The Emerging Role of Buprenorphine

By Howard Kornfeld, MD

Many practicing physicians need to make decisions on a daily basis about treating chronic pain. Treatments based on lifestyle modification, mind-body methods, and psychological or spiritual perspectives should always be considered as preferable to pharmacotherapy initially. These non-pharmaceutical approaches are free of the myriad adverse effects, including addictive complications, that may accompany medications. In addition, non-pharmaceutical treatments may awaken deeper healing mechanisms essential to recovery from chronic pain.

Conversely, oral pharmacotherapy may be applied with, before, or after interventional approaches such as epidurals or other nerve blocks, implanted spinal cord stimulators or intrathecal pumps. Medications are often appropriate prior to the application of these interventions, which can have their own serious complications.

Pharmacologic treatments for chronic pain include several families of medications not considered having substantial risk for addictive use, such as NSAIDs and acetaminophen, anticonvulsant drugs, antidepressants and local anesthetic patches. In contrast, the controlled substances, particularly opioids and benzodiazepines, often create the most difficult dilemmas in assessment, treatment, and monitoring in our current, heavily scrutinized, medical-legal environment.[1]

A growing understanding of the treatment of chronic pain with buprenorphine, a potent mu opioid analgesic antagonist, may be poised to improve the level of evidence for both the effectiveness and safety of chronic pain treatment, particularly when used as a component in a well-formulated treatment plan. Unlike other opioids commonly prescribed for moderate to severe pain, buprenorphine has a greater margin of safety for both overdose and addiction. It is also the only controlled substance approved for opiate dependency for use in the office setting, and it therefore confers greater protection to the practitioner, who must remain ever vigilant against triggering an addictive process that would bring regulatory scrutiny.[2,3]

Since the time of Hippocrates and the use of willow bark, the antipyretic analgesics—primarily aspirin, other NSAIDs and acetaminophen—have played an essential role in managing pain. The pharmacology of pain, however, is built on the historical foundation of opium. How buprenorphine emerged in this history is of particular significance for pain medicine.

The opium poppy, *Papaver somniferum*, is the only one of dozens of poppy species to contain appreciable amounts of morphine. Opium poppies have been found in archaeological sites in Switzerland, France and Spain, dated to prehistoric eras more than 7,000 years ago. Neolithic human societies may have created the opium poppy through cultivation and selective breeding, techniques believed to have been also used to domesticate plant foods from wild strains. Opium eventually became well established in the healing and ceremonial customs of ancient Egypt, Mesopotamia, Greece and Rome.[4]

After the fall of the Roman Empire, the epicenter of opium use moved to Asia Minor and the Islamic civilizations in Arabia and Persia. India became a center for opium cultivation and manu-

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facture, and opium also became part of traditional Chinese medicine.

As opium diffused back through Europe during the 1600s, it was praised by Thomas Sydenham, the English Hippocrates. His famous quote bears repeating: "Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium."[5] The Romantic poets, most famously Coleridge, were inspired by opium and often addicted to it.

After the British gained control of opium-growing areas of India during the 1700s and 1800s, they used their commercial and military prowess to create a vast market for opium in China. By this point, opium was smoked rather than ingested orally. The smoking of tobacco by Native Americans had inspired Dutch merchant marines to emulate this habit as they sailed about the East Indies, and the sprinkling of opium onto tobacco is thought to have demonstrated the potency of this means of ingestion.[4]

Between 1839 and 1856, the Chinese emperor led two unsuccessful wars with the British to stop the opium trade that was enslaving thousands of his subjects to the harsh master of opiate addiction. Ironically, the British needed the silver they obtained from the opium trade to purchase Chinese tea, whose caffeine had become an essential drug for fueling the industrial revolution.[6]

Morphine was extracted from the opium poppy in the early 1800s, the first purified molecule to be obtained from a botanical source. The hypodermic syringe was available by the Civil War, and morphine powder was both dusted in wounds and injected subcutaneously. By the late 1800s, opium and morphine consumption was at its highest point in American history, not only as an essential tool in the black bag of the traveling horse-and-buggy physician, but also universally found in patent medicines, infant syrups, and general stores and apothecaries.

In the late 1890s, Bayer began marketing Heroin (their brand name for the recently invented diacetylmorphine) as a more effective cough suppressant. Working class youth in New York and other cities, who up to that time had been sniffing or injecting morphine, now found heroin to be significantly more compelling. Heroin is more lipophilic and potent than morphine, and after crossing the blood-brain barrier, it is metabolized into morphine.[7]

By the early 1900s, the winds of prohibition, of both alcohol and the opiates, were blowing strongly, and in 1915 Congress passed the Harrison Act, a tax law, to confine opium and opiate use to medical supervision. The U.S. Treasury Department, subsequently supported by Supreme Court rulings and popular sentiment that viewed the opiate addict as the most despicable of citizens, decreed that physicians no longer had the right to treat addiction. In particular, they could only use morphine in limited contexts for pain, and never to ease the withdrawal suffering of an addict.[7]

In contrast with the ideological constraints of opiate prohibition, the early scientists of the National Research Council and the National Institutes of Health were directed by Congress to investigate the morphine molecule and invent modifications that might relieve pain, without triggering the dread of addiction and abuse. During the early to middle decades of the 20th century, hundreds of new molecules were given to tens of thousands of laboratory animals, and the age of semi- and fully synthetic opioids emerged.[8]

These new opioids were added to the list of opioids already present in the opium poppy, namely morphine and codeine, and included hydromorphone, hydrocodone, oxymorphone and levorphanol, all of which share the morphine skeleton. Fully synthetic opioids with different chemical structures included fentanyl, methadone, and propoxyphene (Darvon). In the 1980s, delayed and controlled-release morphine was introduced, which greatly simplified and enhanced chronic opioid pain management. The introduction of a similar product utilizing oxycodone (OxyContin) then fueled much of the prescription opioid abuse epidemic in which we are currently engulfed.[9]

In the early 1970s, a molecule was found that appeared to most closely resemble a non-addicting morphine, a theoretical entity that was often called the Holy Grail of opiate pharmacology. Named buprenorphine, this substance was tested on drug prisoners at the Narcotic Farm in Lexington, Kentucky, where it was found to be effective as both an analgesic and as a treatment for opiate withdrawal and dependency. Buprenorphine was first marketed in England in 1979 as a parenteral analgesic (Buprenex) in 0.3 mg ampoules, followed in 1981 by a sublingual tablet (Temgesic) containing 0.2 mg. The FDA approved Buprenex in 1981, and that is where buprenorphine stayed in the U.S. until 2002, when it was approved by the FDA in a high-dose form for treating opiate dependency.

In the mid-1990s, the French began using buprenorphine as a high-dose (2 mg and 8 mg) sublingual medication for opiate addiction. Instead of waiting for the extensive FDA trials that were ultimately carried out in the U.S., the French implemented the treatment early in the belief that widespread use of buprenorphine could reduce HIV and hepatitis C infections. Their efforts were subsequently judged to be quite successful.[10]

In 2001, a transdermal form of buprenorphine was introduced in Europe. Originally available in a higher dose form, it became available in a lower dose form in 2005. This latter form (Butrans) has recently been approved by the FDA for marketing in the U.S. by Purdue Pharma, ironically the same pharmaceutical company that introduced OxyContin. Purdue Pharma has received tremendous criticism for its marketing of OxyContin, and they have pleaded guilty to criminal charges for inaccurate representations that contributed to the abuse, morbidity and mortality associated with misuse of OxyContin.[11]

The low-dose form of buprenorphine

has been found to be useful in elderly patients with chronic non-cancer pain as well as cancer pain.[12] Buprenorphine appears to be less associated with the development of hyperalgesia and to be effective in neuropathic pain, which is often considered to be opioid resistant.[13] Because there is less euphoria associated with buprenorphine, it may also be useful for patients who are prone to addictive behaviors.

Because of the ceiling effect for respiratory depression, buprenorphine is less prone to overdose than conventional opioid drugs. Because of its tight binding to the mu opioid receptor, in newly detoxified opioid addicts who have lost tolerance, relapse to opioid use is also associated with decreased risk of overdose. Buprenorphine injection, however, when associated with sedative use, particularly parenteral, has led to respiratory depression and death. Usually this combination has been associated with illicit use and has been best documented in France, where buprenorphine without naloxone (Subutex rather than Suboxone) had been widely prescribed by general practitioners and was available on the streets. Nevertheless, practitioners should use reasonable caution when buprenorphine, even in its sublingual or transdermal form, is prescribed with other sedatives or to patients with compromised respiratory function as a result of COPD or cor pulmonale.[14]

Initial dosing of buprenorphine, in an opioid naive or relatively naive patient, should be quite cautious, to avoid dysphoria and nausea. The lowest dose of Suboxone (2mg of buprenorphine) may be too high by an order of magnitude for pain in this population. Buprenorphine causes constipation and can cause pruritis, but generally less so than the full agonist opioids, such as morphine or oxycodone. Buprenorphine may be associated with temporary urinary hesitancy or retention more pronounced than with other opioids, but usually responding adequately to standard remedies such as bethanechol.

Buprenorphine can be cautiously used in patients with renal impairment without dose adjustment and is considered less problematic than most other opioids in patients with hepatic impairment, as long as appropriate monitoring of liver function tests is maintained. Buprenorphine can suppress laboratory indices of immune function, but appears to do so less than any other opioid.[2]

The use of buprenorphine is further complicated by the need for the opioid-dependent patient to undergo an induction protocol where the opioid is stopped and early withdrawal is allowed to emerge. This process may be difficult for a chronic pain patient, but it can be orchestrated with careful management in the office or, if needed, in the hospital setting. Unless the induction protocol is carried out, administration of buprenorphine can induce precipitated naloxone-type withdrawal, due to buprenorphine's tighter binding than morphine at the mu receptor.[3]

The FDA-approved form of buprenorphine for addiction treatment

is a combination product (Suboxone) that contains naloxone in one-quarter the amount of the buprenorphine. The naloxone in these tablets is not absorbed when the tablet is taken sublingually, but it does becomes an active antagonist when the tablet is crushed and injected. This feature greatly reduces the abuse potential of the medication.[3]

There is a growing literature on strategies for pharmacologic assessment and monitoring of chronic pain patients. One example is "Guidelines for Prescribing Controlled Substances for Pain," published by the Medical Board of California in 1994 and revised in 2003.[15] The guidelines reflect the practice of conscientious medicine and include the following required components: history/physical examination; treatment plan, objectives; informed consent; periodic review; consultation; records; and compliance with Controlled Substance laws and regulations. The informed consent can also be paired with a treatment agreement for the long-term use of controlled substances.[16]

Another model is the Ten Principles of Universal Precautions. Based on the model that originated in infectious diseases, where all patients were assumed to be at risk of being vectors for infection, the 10 principles are to be applied to all chronic pain patients being treated with opiate medications.[17] These principles enhance the MBC guidelines by including assessments for psychological status and risk of addictive disease, along with regular assessments of pain scores and levels of function. Finally, they direct specific attention to documenting the "Four A's of Pain Medicine," which can be posed as questions and answered as part of the written record of an office visit.[16]

- **Analgesia?** (Are the medications effective?)
- **Activities of daily living?** (How is the quality of life and function?)
- **Adverse effects?** (What are the side effects?)
- **Aberrant behaviors?** (Which behaviors are significant?)

Which aberrant behaviors are more predictive of addiction and/or illegal activity and which are less predictive has been discussed widely but not yet validated.[18] A common but frowned-upon behavior is the sharing of medications with friends and family. This would need to be corrected, once discovered, but is not generally strongly suggestive, in itself, of addiction. Snorting or injecting an oral medication would be much more predictive of an addictive process.

Addiction is often defined as a primary, chronic, neurobiologic disease with genetic, psychosocial and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, craving, and continued use despite harm.[17]

Ultimately, the chronic pain patient needs to be triaged to determine the correct level of care needed, with respect to addiction liability, pain complexity and psychiatric stability. Are they primary care patients, primary care patients with specialist support, or patients in the realm of specialty pain and/or addiction medicine management?

Pharmacologic management of chronic pain has become an essential skill for primary care physicians and for many specialists. A good working relationship with a pain or addiction medicine specialist is a valuable component of such management. The wider use of buprenorphine for pain, as well as for addictive disease, introduces a useful tool and may improve outcomes for managing chronic pain. ◇

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