

# Opiates: Their History and Its Relevance to Today's Treatment

*By Joseph A. Troncale, MD*

Opiates have existed as substances of use and abuse for at least 5,000 years. The Sumerians in Mesopotamia began refining poppies for use in 3400 B.C. Their knowledge and use of the "Hul Gil" or "joy plant" would later be transferred throughout the civilized world.

The Egyptians began an international opium trade around 1300 B.C., spreading the use of opium throughout the Mediterranean region (NIDA, USDHEW, 1978). Pictures of poppies can be found in many ancient Greek, Roman, and Egyptian artifacts. Opium was considered by many to be of divine origin. Alexander the Great later brought opium to Persia and India. By 400 A.D., China was introduced to opium by Arab traders who brought in Egyptian opium. Depending on which source you read, either the Arabs, Turks, or the Portuguese are credited with the introduction of opium smoking about 500 years ago. The Dutch then introduced tobacco and opium smoking to the Chinese. The Chinese used both products separately or in combination.

Around the same time, opium was being used in Europe as a prescription for pain. Paracelsus, a practitioner of the 16th century, discovered opium's characteristic solubility in alcohol and developed "laudanum" or tincture of morphine. The problem with laudanum, in addition to the risk of opium addiction, was the tolerance developed to both the opiates and the alcohol, which created significant withdrawal problems for those attempting to cease its use.

During the 17th and 18th centuries, opium was becoming a popular compound of recreation and abuse in many other parts of the world. Even 300 years ago, there was considerable "street value" to opium. British and Dutch traders began developing markets in Asia for its consumption and there were British attempts to monopolize the opium trade. By the start of the 18th century, the British East India Company was importing large quantities of opium into China. At the same time, opium was imported by the British from Turkey into Europe and the United States.

Morphine was refined from opium in Germany in 1803, which increased the popularity of narcotics, as it was thought that morphine was medically acceptable and safe. At this time in history, geopolitics were beginning to mingle with the medical treatment of pain. In 1839, the Chinese tried keeping opium out of their country. They were met with British warships enforcing the importation of opium into China, thereby beginning the First Opium War which ended with the Treaty of Nanjing in 1842. This forced China to hand over Hong Kong to the British. A year later in 1843, Dr. Alexander Wood demonstrated the efficacy of

intravenous morphine. It was believed that intravenous morphine was not addictive and therefore beneficial.

Large amounts of opium began travelling all over the world. The British continued to pour enormous amounts of the drug into China, and it is estimated that a large percentage of males in China were addicted to opium by the end of the 1800s. Opium was used in patent medicines for the treatment of various ailments. At the same time, it was being used throughout the world in "opium dens" as a clandestine euphoric. The United States was very tolerant of opium in the late 1800s.

The epidemiology of opiate use in the United States has changed radically since the late 19th century. Most of the opiate addicts in the late 1800s included middle- and upper-class women addicted to laudanum and wounded Civil War veterans. Eventually, physicians acquired an understanding of the addictive nature of their opiate prescriptions, and the prescriptions decreased, but only after the creation of hundreds of thousands of addicts. Finally, governments all over the world began attempting to curb opiate use either by banning, taxing, or confiscating.

### **Entering a modern age**

It was only in 1910 that the British finally stopped imports into China. The Harrison Act of 1914 was the first to regulate narcotic manufacturing and distribution. During this period of time, a parallel movement was started in the South and some of the larger northeastern cities in an attempt to establish opiate maintenance programs.

The Treasury Department eventually banned these programs in the United States in 1923, as opiate maintenance was not considered a legitimate use of narcotics Ñ thus beginning the United States' black market for opiates. By the 1930s, ironically, the Chinese were exporting opium to the United States. Germany developed methadone during World War II as an alternative to morphine because the war made it difficult to acquire opium in Europe. Methadone was studied in the United States after the war, and it was deemed to be similar enough to morphine that it was considered efficacious for use as a medicine for opiate withdrawal.

After the World War II, the United States became involved with opium producing countries in Southeast Asia, and as part of an economic barter and arms trading, large amounts of opium began to enter into the United States. The Vietnam War exacerbated the Southeast Asian opium situation in the 1960s. During the 1960s methadone maintenance programs were introduced as an alternative to street use of opiates, representing the first legitimate maintenance programs since 1923.

By the 1990s, opium and heroin were flooding into the United States from Mexico, Columbia, and Southeast Asia (McCoy, 1994). Today there is concern surrounding Afghanistan beyond the current military events, since Afghanistan supplies much of Europe's current opiate demand.

Estimates of current users are in the hundreds of thousands, but accurate figures are difficult to obtain. Morbidity and mortality figures are also somewhat elusive, but Emergency Department statistics indicate that tens of thousands of heroin-related emergencies are seen in the United States each year, and that number doubled from 1991 to 1996. What is known are statistics from metropolitan areas in the U.S. demonstrating increasing numbers of heroin-related deaths in cities such as Philadelphia.

### **Social issues**

Part of the historical problem associated with opiates is their medicinal and pain relief properties. Looking back at history, opiates have been the mainstay of effective pain relief for many years as well as a recreational drug. Ongoing controversies in opiate use include the compassionate use of opiates for chronic pain in the face of their potential for addiction and abuse, opiate maintenance therapy, and detoxification regimens using opiates.

With regard to opiates, the classic story of the three blind men describing the elephant comes to mind. Within professional disciplines, there remain a number of controversial issues regarding use of opiates. Law enforcement officials deal with the side regarding the criminal smuggling and street use of opiate-based drugs. Pain management physicians recognize the need for opiates in debilitating pain syndromes. Addiction specialists see people with the effects and consequences of the addictive side of opiates, whether used for recreation or pain relief.

The book, *Opium: A History*, by Martin Booth, was criticized in two prominent reviews because of the author's lack of distinction between opiate abuse and opiate addiction. Booth also was criticized for exaggerating the problems associated with opiates as compared to other addictive substances, such as alcohol. These controversies have led to many arguments regarding the proper and improper use of opiates, which still remain unresolved (Sullum, 1998; Booth, 1999).

### **Neurochemistry**

The physiology of opiate receptors in the brain has been well researched and described. The human brain and nervous system have several types of opiate receptors.

These receptors are able to selectively identify and bind opiate molecules to brain and nerve tissue which, in turn, begin the chemical process that causes the opiate's effects. These receptors are predominately, but not exclusively, located in deep brain structures associated with what is called the limbic system. This system is responsible in part for things such as pleasure, autonomic function (life functions not under conscious control of the individual) and emotions. The brain has been widely studied in multiple animals from rats to humans. These studies have shown how stimulation of certain areas causes intense pleasure and euphoria identical to pleasurable sensations associated with drug "highs," sexual stimulation, as well as other intense feelings of well-being.

There is also a great deal of overlap of function in this area of the brain in that the same neural pathways serve multiple addictive behaviors and pleasure sensations. There are numerous receptors and neurotransmitters associated with the stimulation of the pleasure centers. For instance, dopamine receptors are associated with cocaine use, gamma amino butyric acid (GABA) receptors with alcohol, and benzodiazepine use and the various specialized opiate receptors associated with opiate use.

The opiate receptor that is thought to be associated with the intense pleasure of opiate use is termed the *mu* receptor, and it is the receptor stimulated by heroin and morphine. Conversely, opiates with an affinity for mu receptors also inhibit the activity of the locus coeruleus, an area of the brain highly involved with the opiate withdrawal syndrome. This area of the brain produces large amounts of norepinephrine when aroused during opiate withdrawal. This surge of norepinephrine is largely responsible for the autonomic hyperactivity seen during withdrawal and contributes to the patients' anxiety, excitability, perspiration, and cramps (Heit, 2000).

### **Opiates and treatment of acute withdrawal**

Opiate withdrawal is a painful syndrome characterized by intense craving, pain, abdominal cramps, dysphoria, excitability, and involuntary movements. A large part of the difficulty in getting people into treatment for their addiction is the fear of withdrawal.

With alcohol withdrawal treatment, for instance, it is legal and appropriate to give sedative-hypnotics such as benzodiazepines to fill gamma amino butyric acid (GABA) receptors in the brain to prevent hyperexcitability and withdrawal seizures. With heroin or opiate withdrawal, however, despite neurobiological and clinical evidence, pure opiates or the opiate agonist/antagonist, buprenorphine is currently illegal to use for detoxification. Symptomatic therapy for opiate withdrawal such as clonidine, phenobarbital or benzodiazepines, and muscle relaxants are currently used.

These medications have limited benefit for withdrawal symptoms, but do not match the efficacy of opiates. The problems with opiates are their addictive properties. However, if there were consistency in the policy toward addictive drugs, benzodiazepines would have to be prescribed for alcohol withdrawal as well. A double standard in policy exists toward medications allowed in opiate-dependent patients versus alcohol-dependent patients (Kasser et al., 1997).

### **Opiate maintenance therapy**

In the area of opioid maintenance therapy, Doyle and Nyswander introduced methadone in the 1960s. It should be noted that there were attempts in the middle part of the 20th century to treat opiate-dependent people in a small government program in the U.S Public Health Service Hospital in Lexington, Kentucky.

The problem with this early treatment program had mostly to do with its prison-like model and the high relapse rate post discharge. The problem, from a

government policy standpoint, has been to view heroin addiction as a once and done treatment problem model vs. a chronic disease model. Patients in treatment programs do fairly well in supportive environments where the availability of drugs is controlled. Methadone use allows a percentage of opiate dependent patients to live relatively normal lives without having to seek street opiates or prescription opiates. Methadone maintenance programs remain controversial. Data exist on both sides of the methadone argument to make compelling cases both for and against the use of methadone. Doyle postulated that defects in opiate-dependent persons' brains were created in the opiate receptor system of the brain with chronic opiate use. These defects could not be totally rectified with abstinence alone. Hence, for many heroin dependent persons, craving and dysphoria from abstinence overcome their ability to stay clean. Doyle and Nyswander began the movement to legalize opiate use in the setting of addiction, filling the niche for maintenance treatment that was outlawed in the 1920s. Dr. M.J. Kreek of The Rockefeller University has outlined the goals of opiate maintenance pharmacotherapy. They are:

- \* Prevention or reduction of withdrawal symptoms.
- \* Prevention or reduction of the drug craving.
- \* Prevention of relapse.
- \* Restoration of normal physiologic function disrupted by former chronic drug use.

It is also important to add to Kreek's list the prevention of comorbidity associated with chronic drug use such as HIV/AIDS, Hepatitis B and C and morbidity and mortality associated with street acquisition of drugs and the potential trauma and violence associated with acquisition and sales.

Kreek and others have pointed out that binge use of opiates leads to a "reset" of the dopamine levels of the brain. There is also the increase of corticotrophin-releasing factor (CRF), a so-called "stress prohormone," which also decreases dopamine and other "good" neurotransmitters. Once reset, there is dysphoria because dopamine levels do not return to their normal baseline. This results in craving or withdrawal.

It also prompts continued opiate use to get dopamine levels to pre-use levels. Methadone or L-alpha-acetyl-methadol (LAAM), also a long-acting opiate, are used to stabilize patients by reducing the rapid "ups and downs" of heroin metabolism, decreasing CRF and preventing cravings and withdrawal.

Problems associated with methadone use include diversion, side effects of the medicine, stigmatization, access difficulties to get medications every day, and disappointment with the loss of autonomy. There also have been articles regarding methadone's association with domestic violence, although it is not clear as to whether methadone is associated any more with violence than street heroin use (Public Policy of ASAM, 2000).

## **Pain management versus addiction**

One of the most difficult areas of medical practice deals with the pain management of patients who suffer from chronic, non-malignant pain who are also addicted to opiates.

Pain is a subjective response to noxious stimuli, trauma or other disruptions of homeostatic mechanisms of the mind or body. Because it is subjective, only the affected person can report symptoms. Pain in the face of addiction or the possibility of addiction becomes a conundrum for practitioners because of the conflict between attempting to alleviate pain and suffering while trying to do no harm.

Ethically, there is no question that pain should be treated adequately. The problem comes in situations where chronic, non-malignant pain is the presenting complaint. Are opiates appropriate in this setting? What should be done for the person who has an addiction? How do we properly train practitioners who under-treat pain and label pseudo-addiction (that is, patients who have medication-seeking behavior because of under-treatment of pain) as addiction? What is to be done to identify addicts who use practitioners as their source of opiates? These are issues of under-treatment of pain by the medical community spurring regulations and standards regarding the use of pain assessment tools, (pain as a "vital sign").

The treatment of pain creates a great deal of ambivalence in healthcare providers as well as a tremendous amount of splitting of emotions between staff, patient, and families. Is it possible to maintain someone with chronic pain on opiates? We know the answer is "yes" for most patients. However, we also know that it is not true for all patients. There is a risk of addiction. Who should take that risk? How are patients properly informed of the risks? Once addiction is known, how is pain best treated? (Heit, 2000). The experts have differing opinions.

### **Future trends**

There is concern for the current population of opiate dependent people. As a whole, our society and government continue to be misinformed about the plight of those who wish to stop opiate use. For example, at a local hospital, they attempted to get methadone for detoxification of opiate dependent patients. Part of the laws in our state required that we obtain community permission. The community met and a large numbers of residents turned out who knew only that they did not want methadone in their community, period. Later that same year, as Medical Director, I was served notice by the Drug Enforcement Administration that I would lose my DEA registration if buprenorphine were used in our hospital. These stories parallel the early 20th century plight of treatment centers attempting to establish opiate maintenance in the south. Both the government and the population who had never experienced what addiction was like wanted opiates to be eradicated or to go underground.

As a treatment community we are not misinformed, yet we are terribly ambivalent about the best way to help this population. If a poll were taken today among

individuals who deal professionally with addiction, it would become evident that there would be disparity in treatment strategies for opiate-dependent patients. Who, if any, are methadone candidates? Who should be placed on naltrexone? What is the best way to detoxify this population when they present for treatment? In the case of patients who have chronic pain and are addicted to opiates, how should their pain be managed?

**Advocacy is the key**

If history is a good indicator, it is imperative that members of the treatment community continue to advocate for our patients and clients in an ethical manner. This advocacy should include the education of the government, the medical community, as well as the general population regarding:

- \* the reality of addiction as a disease,
- \* the efficacy of treatment,
- \* the compassionate availability of proper detoxification and also treatment services,
- \* an open-minded approach to opiate maintenance when necessary.

The answers to the problems are still a subject of debate. For the sake of our patients, this debate must be carried to forums where both patients and society will ultimately benefit.

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