

In Search of Sleep

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Millions of Americans are plagued by insomnia. It's a serious public-health risk that too many doctors ignore. But new brain science offers hope that we may someday stop all that tossing and turning

By Barbara Kantrowitz

I didn't sleep well last night, but that's nothing new. My sleep problems began 20 years ago, just before my oldest son was born. Since then, I've spent far too many nights worrying about how I can't get to sleep and how I'll be too tired to do all the things I have to do the next day. Every morning I grab my coffee with the eagerness of an addict looking for a fix.

IT ISN'T MUCH comfort to learn that there are as many as 70 million of us problem sleepers out there, according to Dr. Carl E. Hunt, director of the National Center on Sleep Disorders Research. All across America, people are tossing and turning in their beds just like me. About half of problem sleepers have a sleep disorder, something physically wrong that keeps them from getting adequate rest. As for the others, Hunt blames too much electric light, cable TV, the Internet, e-mail and jet travel—a world that *never* sleeps.

That's more than just a boon to Starbucks; it's a major threat to public health. The average American now sleeps about seven hours a night, about 90 minutes less than people did a century ago. This means a huge sleep debt, which shows up in higher accident rates on the highway and in the workplace. Going more than a day without sleep affects performance as much as a blood alcohol level above the legal limit, according to some studies. There's convincing evidence that untreated sleep disorders can increase the risk of high blood pressure, coronary-artery disease, heart failure and stroke. Hunt says researchers also think lack of sleep can up the odds of developing obesity and diabetes.

FINDING THE 'SLEEP SWITCH'

With all that to worry about, now I *really* won't be able to sleep. But there's reason to hope: the more we learn about why we can't sleep, the more light scientists can shed on how we might be able to solve our sleep problems. One of neuroscience's most promising recent discoveries is the "sleep switch" in our brains, which gives us an even better understanding of the biological mechanisms that regulate wakefulness and sleep. Unfortunately, we're still a long way from being able to pull that switch ourselves.

Even if we don't have one of the many sleep disorders doctors have now recognized, other factors can keep us from the rest we need: too much caffeine, smoking, alcohol, not enough exercise, irregu-

lar hours, a new baby, noise in the bedroom, even an uncomfortable mattress.

Some of these lifestyle habits may seem so trivial that many insomniacs ignore them, not realizing that sleep problems—like any other medical issue—can be managed. Each story is individual, but mine is fairly typical. Like many insomniacs, I've spent years trying various remedies of my own: hot milk, lavender-scented pillows, soothing music at bedtime. Nothing has worked. So, a couple of weeks ago, I sought help from Dr. Jean Matheson, medical director of the Sleep Disorders Clinic at Beth Israel Deaconess Medical Center in Boston. Matheson, whom I've known for many years, arranged to have me undergo a sleep evaluation at her hospital. She didn't promise a total cure, but she did assure me that the evaluation, which would include a night in a sleep lab, could give me a much better idea of what was going wrong. Then, maybe, we could fix it.

Although there are hundreds of sleep clinics like Matheson's accredited by the American Academy of Sleep Medicine, primary-care physicians are often slow to refer patients who complain of sleep problems. That's because sleep is still largely ignored in the typical medical-school curriculum. As a result, people with sleep problems are too often incorrectly diagnosed with psychiatric disorders, like depression, or dismissively told that they should take a nice, long vacation. Dr. William Dement, a pioneer in sleep research and the founder of the Stanford University Sleep Research Center, finds this ignorance particularly frustrating, since our knowledge of sleep has expanded so dramatically. "My mission, passion and total disgruntlement," he says, "is that the public should know the things we've known for a quarter of a century." Dement's colleague at Stanford, the French-born neurologist Christian Guilleminault, recalls one of his medical professors in Paris vigorously trying to discourage him from going into the field. "Sleep," the professor told Guilleminault, "is for dreamers."

A RAINBOW IN A BLACK HOLE

As it turns out, the nature of dreaming is just one of many discoveries from researchers like Dement and Guilleminault. Until about 50 years ago, even most scientists considered sleep a kind of black hole defined primarily by what it was not: consciousness. But in the 1950s, they began to see shades of gray, and even glimmers of a rainbow, in that black hole.

These insights were possible because of the earlier development of electroencephalography, which allows researchers to chart brain activity during the night by attaching electrodes to the head and scalp. This is still basically the same technology that sleep labs use today, with a few new refinements.

In the 1950s, Dement and colleagues described how the sleeping brain goes through repeated cycles and also showed that dreaming occurs during REM (for rapid eye movement)—the sleep state when the body is essentially paralyzed and the brain is active. In the non-REM sleep state, which itself is divided into four stages of progressively deeper sleep, the brain is relatively idle while the body may still move. People pass through these states several times during the night in a fairly standard pattern called “sleep architecture” that varies with age. But things can go wrong. For example, in REM behavior disorder, patients cross the boundaries between REM and non-REM in bizarre ways by acting out dreams while sleeping. In other words, they’re dreaming but not paralyzed. It is most common in men over 50, and often the dreams are violent, with the dreamer fighting attackers—which can be very hard on the people they share a bed with.

In more recent years, scientists have pinpointed the part of the brain that Harvard neurologist Clifford Saper and his team at Boston’s Beth Israel Deaconess call the sleep switch. This sleep-regulating center is a clump of cells in the front of the hypothalamus—often called the “brain of the brain”—that are active in sleep but not in waking. These cells connect chemically to cells in the back of the hypothalamus that are known to keep both animals and humans awake. Nerve cells at the front of the hypothalamus release chemical messengers that travel to the back and essentially shut off activity there. Last year Saper’s team proposed a model for how a similar process occurs in the reverse direction to keep us awake.

THE BODY’S ‘FORBIDDEN ZONE’

The switch doesn’t work alone. The body also responds to its own circadian rhythm, our biological clock. You need to sleep for a certain number of hours within a cycle of approximately 24 hours in order to function. And when are you the most sleepy in this cycle? It’s not late afternoon, when I have the urge to gulp down another latte. The height of sleepiness is actually at the end of the night. “In that hour right before you wake up, your circadian drive to sleep has to be at its maximum to keep you asleep,” says Saper. The risk of accidents is higher during this circadian dip in alertness. The time of day when you feel the least need to sleep is just before your regular bedtime, Saper says. For example, if you usually fall asleep at 11, the drive to stay awake is going strong at 10—or you would fall asleep then.

asleep then. Saper says this last hour or so is the “forbidden zone” because your body doesn’t allow itself to sleep at that time.

This rhythm isn’t immutable. Most people regularly change it by, for example, having different bedtimes on weekends. But if you want to test the circadian rhythms yourself, think about that last half hour on Sunday night, when you’re trying to go to sleep a little earlier again to get ready for work Monday morning. Not easy, is it? Sleep doctors call messing with that forbidden zone on the weekend “Sunday insomnia.” And there is also a class of sleep disorders, some hereditary, that affect circadian rhythm. People with delayed sleep-phase syndrome (so-called night owls) may have body clocks out of sync with the 24-hour day.

So now we’ve got the sleep debt, the switch and the circadian rhythm. All these interact with emotion, stress and cognition to influence your ability to go to sleep. In other words, if you’re worried about your kids, or the mortgage or a big project at work, you have trouble sleeping. Many Americans experienced this disruption in their natural sleep patterns just after September 11. Of course, we all have trouble sleeping from time to time; it’s part of life. But when sleep problems continue for weeks and months, you need extra help.

CAFFEINE AND SLEEP

And that’s how I ended up at the sleep clinic. (An overnight stay, which costs between \$1,200 and \$1,600, is covered by most health insurance.) A few days before my sleep study, I received a set of instructions. Most seemed fairly routine: eat a normal dinner, bring comfortable pajamas. But one admonition stopped me cold: I had to avoid caffeine after noon. As my friend, Matheson has been telling me for years that I need to cut down on caffeine, but this has not prevented me from acquiring a three-cup-a-day habit. (OK, four ... maybe five—but only on a really bad day.) Kicking caffeine, if only for a few hours, was the roughest part.

The first step was taking my “sleep history.” Matheson asked me a long series of questions: How long does it take you to fall asleep? Once asleep, do you have trouble staying asleep? Do you have any discomfort in your legs when you are lying in bed trying to sleep? Do you snore? Do you fall asleep unintentionally during the day? The questions are designed to ferret out real sleep disorders like apnea, in which a patient’s breathing is interrupted many times during the night, or restless-leg syndrome, characterized by sleep-disrupting aching or crawling sensations in the lower legs. A sleep evaluation also includes a complete medical history and a general physical examination. Matheson asked about my daily routines, habits, illnesses and whether I was taking prescription or over-the-counter medications.

This kind of detailed evaluation is critical, Matheson says, but often too time-consuming for harried doctors. In many cases, the patient is having trouble sleeping because of a combination of factors—some physical, some emotional—and it can take considerable effort to uncover them and see how they influence each other.

That night, I was one of four patients in the Sleep Health Center laboratory affiliated with the hospital. I was greeted by the manager, Melissa Nappi. She expertly stuck electrodes on my head, chin and legs, and taped tubes below my nose that checked my airflow. She also strapped bands around my upper chest and abdomen that measured my efforts to breathe and a small microphone to my throat to check for snoring, often a sign of apnea. This was all connected to monitors outside the room. From there, Nappi tracked me all night.

Despite all this equipment, I had no trouble falling into what I thought was a very deep sleep. Matheson says sleep-lab patients often report that they're more relaxed when they're away from their own bedrooms, the scene of so many failed attempts at slumber. I remember waking up only once, around 5 a.m., and then quickly falling back to sleep. But what seemed to me like seven fairly uneventful hours actually turned out to be something very different (more about that later).

SNACKING ON SLEEP

Much of our current knowledge about sleep—and what happens when you don't get enough of it—grows out of the kind of clinical observation I underwent that night. As the science of sleep has evolved, doctors have studied many thousands of patients in the lab—some sleeping normally, others deliberately deprived of rest. The results aren't encouraging for those Type A's who boast about getting by on just four or five hours a night. "Despite what they claim and believe about themselves, they are impaired," says David Dinges, a professor of psychiatry at the University of Pennsylvania School of Medicine who studies sleep and wakefulness. "What they are doing is just sort of snacking on sleep. They want to take sleep the same way they take fast food." But, he says, people who chronically deprive themselves of an hour or two of sleep a night ultimately are as sleep-deprived as someone who's been awake for 40 hours. And that means they're, in effect, operating as though they were under the influence. Caffeine and other stimulants only temporarily mask the symptoms.

If you need an extra incentive to stay asleep a little longer, consider the results of studies published last week by researchers at Harvard. They found that people who slept well remembered a new task they'd learned the night before better than those who didn't. The researchers say that there was a significant cor-

relation between improved performance and the amount of Stage 2 non-REM sleep late in the night. They also found that "power napping"—up to an hour in the middle of the day—helps stop deterioration in performance. "You work on something until your brain screams, 'No more, no more!'" says Robert Stickgold, assistant professor of psychiatry at Harvard Medical School. "Then you take a little nap and you're all better."

Those little naps could really help people who work irregular hours. More than 20 million Americans work nights or evening shifts, and studies have shown that they are much more likely to have sleep problems. That's bad enough if you're, say, a night watchman, but catastrophic if you're a bus driver, an airline pilot or, ironically, a medical resident—recent medical-school graduates who spend three to seven years training in a specialty like pediatrics or cardiology and often work more than 100 hours a week all around the clock. Just last month, the group that accredits the nation's teaching hospitals imposed strict new limits on their hours—although the new rules will still mean grueling schedules of up to 80 hours a week with as little as 10 hours of rest between shifts.

NARCOLEPSY AND CATAPLEXY

As we get less and less sleep, scientists are learning more and more about how sleep works. These breakthroughs could point the way to a sleeping pill that more closely resembles the natural process of falling asleep. Some of the most interesting discoveries in the past few years have grown out of one of the most devastating sleep disorders: narcolepsy. Narcoleptics fall asleep uncontrollably throughout the day. Most often, symptoms appear in early adulthood, and they can destroy personal and professional lives. For years, Bob Cloud, a 58-year-old Cincinnati lawyer, would doze off in mid-sentence. He once fell asleep during an opposing attorney's closing argument, and again sitting in front of a judge. Narcoleptics like Cloud also suffer from a bizarre condition called cataplexy, in which they can collapse in a heap on the ground, conscious but essentially paralyzed. Cataplexy is often brought on by intense emotion, so Cloud couldn't even play baseball with his kids. "Just the excitement of playing with them would cause the cataplexy to kick in," says Cloud, now president of the Narcolepsy Network, a support group. But today, Cloud is able to work part time, thanks to new medication.

In 1999, after a decadelong search, a team led by Stanford University researcher Dr. Emmanuel Mignot found the gene that causes narcolepsy in dogs that carried the disorder. Mignot says he pursued this gene for so long because he thinks narcolepsy holds the key to other mysteries about sleep. The gene turned out to be a receptor for a neurotransmitter

called hypocretin or orexin (it has two different names because it was discovered at two different research labs the same year and named independently by both). The receptor has a mutation in narcoleptic dogs, leaving hypocretin with nothing to bind to. Several weeks after Mignot's team published its finding, another team at the University of Texas Southwestern Medical Center at Dallas published a study showing that if hypocretin is knocked out of mice, the result is also a condition that resembles narcolepsy.

MIRACLE PILLS?

After the discovery in dogs, Mignot and his team moved on to people. In 2000, they published another study showing that in seven of nine patients with narcolepsy, hypocretin levels were too low to detect. That meshes with Saper's sleep-switch model: he proposes that hypocretin is the chemical in the hypothalamus most likely responsible for pushing the switch in the direction of wakefulness. Which raises another interesting possibility: the creation of a drug that keeps us awake for long periods of time. No one has come up with such a miracle pill yet, but researchers are working hard on it.

In order to succeed, they'll have to answer the most basic question about sleep: why we need it at all. "It's really the last remaining mystery," says Mignot. Some researchers, like Saper, think that one possibility is that during the day the nerve cells in your brain fire away and build up messenger mole-

cules that carry information. It's like a blackboard that you write on, Saper says. You fill up all the free space, and then you have to write over what you've already written unless you find a way to erase what you don't need anymore. "You have to let all of these signals clear and convert that information into something that is long-lasting," Saper says. That's what cells seem to do during sleep. If that theory is true, it suggests that sleep is even more vital than we imagined.

As for my own sleep study, those seven hours were surprisingly revealing. Matheson told me that I was actually aroused from sleep 90 times. Each disturbance in my sleep was preceded by a slight drop in my blood oxygen level and difficulty getting air through my nose and throat. Matheson's preliminary diagnosis: mild sleep-disordered breathing, probably exacerbated by allergies. The solution? She recommended starting with sleeping on my side, getting a prescription nasal spray for my allergies and cutting down on caffeine. She also suggested behavior-modification therapies to help me when I worry about how I'm not falling asleep. If these don't work, we can experiment with other things. And I'm going to do it, really, except right now, I think I'll just ... take a quick nap

With Claudia Kalb, Karen Springen and Mary Carmichael

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Taking Control

A therapist teaches techniques to help tame your nightmares

By Marcia Hill Gossard

Of all the components of a good night's sleep, dreams seem to be least within our control. In dreams, a window opens into a world where logic is suspended and dead people speak.

A CENTURY AGO, Freud formulated his revolutionary theory that dreams were the disguised shadows of our unconscious desires and fears; by the late 1970s, neurologists had switched to thinking of them as just "mental noise"—the random byproducts of the neural-repair work that goes on during sleep. Now researchers suspect that dreams are part of the mind's emotional thermostat, regulating moods while the brain is "off-line." And one leading authority says that these intensely powerful mental events can be not only harnessed but actually brought under conscious control, to help us sleep and feel better. "It's your dream," says Rosalind Cartwright, chair of psychology at Chicago's Rush-Presbyterian-St. Luke's Medical Center. "If you don't like it, change it."

Evidence from brain imaging supports this view. The brain is as active during REM sleep—when most vivid dreams occur—as it is when fully awake, says Dr. Eric Nofzinger of the sleep laboratory at the University of Pittsburgh. But not all parts of the brain are equally involved; the limbic system (the "emotional brain") is especially active, while the prefrontal cortex (the center of intellect and reasoning) is relatively quiet. "We wake up from dreams happy or depressed, and those feelings can stay with us all day," says Stanford sleep researcher Dr. William Dement.

The link between dreams and emotions shows up among the patients in Cartwright's clinic. Most people seem to have more bad dreams early in the night, progressing toward happier ones before awakening, suggesting that they are working through negative

feelings generated during the day. (In studying divorced couples, Cartwright has found that those who don't follow this dream progression have a much harder time getting over the trauma.) Because our conscious mind is occupied with daily life we don't always think about the emotional significance of the day's events—until, it appears, we begin to dream.

And this process need not be left to the unconscious. Cartwright believes one can exercise conscious control over recurring bad dreams. As soon as you awaken, identify what is upsetting about the dream. Visualize how you would like it to end instead; the next time it occurs, try to wake up just enough to control its course. With much practice people can learn to, literally, do it in their sleep.

At the end of the day, there's probably little reason to pay attention to our dreams at all unless they keep us from sleeping or "we wake up in a panic," Cartwright says. Terrorism, economic uncertainties and general feelings of insecurity have increased people's anxiety. Those suffering from persistent nightmares should seek help from a therapist. For the rest of us, the brain has its ways of working through bad feelings. Sleep—or rather dream—on it and you'll feel better in the morning.

It's a health problem of sorts, but you probably don't want to talk about it. Still, you—and millions of

other people like you—can't help but wonder: *how come I don't have more sex?*

RESEARCHERS AGREE THE likely answer is not "because I'm sleeping too much instead." Like other fields of human endeavor, lovemaking is best with a well-rested mind and body. By the same token, the things that interfere with sleep can also stifle the libido. "The common wisdom among therapists is that our sex drive dips along with the Dow," says author and psychologist Dr. Judy Kuriansky. (That is not, however, the origin of the phrase "bull market.") "The libido is very sensitive to one's emotional state." Stress and anxiety, over the stock market or anything else, are nature's antiaphrodisiac; a recent survey by the Kinsey Institute found that 80 percent of men between 30 and 40 are sometimes too anxious to copulate, or even to think about it much. Unfortunately, the antidepressants that treat the anxiety may have the side effect of depressing the sex drive. Twelve-hour days at the office or night work at the plant are the enemies of connubial bliss; many a marriage has been buried on the graveyard shift. "To have a successful sex life, couples have to make time for sexual intimacy," says sex researcher Pepper Schwartz. And find that time without taking it away from the *other* important activity that takes place in bed.

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Sounds of Sleep

Half of men over 50 do it, but the real danger comes from apnea.

By Mary Carmichael

Marcel Ascue used to snore so loudly that his 5-year-old son Nathan made a joke of ZZZing whenever he came near. Tired of being a punch line (and just plain tired), Ascue, 44, finally went to the doctor and found he had sleep apnea. Last month he started sleeping with a mask, hooked to an air pressurizer, that covers his nose and forces a steady stream of air down his throat. The jokes haven't stopped yet—now his wife quips that she's sleeping with Darth Vader—but at least the snoring has.

ASCUE'S STORY MIGHT amuse people who don't snore or have bed partners who do. But that's not many people. By 50, half of men and a quarter of women snore; 10 to 20 percent of Americans seek treatment for snoring each year. The numbers are expected to jump as baby boomers age, since snoring is a side effect of growing old, gaining weight and losing muscle tone. During the day the brain keeps the throat muscles taut and the airway open. When sleep descends, the muscles relax and vibrate as air rushes by. Most snorers have airways that are natu-

rally small or partially blocked by the tonsils, soft palate or the uvula, the floppy tissue that hangs in the back of the throat. The obstructions make the vibrations louder.

For "simple snorers," the nightly noisemaking is merely a nuisance. But in a third of cases, it's a sign of sleep apnea, in which a faulty feedback loop between the brain and the respiratory system lets the airway completely collapse until the brain registers low oxygen levels and jerks the patient awake. The constant jump-starts, which can happen as often as once a minute, send the heart rate on a roller coaster. Recent research shows that apnea is a risk factor for cardiovascular disease on par with high cholesterol, smoking and obesity.

Apnea sufferers need medical help; too often, though, they self-medicate with over-the-counter snoring remedies like nasal sprays or strips that quiet the snores without curing the apnea. Even some doctors confuse the two ailments. Daniel Loube, associate director of the Sleep Medicine Institute at Swedish Medical Center in Seattle, says surgeons some-

times treat apnea by cutting away tissue in patients' throats, "thinking they're helping people." They're not. The airway can still collapse.

Ascue's cure, on the other hand, is 100 percent effective. The most commonly prescribed apnea treatment, it's called CPAP, or continuous positive airway pressure. CPAP is neither comfortable nor portable, unfortunately. Patients who don't want to be bothered can elect surgery to expand the airway

Going To Bed Beats Popping Pills

Sleep is an important biological function. Cheating on it can take a serious toll on our health

July 8 — Can a pill cure our sleep-deprived society? As more of us work and play from the early morning hours to past midnight, 21st century America has become a 24-hour society. In fact, a recent poll from the National Sleep Foundation poll found that more than two-thirds of the nation's adults get less than the recommended eight hours of sleep on week nights.

Whether it's to maintain a competitive advantage on the job or party till the crack of dawn, we're squeezing every moment of wakefulness out of our lives at the expense of sleep.

That's a bad idea. The simple truth is that sleep is an important biological function that does more than provide us with an opportunity to dream about future riches. While experts still aren't exactly sure what sleep does, it's widely believed to be instrumental in recharging our batteries and giving our many bodily systems a chance to rest for optimal performance during periods of wakefulness. Cheating sleep, while it sounds like something that's OK to do every once in a while, can take a serious toll on our health if we do it too often.

One study, led by Eve Van Cauter at the University of Chicago, has shown that inadequate sleep may prompt the development of insulin resistance (IR). IR is a condition in which the body doesn't properly respond to the insulin hormone that's critical in regulating our blood sugar levels. Insulin resistance is a well-known risk for diabetes and could be involved in other related metabolic problems such as high blood pressure, abnormal lipid levels and obesity.

Sleepiness, however, isn't always a result of the lifestyle choices that we make. As many as 1 in 5,000 Americans suffer from excessive sleepiness that's no fault of their own. They are narcoleptics who constantly battle a disabling neurological disorder of sleep regulation that affects the control of sleep and wakefulness. Narcoleptics rarely get sound sleep as their nightly rest is disturbed by tossing and turning in bed, leg jerks, nightmares, and frequent awakenings. Because their nighttime sleep routine is so poor, they spend most of the day battling drowsi-

ness and nodding off even in the middle of conversations.

by pulling the jaw forward, or use retainer-type mouth guards to achieve the same result. Recently scientists found that speeding up the heart rate with a pacemaker can correct apnea. The trouble is, no one knows why it works. But there's also an effective low-tech cure: weight loss. With the flab goes the floppy tissue. No doubt bed partners appreciate the disappearance of both.

ness and nodding off even in the middle of conversations.

Many narcoleptics are now singing the praises of a drug called modafinil, sold under the trade name Provigil. Specifically approved three years ago for the treatment of narcolepsy, researchers are now asking whether this drug can be used for other conditions such as sleep apnea or a type of sleep disorder found in shift workers. The advantage of this new drug over the older stimulants is that it specifically targets the hypothalamus, the small area of the brain that houses our sleep center. Unlike the amphetamine-like stimulants, it doesn't leave users feeling jittery or fatigued once the arousal effect has worn off.

Modafinil, like any other drug, does have its side effects, but they're considered to be relatively minimal. The most commonly reported are headache, nausea, and a runny nose. This drug has been used in Europe much longer than in the U.S., and experts claim that there has been little—if any—reporting of addictive behaviors or abuse.

This, however, may be a mixed blessing. Many researchers are now discussing whether a new generation of drugs will be developed that can double and even triple the time we spend awake without causing harm.

The U.S. Army has already conducted studies on Blackhawk helicopter pilots to test whether performance can be maintained with increased wakefulness. There have also been reports of other studies conducted on military operatives examining the potential of longer consecutive hours of productivity to carry out certain missions. But where will this stop? And what will it mean for our traditional sleep patterns? Some don't think it's a bad idea to have soldiers who can fight for a week straight and never lose their mental or physical toughness. College students would likely be thrilled to have a drug with little addictive quality or side effects that can keep them awake for several days at a time during exam period.

As more companies continue to develop newer classes of medications, the concept of how we manage our sleep will inevitably be altered. Sleep ex-

perts believe this could be a serious mistake. Regardless of how effective and safe these newer medications might be, there's a biologic fundamental that can't be altered. The body needs sleep, between five and ten hours a night in most cases, and anything that alters this physiologic function will ultimately take a toll. You might be able to work into the wee hours of the morning or party till the sun comes up, but no fancy medication or ancient herb can fool the

body and prevent the potential health consequences that come from not getting enough of those zzzzzs.

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