such as barbiturates (Roehrs and Roth '97). For this reason, fatal overdose of a benzodiazepine is extremely rare (Caldwell '03).

However, benzodiazepines do have certain adverse side effects. As do most hypnotics, benzodiazepines often cause residual daytime sleepiness. Benzodiazepines inhibit the charging of neurons in the central nervous system, and if this effect lingers, drowsiness as well as a slowing of thought processes occurs (Caldwell '03). Coordination and judgement are impaired (Committee on the Review of Medicines 80'), and a general deterioration of neurological functioning is observed (Caldwell '03). Most often these effects are quite subtle, but occasionally they may be severe, resulting in confusion and disorientation and memory loss of preceding events (Caldwell '03). This happens especially with elderly patients who are taking benzodiazepines, as the aging brain seems to be more susceptible to this type of side effect (Caldwell '03). This residual drowsiness has led benzodiazepines to be associated with an increased risk for falls and car accidents, especially within the first week of taking them (A.D.A.M. '03). This is why users of benzodiazepines are advised not to drive or operate heavy machinery while on the medication.

The inhibitive properties of benzodiazepines also cause relaxation of muscles. If this effect persists, patients will experience poor fine motor coordination and generalized weakness. A mild spinning sensation or blurred vision may also occur (Caldwell '03).

Benzodiazepines can also have an effect on one's mood and may increase depression (A.D.A.M. '03). In addition, respiratory depression may occur as a result of taking benzodiazepines. This happens especially in patients with preexisting respiratory disorders, for whom the benzodiazepines exacerbate the respiratory malfunctions (Pagel and Parnes '01).

Some experts do not like to promote the use of benzodiazepines as they distort the normal patterns of sleep. While benzodiazepines increase the time spent in Stage Two sleep, they decrease the time spent in Stage Four sleep and in the restorative REM sleep (Pinel '03). This causes another negative side effect of benzodiazepines: the patients experiences disturbing dreams (Caldwell '03).

Benzodiazepines are also problematic in that tolerant to the medication and it no longer works well as the treatment continues (Caldwell '03). This requires the patient to take continuously higher doses of the benzodiazepine to maintain the same results (Pinel '01). A study done by the White House Office of Drug Policy and the National Institute on Drug Abuse found that many benzodiazepines tend to lose their efficacy after three to fourteen days of continuous use (Committee on the Review of Medicines '80).

In addition to tolerance, the body develops dependence on benzodiazepines. This is a state in which unless drug use continues, the body will go into a withdrawal or drug-absence stage (Caldwell '03). If a patient taking benzodiazepines stops the medication abruptly, he will experience many withdrawal symptoms. One symptom almost always experienced, especially by those who have been taking benzodiazepines over a long period of time, is rebound insomnia. This entails one to two nights of poor sleep and daytime tiredness. Patients may also suffer from increased anxiety and apprehension and perceptual disruption of noise, touch, and movement (Tyrer '93). Gastrointestinal irritation and disturbed heart rhythm are common withdrawal symptoms as well. Sometimes, patients may suffer the same severe insomnia that caused them to start the drug in the first place (A.D.A.M. '03). This severe rebound insomnia lasts about one to three weeks until it returns to the level it was at before the drug was stopped (Tyrer '93). This can be dangerous because doctors observing the return of the original insomnia may conclude that the treatment was ineffective and then prescribe a higher dose of the medication (Committee on the Review of Medicines '80).

To circumvent these withdrawal symptoms, it is advised to withdraw from the benzodiazepine drugs gradually (Committee on the Review of Medicine '80). This can be over a period from two weeks to many months (Tyrer '93). This allows enough time for the central nervous system to adapt to the withdrawal of the inhibitory drug (Tyrer '93).

Another suggestion to decrease the severity of withdrawal symptoms is to withdraw from the benzodiazepines along with cognitive behavior therapy. A study done in Canada in 2003 studies the differences between gradual tapering of the benzodiazepines and gradual tapering combined with cognitive behavior therapy. The researchers randomly assigned these two withdrawal methods to the patients in the study who had been using benzodiazepines at bedtime for the previous three months or longer. Out of the sixty-five patients, thirty received a gradual tapering schedule of 25% reduction in dosage at one to two week intervals. The other thirty-five received the same withdrawal schedule as well as a ninety-minute weekly session of therapy with a psychologist who gave sleep hygiene education and instructions for stimulus control. Each patient met weekly with a doctor who looked for withdrawal symptoms. Based on the patient's symptoms the doctor prescribed either the same or a lower dosage of the benzodiazepines. After eight weeks of treatment an evaluation was done. The evaluation found that 38% of those undergoing gradual tapering only had completely withdrawn from the benzodiazepines, while in the combined group the percentage of patients off the benzodiazepines was 77%. Additionally, a

reduction in the dosage of benzodiazepine greater than 50% occurred in 69% of the first group and 97% of the combined patients. After a twelve month follow-up, some patients had reverted back to taking the benzodiazepine or had increased the dosage; however, the percentages were once again much higher for those in the combined group. This study clearly showed that the combination of cognitive behavior therapy with gradual tapering is superior to gradual tapering alone (Baillargeon et al. '03).

**Changes in benzodiazepine use**

Patient status and time of measurement	Group; no. (and %) of patients		OR (and 95% CI)	
	Combined treatment	Tapering alone	Crude	Adjusted*
<b>Benzodiazepine-free</b>				
Immediately after treatment	26/34 (77)	11/29 (38)	5.3 (1.8–16.2)	7.9 (2.4–30.9)
At 3 mo	22/33 (67)	10/29 (34)	3.8 (1.4–11.3)	3.9 (1.4–12.1)
At 12 mo†	23/33 (70)	7/29 (24)	7.2 (2.4–23.7)	7.6 (2.5–26.6)
<b>Dosage reduction ≥ 50%</b>				
Immediately after treatment	33/34 (97)	20/29 (69)	14.8 (2.5–284.3)	16.5 (2.7–321.2)
At 3 mo	25/33 (76)	19/29 (66)	1.6 (0.5–5.0)	1.6 (0.5–5.0)
At 12 mo†	26/32 (81)	15/29 (52)	4.0 (1.3–13.6)	4.1 (1.3–13.8)

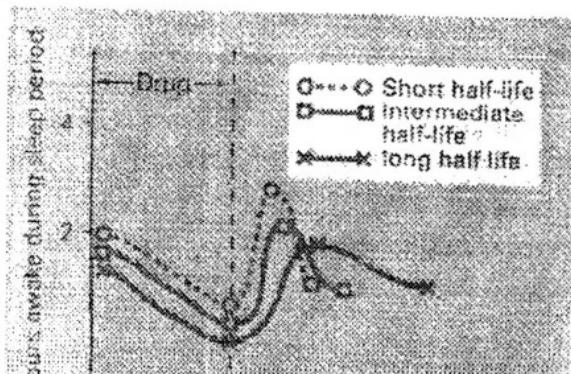
Note: OR = odds ratio, CI = confidence interval.

\*Adjusted for initial daily dose of benzodiazepine.

†For one patient in the combined treatment group, information about benzodiazepine withdrawal was obtained at 12-month follow-up, but data for the dosage reduction variable was not available at that time; hence the difference in denominators.

Due to the many adverse side effects the use of benzodiazepines entails, doctors recommend that the regular use of benzodiazepines should be limited (Roehrs and Roth '97). The Committee on Safety of Medicines advised that benzodiazepines should not be used for more than four weeks (Bashir et al. '94). Benzodiazepines should be prescribed at the lowest possible effective dose and prescriptions should be within the therapeutic range (Committee on the Review of Medicines '80)

However, there is another type of benzodiazepine that produces fewer negative side effects. This type of benzodiazepine may be excluded from the limitation of regular benzodiazepines due to the decreased risks it involves. These are the short-acting benzodiazepines that have much shorter half-lives than the regular benzodiazepines. These come very close to the “ideal sleeping pill”, as they have a quick onset, last for a typical night’s sleep of six to eight hours, and then are quickly metabolized or eliminated from the body and the hypotonic effects stop. (Caldwell '03).



There is quite a range of short half-life benzodiazepines. Some, like triazolam, have a very rapid onset but last for only a short while. This medication can be helpful for a patient who has difficulty falling asleep but not for a patient who tends to awaken throughout the night, as the drug is cleared from the body before the night is over (Caldwell '03). Other short half-life benzodiazepines wear off by the next morning. This decreases the “hangover” side effects of drowsiness and impaired neurological functioning (Committee on the Review of Medicines '80). For this reason, short-acting benzodiazepines are usually prescribed over long-acting ones for the elderly (Hallfors and Saxe '93).

The withdrawal symptoms from short-acting benzodiazepines differ from the symptoms of withdrawal from long half-life benzodiazepines. In 1991 a meta-analysis was conducted of seven studies done to determine the differences. Each of the studies had a few more dropouts of the withdrawal from the short half-life benzodiazepines than the long half-life ones. When all the studies were combined, the meta-analysis found the difference to be significant. Additionally, the meta-analysis found that the patients on a short half-life benzodiazepine had a 25% greater chance of experiencing anxiety after withdrawal than those on a long half-life benzodiazepine. The authors concluded that patients withdrawing from short half-life benzodiazepines “may be exceedingly uncomfortable and less likely to successfully complete withdrawal” (Hallfors and Saxe '93).

The claims that short half-life benzodiazepines cause excessive withdrawal symptoms and rebound insomnia led to the banning of one such drug, triazolam, by several countries including Britain (O'Donovan and McGuffin '93). A review of the topic written in 1993 gave many examples of studies that showed memory impairment and anxiety associated more with short half-life than long half-life benzodiazepines. The United States Food and Drug Administration received reports on adverse side effects on hundred times more commonly for triazolam than temazepam, a different short-acting benzodiazepine with a slightly longer half-life. The review concluded that amnesia and rebound insomnia, “although not unique to triazolam, are more often associated with its use than with other benzodiazepines.” The authors pointed out that there are numerous treatment methods for insomnia, both pharmacological and behavioral, and “triazolam has no compelling singular benefits that outbalance the risks” (O'Donovan and McGuffin '93).

However, the review warned that “obviously case reports and drug monitoring data are open to many sources of bias, and a drug that has been the subject of media attention may attract

closer scrutiny of its apparent adverse effects by both doctors and their patients” (O’Donovan and McGuffin ’93). Furthermore, a letter to the editor written by two doctors in response to the 1993 review pointed out that the only countries in which triazolam is suspended are the United Kingdom, Norway, and Brazil. The authors of the letter claimed that the evidence brought in the review does not support the position that triazolam is more likely to produce withdrawal symptoms than other benzodiazepines. They explained that the authors of the review gave “enormous weight to some studies with exceptionally small sample sizes” and they showed a “tendency to magnify some studies while minimizing large scale work.” This resulted in a “conclusion that we believe is not supported by objective fact.” Their idea is the same conclusion that the Collegium International Neuropsychopharmacologium and the World Psychiatric Association reached in their reports on the subjects. They conclude that patients who use short half-life benzodiazepines “derive remarkable benefit” (Dinan and Leonard ’93).

This conclusion is supported by other studies which claim that although the withdrawal symptoms from a short half-life benzodiazepine occur sooner and are more severe, they last for a shorter time than the withdrawal symptoms from long half-life benzodiazepines (Tyrer ’93). A study was done in 1994 over a six-month period to test the effects of physician intervention during benzodiazepine withdrawal. Incidentally, this study found that those patients on a short half-life benzodiazepine were more likely to reduce their dosage than those on a long half-life benzodiazepine. The authors pointed out that the current trend was to switch short half-life benzodiazepine users to a long half-life benzodiazepine when considering withdrawal, as the shorter half-life benzodiazepines were thought to have increased risks of withdrawal symptoms. However, the authors suggested based on their results that “it may be better to leave patients on their short-acting preparations when a dose reduction is being attempted” (Bashir et al. ’94).

#### Some Long- and Short-Acting Benzodiazepines and Their Commercial Names

<b>Long-Acting</b>	<b>Short-Acting</b>
chlorazepate (Genene, Tranxene)	alprazolam (Apro-Alprax, Xanax)
chlordiazepoxide (Librax, Librium)	bromazepam (Lectopam)
clonazepam (Klonopin, Rivotril)	estazolam (ProSom)
diazepam (Valium, Rivotril)	flunitrazepam (Rohypnol)
flurazepam (Dalmane, Somnol)	halazepam (Paxipan)
nitrazepam (Inomax, Mogadon)	ketazolam (Loftan)
quazepam (Doral)	lorazepam (Ativan, Nu-Luraz)
	midazolam (Versed)
	oxazepam (Serax)
	prazepam (Centrax)
	temazepam (Restoril)
	triazolam (Halcion, Nutriazo)

Although benzodiazepines are currently most often prescribed hypnotic, a new group of drugs called benzodiazepines receptor agonists (BZRAs), is increasingly being prescribed and is becoming the new hypnotic drug of choice (A.D.A.M. ’03). These non- benzodiazepine BZRAs are even shorter acting than short half-life benzodiazepines and include “Z drugs” zolpidem, zaleplon, and zopiclone, known commercially as Ambien, Sonata, and Imovane.

The National Institute for Clinical Excellence (NICE) in Britain recommends that hypnotic drugs be used only for short periods. In their guidance, they do not distinguish between short-acting benzodiazepines and the BZRAs, explaining that they have found “no compelling evidence of a clinically useful difference” between them. Instead, they recommend using the drug with the “lowest purchase cost” (Gibson '04). However, many researchers and practitioners disagree with NICE's conclusion. The British Sleep Society, a professional organization of medical and scientific staff who focus on sleep disorders, does not support NICE's decision. Professor David Nutt, the society's representative, expressed that “it seems perverse that patients will be forced to run the risk of significant daytime hangover to save a few pence on drug costs” (Gibson '04).

Just like the British Sleep Society, many physicians believe that BZRAs have fewer side effects than even short half-life benzodiazepines (Pagel and Parnes '01). Although they might produce minimal early-morning confusion and nausea (Caldwell '03), BZRAs have much lower risk of lingering sedative effects that will interfere with daytime functioning (Zammit and Kramer '01). This is especially helpful in the treatment of elderly patients, when this results in fewer risks for falls or memory loss (A.D.A.M. '03). BZRAs only slightly alter sleep patterns, and their potential for abuse is minimal (Pagel and Parnes '01). In patients with respiratory disorders, BZRAs have fewer respiratory suppressant effects (Pagel and Parnes '01). They have a lower risk than benzodiazepines for tolerance and dependence (Lieberman '07). Studies done to evaluate the long-term effectiveness and safety of BZRAs showed that discontinuation did not produce withdrawal symptoms (Zammit and Kramer '01). The drawback to BZRAs, however, is that these drugs are expensive (A.D.A.M. '03).

Most recently, Evotec, a research company that “is a leader in the discovery and development of novel small molecule drugs” (WebWire '06), has been working on a new drug to treat insomnia. This drug, labelled EVT 201, is a partial agonist of the GABA<sub>A</sub> receptor. As a partial agonist, it employs a difference mechanism than benzodiazepines and BZRAs which are full agonists of the GABA<sub>A</sub> receptor.

EVT 201 is currently in the middle of extensive testing process conducted on all new drugs. It recently completed a Phase II clinical trial conducted on sixty-seven patients in sleep labs in the United States. This trial showed that the drug caused significant improvements in the quality of sleep, measured both by subjective assessments and polysomnography. The subjects in the trial did not report any residual sedation. In this trial, EVT 201 was shown to be safe and well-accepted without any significant adverse effects (WebWire '06).

In further trials to be conducted on the drug, additional measures will be studied and researchers will check for any adverse effects. Dr. John Kemp, Chief Research and Development Officer in the Evotec company, pronounced, “If we can confirm this profile of efficacy together with freedom from significant adverse effects in patients with primary insomnia, this would represent a very attractive product in a market in which we believe there are significant opportunities based on a high unmet medical need” (WebWire '06). Perhaps in a few years from now, EVT 201 will be the only medication that can be found on the shelf in the insomnia section of the pharmacy.

The way people think about insomnia has changed drastically over the past fifty years. In the past, if someone complained of having sleep difficulties, “medications that were often

dangerous and addictive were prescribed to induce sleep, while the basis of the patient's complaint was not addressed" (Pagel and Parnes '01). Today, however, the safety of treatments has improved (Lieberman '07), and researchers are still working on finding drugs with better results and fewer adverse side effects. Additionally, our understanding of sleep has grown tremendously, and we are better able to pinpoint the source of the insomnia and treat accordingly. Doctors now understand that not all cases of insomnia are alike. From the psychological, biological, or physiological factors that caused the insomnia, to the endocrinological, behavioral, and emotional outcomes that result, no two cases of insomnia are perfectly alike. Consequently, each case must be treated differently. A method that produced wonderful results when used for Patient X might backfire when tried for Patient Y. Each case of insomnia is unique, and the plethora of treatments available today allows the practitioner to find and prescribe the ones that will work best for each patient.

## **CONCLUSION**

Insomnia is a condition that can happen to anyone. Whether due to improper sleep hygiene, consumption of beverages such as caffeine or nicotine, as a side effect from a particular medication, or during a period of depression, many people are susceptible and may become unable to sleep. This can be dangerous, because as this paper has shown the resulting sleep deprivation has many significant negative consequences. Not only do these effects persist as long as the insomnia lasts, we have seen that some results may have lifelong repercussions. Fortunately, though, there are many treatments available to help in the battle against insomnia. This paper has discussed a few behavioral techniques that are helpful. Additionally, this paper has presented many medications that are used to treat insomnia and has explained the benefits and risks of each type. This paper has shown that although drugs might be more effective than behavioral techniques for many people, no medication is perfectly effective or completely free from negative side effects. Thus, any patient suffering from insomnia must discuss with his doctor the various remedies, weighing the risks and benefits of each. They will then be able to choose the treatment or treatments that will help with his individual case and will best cure him of his insomnia.



## REFERENCES

### REFERENCES

- A.D.A.M. 2003. Insomnia. In: Sleep Disorders Sourcebook (ed. Sutton, Amy L.), 2<sup>nd</sup> ed., Michigan: Omnigraphics, pp. 297-333
- Baillargeon, Lucie; Landreville, Philippe; Verreault, Rene; Beauchemin, Jean-Pierre; Gregoire, Jean-Pierre; and Morin, Charles M. (2003, November). Discontinuation of benzodiazepines among older insomniac adults treated with cognitive-behavioural therapy combined with gradual tapering: a randomized trial. *Canadian Medical Association Journal* 169(10):1015-1020. Retrieved November 27, 2007 from <http://www.ncbi.nlm.nih.gov/sites/entrez>
- Bashir, Khaver; King, Michael; and Ashworth, Mark. (1994, September). Controlled evaluation of brief intervention by general practitioners to reduce chronic use of benzodiazepines. *British Journal of General Practice*, 44(386):408-412. Retrieved November 27, 2007 from <http://www.ncbi.nlm.nih.gov/sites/entrez>.
- Bootzin, Richard R. and Rider, Steven P. 1997. Behavioral Techniques and Biofeedback for Insomnia. In: Understanding Sleep: The Evaluation and Treatment of Sleep Disorders (eds. Pressman, Mark R., and Orr, William C.) Washington, D.C.: American Psychological Association, pp. 315-333.
- Caldwell, J. Paul. 2003. Sleep: The Complete Guide to Sleep Disorders and A Better Night's Sleep, Rev. ed., New York: Firefly Books, pp. 55-67, 81-118, 217-236.
- Committee on the Review of Medicines. (1980, March). Systematic review of the benzodiazepines. *British Medical Journal*, 280(6218):910-912. Retrieved November 11, 2007 from <http://www.pubmedcentral.nih.gov/pagerender.fcgi?artid=1601049&pageindex=2>
- Dinan, T.G. and Leonard, B.E. (1993, May). Triazolam. As safe as other benzodiazepines. *British Medical Journal*, 306(6890):1475. Retrieved November 27, 2007 from <http://www.ncbi.nlm.nih.gov/sites/entrez>.
- Dinges, D.F.; Douglas, S.D.; Zaug, L.; Campbell, D.E.; McMann, F.M.; Whitehouse, W.G.; Orne, E.C.; Kapoor, S.C.; Icaza, E and Orne, M.T. (1994, May). Leukocytosis and natural killer cell function parallel neurobehavioral fatigue induced by 64 hours of sleep deprivation. *The Journal of Clinical Investigation*, 93(5): 1930-1939. Retrieved December 13, 2007 from <http://www.pubmedcentral.nih.gov/pagerender.fcgi?tool=pmcentrez&artid=294300&pageindex=1>
- Dunn, Amanda. 2004. Fatigue: It's Enough to Make You Sick. In: Sleep Disorders Sourcebook (ed. Sutton, Amy L.), 2<sup>nd</sup> ed., Michigan: Omnigraphics, pp. 18-19.
- Gibson, Liza. (2004, May). Newer hypnotics no better for insomnia than short acting benzodiazepines. *British Medical Journal*, 328(7448):1093. Retrieved November 27, 2007 from <http://www.ncbi.nlm.nih.gov/sites/entrez>.
- Hallfors, D.D. and Saxe, L. (1993, September). The dependence potential of short half-life benzodiazepines: a meta-analysis. *American Journal of Public Health*, 83(9):1300-1304. Retrieved November 27, 2007 from <http://www.pubmedcentral.nih.gov/pagerender.fcgi?tool=pmcentrez&artid=1694983&pageindex=2>.
- Jacobs, Gregg D. 2004. Individual Responses to Sleep Deprivation. In: Sleep Disorders Sourcebook (ed. Sutton, Amy L.), 2<sup>nd</sup> ed Michigan: Omnigraphics, pp. 40-41.
- Lange, Tanja; Perras, Boris; Fehm, Horst L.; Born, Jan. (2003). Sleep Enhances the Human Antibody Response to Hepatitis A Vaccination. *Psychosomatic Medicine* 65: 831-835. Retrieved December 18, 2007 from <http://www.Psychosomatic> medicine.org/cgi/content/abstract/65/5/831
- Lieberman, Joseph A. (2007, September). Update on the Safety Considerations in the Management of Insomnia With Hypnotics: Incorporating Modified-Release Formulations Into Primary Care. *Primary Care Companion Journal of Clinical Psychiatry*, 2007;9(1):25-31. Retrieved November 27, 2007 from <http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=18945851>.
- Lurie, Stephen J. (2002, September). Effect of Sleep Deprivation on Response to Immunization. *The Journal of the American Medical Association*, 288 (12): 1471-1472. Retrieved December 18, 2007 from <http://jama.ama-assn.org/cgi/content/full/288/12/1471-a>.
- Merritt, Sharon L. 2002. Inadequate Sleep: The Consequences beyond Excessive Daytime Sleepiness. In: Sleep Disorders Sourcebook (ed. Sutton, Amy L.), 2<sup>nd</sup> ed., Michigan: Omnigraphics, pp. 16-18.

National Institutes of Health, National Institute of Mental Health (NIMH). 2002. The Brain Benefits of Naps. In: Sleep Disorders Sourcebook (ed. Sutton, Amy L.), 2<sup>nd</sup> ed., Michigan: Omnigraphics, pp. 19-22.

National Institutes of Health, National Institute of Nursing Research. 2003. Sustained Reduced Sleep Can Have Serious Consequences. In: Sleep Disorders Sourcebook (ed. Sutton, Amy L.), 2<sup>nd</sup> ed., Michigan: Omnigraphics, pp. 42-43.

National Institute of Neurological Disorders and Stroke (NINDS). 2003. Brain Basics: Understanding Sleep. In: Sleep Disorders Sourcebook (ed. Sutton, Amy L.), 2<sup>nd</sup> ed., Michigan: Omnigraphics, pp. 3-14.

National Sleep Foundation (NSF). 2002. Medications for Sleep Problems. In: Sleep Disorders Sourcebook (ed. Sutton, Amy L.), 2<sup>nd</sup> ed., Michigan: Omnigraphics, pp. 443-450.

O'Donovan, Michael C. and McGuffin, Peter. (1993, April). Short acting benzodiazepines. *British Medical Journal*, 306(6883):945-946. Retrieved November 27, 2007 from <http://www.ncbi.nlm.nih.gov/sites/entrez>.

Pagel, J.F. and Parnes, Bennett L. (2001, February). Medications for the Treatment of Sleep Disorders: An Overview. *Primary Care Companion Journal of Clinical Psychiatry*, 2001;3(3):118-124. Retrieved November 27, 2007 from <http://www.ncbi.nlm.nih.gov/sites/entrez>.

Pinel, John P. J. 2003. Biopsychology, 5<sup>th</sup> ed., Massachusetts: Allyn and Bacon, pp. 100-101, 350-377.

Roehrs, Timothy and Roth, Thomas. 1997. Hypnotics, Alcohol, and Caffeine: Relation to Insomnia. In: Understanding Sleep: The Evaluation and Treatment of Sleep Disorders (eds. Pressman, Mark R., and Orr, William C.) Washington, D.C.: American Psychological Association, pp. 340-345.

Rothenberg, Saul A. 1997. Introduction to Sleep Disorders. In: Understanding Sleep: The Evaluation and Treatment of Sleep Disorders (eds. Pressman, Mark R., and Orr, William C.) Washington, D.C.: American Psychological Association, pp. 63-64.

Tyrer, Peter. (1993, March). Withdrawal from Hypnotic Drugs. *British Medical Journal*, 306:706-708.

The University of Chicago Medical Center. (1999, October). Lack of sleep alters hormones, metabolism, simulates effects of aging. Retrieved December 18, 2007 from <http://www.uchospitals.edu/news/1999/19991021-sleepdebt.html>.

The University of Chicago Medical Center. (2006, September). Study adds to links between sleep loss and diabetes. Retrieved December 18, 2007 from <http://www.uchospitals.edu/news/2006/20060918-sleep-diabetes.html>.

Van Cauter, Eve. (1999, October). Sleep Debt Affects Metabolic Functions. Retrieved December 18, 2007 from <http://www.cfah.org/hbns/newsrelease/sleep10-21-99.cfm>

Walsh, James K. and Lindblom, Scott S. 1997. Psychophysiology of Sleep Deprivation and Disruption. In: Understanding Sleep: The Evaluation and Treatment of Sleep Disorders (eds. Pressman, Mark R., and Orr, William C.) Washington, D.C.: American Psychological Association, pp. 73-104.

WebWire. (2006, September). Evotec Initiates Phase II Clinical Trial with EVT 201 for the Treatment of Insomnia. Retrieved September 25, 2007 from <http://www.webwire.com/ViewPressRel.asp?aId=20808>.

Zammit, Gary K. and Kramer, Jeffrey A. (2001, March). The Importance of Residual Effects When Choosing a Hypnotic: The Unique Profile of Zaleplon. *Primary Care Companion Journal of Clinical Psychiatry*, 2001;3(2):53-60. Retrieved November 27, 2007 from <http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=181162>.