

# The Sandman in a Bottle

The Types and Functions of Sleep Aids

by Matthew Koh

For millions of Americans who lay awake at night unable to fall asleep, sleeping pills offer a quick and easy way to prevent drowsiness and fatigue the next day. As of 2006, according to an article in *Forbes*, prescription sleeping pills garnered around \$2 billion annually in the United States (Wells 2006). In 2005, 43 million prescriptions were written for prescription sleep aids, and sales of these drugs are projected to rise to \$5 billion annually by 2010 (Lazarus 2006). A poll conducted by the National Sleep Foundation found that 10% of working Americans use either a prescription or over-the-counter medication to help them fall asleep (NSF 2008). Yet even as the use of sleep aids rises, scientists are still in the process of figuring out the details of how these drugs work.

Today, sleep aids, also known as sedative-hypnotics, fall into three main categories. The first category consists of drugs that act at the GABAA receptor. These include the benzodiazepines and the barbiturates. The newest additions to this group are the "z-drugs" such as Ambien® and Lunesta®, so called because their chemical names all begin with z. The second category of drugs is the antihistamine family of drugs. These drugs are the primary sedative ingredients in medicines like Benadryl®, NyQuil® and other over-the-counter sleep aids. Finally, newest category of sleep aids consists of drugs that act as melatonin receptor agonists. Currently, the only such drug approved for use by the FDA is Rozerem®, although others are undergoing clinical trials.

## The Neural Circuitry of the Sleep-Wake Cycle

Like many animals, humans cope with the daily rising and setting of the sun by sleeping at night and being awake during the day. This cycle involves two competing brain pathways—one involving arousal and the other involving sleep promotion. The arousal and sleep promotion pathways inhibit one another so that when one becomes strongly activated, the other is rapidly inactivated. This circuit has been called a flip-flop switch, named after the similarly functioning circuit known to electrical engineers. This mechanism accounts for the suddenness of falling asleep and waking up (Saper et al. 2005).

The arousal pathway actually consists of two separate pathways. The first pathway activates the thalamus, the area of the brain responsible for transmitting information to the cortex. The second pathway activates the cortex and involves a number of different brain regions. One area that is

particularly relevant to the action of sleep aids is the tuberomammillary nucleus (TM). The TM contains neurons that respond to the neurotransmitter histamine. From the TM, these neurons project to multiple regions of the brain, including the basal forebrain, hypothalamus, and amygdala. H1 receptors are located on the postsynaptic cells of these pro-

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jections and promote wakefulness by stimulating these cells (Barbier and Bradbury 2007).

The ventrolateral preoptic nucleus (VLPO) is the main area involved in sleep promotion. The cells in this region contain gamma-amino butyric acid (GABA) and galanin, two inhibitory neurotransmitters. The VLPO projects to all of the major wakefulness-promoting areas of the brain and inhibits these regions (Saper et al. 2005).

Central control of all circadian rhythms is provided by the suprachiasmatic nucleus (SCN), a brain region located directly above the optic chiasm. The SCN receives information from the retina that it uses to coordinate the body's internal clock with the outside world. Cells in the SCN contain receptors for melatonin, which is secreted by the pineal gland in response to signals from the SCN itself (Moore 2007). When activated, melatonin receptors inhibit the SCN. Next, the dorsomedial nucleus of the hypothalamus (DMH) receives input from the SCN and sends output to the VLPO and LHA. The connections to the VLPO are inhibitory whereas those to the LHA are excitatory (Chou et al. 2003). So, when the SCN is inhibited by melatonin, the VLPO becomes less inhibited while the LHA becomes more inhibited and sleep is induced.

These details of the anatomy involved in sleep regulation are necessary for an overall picture of the mechanisms of sleep aids. All of the sleep aids that are mentioned below interact with some step in the sleep-wake neural circuitry.

## GABAA Receptor Drugs

Many drugs that have traditionally been used as sedatives exert their effects at GABAA receptors in the brain. For instance, alcohol, perhaps the world's oldest known sedative, is a GABAA receptor agonist, although the details of this interaction are still unknown. In addition, barbiturates, benzodiazepines and anesthetics act at the GABAA receptor. GABAA receptors are ligand-gated chloride ion channels activated by the neurotransmitter  $\gamma$ -amino butyric acid. When these channels are opened, the membrane potential of the neuron becomes more negative, resulting in inhibition of the neuron's activity. The effects of GABA binding are modulated by the binding of benzodiazepines and barbiturates. When these drugs bind to GABA receptors, the inhibitory effects of GABA are enhanced (Delorey and Olsen 1992).

GABAA receptors are composed of five protein subunits arranged around a central ion channel. There are at least nineteen different subunits, grouped into families by amino acid sequence similarity. The subunit composition of a receptor varies between different cells and even between different locations within the same cell (Nutt 2006). It is believed that the large number of possible combinations accounts in part for the wide variety of effects that are mediated by GABA receptors (Paronis 2005).

Most prescription sleep aids work by activating the benzodiazepine site of GABA receptors. As a result, wake-promoting neurons that receive GABAergic projections from the VLPO become more inhibited (Lu 2006). In the past, barbiturates were prescribed as sleep aids. However, due to their high potential for abuse and dependency, their use in this capacity was phased out with the introduction of benzodiazepines in the 1970s. The ones most commonly used as sleep aids included triazolam (Halcion®), estazolam (Prosom®), and temazepam (Restoril®). Most recently, non-benzodiazepine drugs have been introduced that mimic the effects of benzodiazepines but while these compounds are not as dangerous, dependency may still be an issue. These are known as the z-drugs and include zaleplon (Sonata®), zolpidem (Ambien®), and eszopiclone (Lunesta®) (Quirk 2005).

Recently, a drug that influences the GABA binding site of the GABAA receptor directly has undergone clinical trials. Gaboxadol was being developed in tandem by Merck and Lundbeck until it was cancelled in early 2007 due to safety and efficacy issues during later trials (Pierson 2007). Gaboxadol is a GABA analog that binds directly to the GABA binding site. It is specific to certain GABA receptor subtypes, especially one type ( $\alpha 4\beta 3\delta$ ) that is located outside of the synapse, meaning it targets a different set of receptors than the benzodiazepines and z-drugs (Bateson 2006). Although it was never sold, Gaboxadol is interesting in that it represents a potential new pharmacological pathway for sleep aids.

### Anti-histamines

As noted above, the main source of histaminergic innervation in the brain is the tuberomammillary nucleus (TM). The TM receives input from the LHA (Saper et al. 2005), as well as from GABAergic neurons in the VLPO (Sherin et al. 1998). When this area is activated, the brain becomes more alert. More specifically, activation of H1 receptors by histamine causes potassium (K<sup>+</sup>) channels to close. When this happens, the neuron depolarizes, making it easier for action potentials to be fired. Blocking the action of histamine can therefore induce sleep (Reiner and Kamondi 1994).

Anti-histamines such as diphenhydramine (Benadryl®) and doxylamine (Unisom®, NyQuil®) achieve their sedative effects by acting as competitive antagonists of H1 receptors (Yanai and Tashiro 2007). These drugs are the only ones approved by the FDA as over-the-counter sleep aids. Although the data regarding tolerance is unclear, daytime side effects are well-documented, including drowsiness and decreased reaction times (Barbier and Bradbury 2007).

### Melatonin Receptor Drugs

The most recent entry into the prescription sleep aid market, ramelteon, targets the melatonin receptors in the suprachiasmatic nucleus. There are three types of melatonin receptors: MT1, MT2, and MT3. MT3 receptors are found in areas throughout the body including the kidney, liver, brain, heart, and skeletal muscle. MT1 and MT2 receptors, on the other hand, are located in the SCN. When these receptors are activated, the SCN is inhibited and sleep is induced.

Ramelteon acts as a selective agonist at MT1 and MT2 receptors. It was found to have six times more affinity for MT1 receptors and three-and-a-half times more affinity for MT2 receptors than melatonin. In contrast, the affinity of ramelteon for MT3 receptors is 1/110 the affinity of melatonin (Kato et al. 2005). This action is responsible for the sleep-inducing effects of ramelteon.

Ramelteon (Rozerem®) is currently the only melatonin agonist approved for use by the FDA as a sleep aid. However, Vanda Pharmaceuticals and Tikvah Therapeutics are both in the process of conducting clinical trials for drugs with the same mechanism of action. Similar drugs are also being investigated for treatment of depression (Becker 2008). The manufacturers of Rozerem® claim that it is the only sleep aid with no evidence of risk of dependence or negative daytime side effects (Takeda Pharmaceuticals 2008).

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