



PHARMACEUTICALS FREQUENTLY EMPLOYED IN SLEEP MEDICINE

Michael J. Decker PhD, RN, RRT, D.ABSM & Jeffrey Durmer MD, PhD

The goal of this column is to provide the reader with a current review of pharmaceuticals frequently employed in sleep medicine. As an exhaustive summary of all drugs employed in this field is beyond our scope, we will focus upon describing classes of drugs frequently encountered when working with patients with sleep disorders. For example, patients with sleep onset and/or sleep maintenance insomnia may receive a benzodiazepine, non-benzodiazepine, an anti-histamine, or a melatonin agonist as part of their therapeutic regimen. A narcoleptic, or a persistently hypersomnolent sleep apneic patient, may receive CNS stimulants or psychostimulants. Alternatively, a patient with depression and fatigue may receive a tricyclic antidepressant (TCA) or a selective serotonergic reuptake

As a result of increased public awareness, annual sales of sleep related drugs are increasing markedly

inhibitor (SSRI). Before delving into specific discussions of these drug classes, a brief overview of the history of pharmaceutical use in sleep medicine is warranted.

Until the mid 1960's, the field of sleep medicine focused primarily upon describing and treating maladies such as insomnia, parasomnias (sleep walking, night terrors) and hypersomnias, such as narcolepsy. Patients experiencing these symptoms typically sought consultation from neurologists, psychiatrists, psychologists, or their family physician. Specific sleep disorders with biological correlates found their way into the clinical lexicon much later in the past century. In fact, the discovery of some human sleep disorders was made several years after similar descriptions in animals. Until recently, treatments generally employed empiric pharmaceutical intervention along with behavioral modification protocols and/or psychotherapy.

Once sleep related breathing disorders were recognized as cause for significant morbidity and mortality, other medical subspecialties (pulmonology, otolaryngology, dentistry and primary preventive medicine) became more involved with diagnosing and treating this patient population. As the field of sleep medicine expanded to include multiple medical disciplines, so to did the research and development of pharmaceutical interventions to treat the myriad of sleep related disorders. This was driven, in part, by increased physician and public awareness of the signs and symptoms of sleep related disorders, as well as the scientific elucidation of neural pathways

involved in the initiation and maintenance of wakefulness and sleep.

Advances in pharmacotherapeutics develop as scientists demonstrate that alterations within specific neural regions and/or neurotransmitter systems are associated with the onset of specific symptoms and clinical signs. For example, degeneration of hypocretin producing neurons in the hypothalamus is associated with the inability to maintain prolonged periods wakefulness and the onset of REM sleep dysregulation, the hallmarks of narcolepsy. New pharmacologic compounds are now being developed to replace the loss of the hypocretin neurotransmitter, and to stimulate the remaining hypocretin receptors to promote wakefulness and alleviate the symptoms of narcolepsy.

As a result of increased public awareness of sleep disorders, and scientific advances, the annual sales of sleep related drugs are increasing markedly. For example, sales of insomnia medications in the U.S. have increased from \$1.3 billion in 2001 to approximately \$4.6 billion in 2006.. The interest in pharmaceutical sleep aids is not a modern invention as the discovery and use of sleep inducing compounds is thousands of years old.

Perhaps the first compound to be used as a sleep inducing aid was the juice from the opium poppy. Some of the earliest written descriptions of the opium poppy have been found on Sumerian clay tablets dating to approximately 3000 BC. At that time, the juice of the poppy was harvested and consumed due to its ability to induce a euphoric state. This, in turn, led to the plant being considered a "Gil Hul" or ("joy plant"). Descriptions of the opium poppy have also appeared in writings of the Assyrians and Persians. Eventually, the Greeks were introduced to the opium poppy, which may represent the first time it was used expressly for sleep induction. Greek mythology depicts many sleep-related deities, including Hypnos (sleep), Morpheus (dreams), Nyx (night) and Thanatos (death, the twin brother of Hypnos) in association with opium extracted from the poppy. Homer described the properties of opium in both "The Iliad" and "The Odyssey," as an intoxicating, pain-relieving and sleep inducing substance. Contemporary literature also expounds the sleep inducing power of opium with Dorothy, her dog Toto, and the Cowardly Lion falling into a deep sleep as they passed through a field of poppies on their approach to the Emerald City in the Wizard of Oz.

The sleep inducing effects of the opium poppy may be attributed to any number of alkaloids contained within this plant

including morphine and codeine. Both are CNS depressants and opioid pain relievers. The ancient Greeks and Romans also employed other herbal sleep-inducers such as the bark of mandrake, the seeds of henbane, and even lettuce juice. During the Middle Ages, and through the Renaissance, the English brewed and consumed a variety of syrups known to promote drowsiness; however, development of sleep inducing compounds was revolutionized in the early 1800's by the synthesis of Opium. Soon after this, chloral hydrate and the bromides were also developed.

Chloral hydrate, a liquid CNS depressant rapidly induces deep sleep. Bromides, invented in the mid 1800's, are also CNS depressants, and induce sleep relatively quickly. These include sodium bromide, potassium bromide, and ammonium bromide. Their popularity as sleep aids increased through the late nineteenth century and into the early twentieth century. Another development in the 1800's was the re-discovery and use of nitrous oxide and ether as inhaled "party favorites" of upper class Europeans and Americans. The initial discoveries of ether by Spanish alchemist Raymundus Lullius in 1275, and nitrous oxide by English chemist Joseph Priestly in 1772 were lost to medical science until their re-introduction in 1842. At that time, Crawford Long, a surgeon in Georgia, employed the "recreational" ether in surgical procedures due to its incredibly rapid induction of "sleep, amnesia and pain relief". In doing so, he unknowingly ushered in the modern era of anesthesia.

Barbiturates, first discovered in the mid-nineteenth century, soon replaced bromides as the "sleeping pills" of choice in the early twentieth century. Barbiturates, a class of drugs comprised of more than 25,000 compounds, are created when barbituric acid is combined with other chemicals. Although multiple barbituric acid compounds were developed, a select few (including a diethyl derivative), resulted in sleep promoting agents. Barbiturates, such as phenobarbital, are very effective at inducing sleep; however, they also result in multiple, unpleasant side-effects. The potential risk for barbiturate addiction is significant and if taken with alcohol can result in respiratory suppression and death.

The 1970's saw the advent of benzodiazepines such as Valium, Restoril and Klonopin. Early formulations of these CNS depressants shared similar side effect profiles to the barbiturates. Benzodiazepines, possess the potential for addiction and due to the amount of time needed to eliminate some benzodiazepines from the body (> 12 – 24 hours) next-day "hangover" effects and memory impairment are common. Although still commonly used for sleep disorders, benzodiazepines are more selectively employed. Since the recent introduction of non-benzodiazepine drugs (zolpidem, zaleplon, eszopiclone), in the 1990's, benzodiazepine use for insomnia has been further supplanted.

When one thinks of pharmaceuticals frequently employed in sleep medicine, it is not surprising that "sleeping pills" immediately come to mind. However, a number of non-CNS depressant medications are used in sleep medicine to alleviate specific sleep-disrupting symptoms. In disorders such as Restless Legs Syndrome (RLS) and Periodic Limb Movement Disorder (PLMD) sleep onset is often delayed and fragmented. Since the association of dopaminergic pathways with these disorders, first-line therapy includes dopamine agonists, which are now recognized as the most effective therapy for RLS and PLMD.

Respiratory stimulants are another class of non-CNS depressant medications employed in the treatment of sleep disorders. Medroxyprogesterone and acetazolamide are often used in an



*The NEW Improved StatCO₂ and Mini StatCO₂ ...
Verification with Enhanced Convenience.*

**Convenient pull tab activation strip.
Convenient 24 hour performance.**

Some CO₂ detectors are activated the minute you open the foil package. Both StatCO₂ and Mini StatCO₂ include a convenient pull tab activation strip that protects them. So you can take StatCO₂ or Mini StatCO₂ out of the package and have it ready for use when and where you need it for a full 24 hours.

But **Convenience** isn't the only advantage of StatCO₂ and Mini StatCO₂. Both also provide enhanced **Economy** and **Reliability**.



StatCO₂ over 15 lbs body weight.
Mini StatCO₂ 1-15 lbs body weight.

*StatCO₂ and Mini StatCO₂ ...
Verification with Enhanced Economy, Reliability and Convenience.*

MERCURY
MEDICAL

Toll Free: (800) 237-6418
www.mercurymed.com

RESPIRATORY

Item # 610000701000 (New Face Only)

CIRCLE READER ACTION CARD # 16

effort to enhance ventilation in patients with high altitude induced central sleep apnea, or obesity-hypoventilation syndrome. More recently, the antidepressant mirtazapine was shown to reduce apnea severity in animal models of sleep apnea, as well as in some patients. An effective pharmaceutical treatment for obstructive sleep apnea does not yet exist; however, this remains an active field of scientific inquiry.

In summary, the increased neurobiological understanding of sleep-wake systems coupled with improved recognition of sleep disorders has created more specific pharmaceutical interventions. Better medications will continue to be developed as scientists and clinicians further elucidate the basic mechanisms of sleep and wake. In addition, technological discoveries which aid in drug discovery and development are essential to bringing compounds to the market. Future articles in this series will focus on describing several key neurochemical systems involved in sleep, wakefulness, and circadian rhythm generation. We will describe the disorders related to dysfunction in these systems and the pharmaceutical agents designed to augment biological activity to restore function.

Dr. Michael Decker PhD, RN, RRT, D.ABSM is the Director of Clinical Services for the Fusion Sleep Center for Sleep Disorders in John's Creek, GA.