Tufts Health Care Institute Program on Opioid Risk Management
Pharmacotherapy for Prescription Opioid Addiction:
Implications for Pain Management

June 10 and 11, 2011

Executive Summary

Introduction

Opioid misuse and addiction are major societal problems in the US today. It is estimated that about 12.4 million Americans used prescription pain relievers for nonmedical purposes in 2009, and 1.9 million of these individuals met the DSM-IV criteria for substance abuse or dependence. Many of these individuals are first exposed to opioids as treatments for chronic pain, resulting in substantial overlap between the chronic pain and substance abuse patient populations. These circumstances have led to a need for the convergence of clinical skills between health care providers who address chronic pain and those who address substance abuse, in order to treat both conditions simultaneously. Effective management of these patients requires the ability to recognize individuals who are at high risk for addiction, to provide appropriate treatment or referral to patients who become addicted, and to continue to manage chronic pain in individuals who are addicted to opioids or other substances.

On June 9 and 10, 2011, the Tufts Health Care Program on Opioid Risk Management convened a summit meeting in Boston to better characterize this growing problem. A group of experts in the fields of chronic pain, substance abuse, opioid pharmacology, and the concomitant regulatory and legal ramifications participated in the summit meeting. Participants reviewed available evidence on the uses of pharmacotherapies to treat prescription opioid addiction and current best practices for the management of chronic pain in addicted individuals, and discussed ways to improve medical practice and disseminate needed changes in this highly challenging clinical area.

Scope of the Problem and Potential Solutions

Epidemiological data suggests that about 2 million Americans suffer from moderate to severe pain and are also misusing prescription opioids. This patient population becomes larger if individuals with moderate to severe pain and who are addicted to other substances, such as alcohol or illicit drugs, are included. Prior substance abuse is the major risk factor for developing prescription opioid addiction and for prescription opioid overdose as well.

Special management of these patients, including the use of appropriate pharmacotherapy, has been shown to improve outcomes. In many areas of medical practice, it is a standard of care to tailor the selection of pharmacotherapy to specific combinations of co-morbidities, for example, in patients who have both hypertension and diabetes. Similarly, it is likely that treating substance abuse and chronic pain as co-morbidities will enable the development of improved management strategies, including specific pharmacotherapeutic choices, which are tailored to this patient population. Such strategies are still in development, and data to inform best practices are lacking in many areas, but some clinical research results are available.

One impetus for developing a more effective, tailored approach to the dual diagnosis of chronic pain and substance abuse is provided by the health economics of prescription opioid misuse and addiction. The total societal cost of prescription opioid abuse is estimated at $55.7 billion annually, including $25.6 billion in workplace costs, $5.1 billion in criminal justice costs, and $25 billion in health care costs. The epidemic of prescription opioid addiction creates a significant monetary burden for health insurers due to increased medical and pharmacy costs among abusers. Health economics research has identified two potential strategies that could reduce these costs: (1) the development and marketing of opioid formulations designed to deter abuse, and (2) improved identification of patients who are at high risk for abusing with the use of pharmacy records and other information available within insurer databases. The latter strategy has already been employed by some forward-thinking health insurers.

The federal government has developed a number of responses to prescription drug abuse, including the passage of the Secure and Responsible Drug Disposal Act of 2010. Prescription drugs such as opioids have a high liability for abuse, because they are perceived as safer than street drugs while at the same time being highly accessible. Frequently abused prescription drugs, including pain relievers and anti-anxiety medications, are designed to be taken as needed, and are often dispensed in larger quantities than necessary. The excess medication is

often kept in the home where it is accessible to potential abusers or diverters. The 2009 National Survey on Drug Use and Health (NSDUH) found that 70% of individuals who abused prescription pain medications obtained these drugs from friends or family members. The Secure and Responsible Drug Disposal Act empowers federal agencies to develop methods by which consumers can dispose of medications properly, to minimize the potential for diversion and abuse, and funds programs to raise awareness among the general population of the problems inherent in storing leftover prescription medications in the home.

Federal agencies, including the US Food and Drug Administration (FDA), are also working on improving education for health care providers around the issues of prescription opioid abuse. Practitioners who prescribe most of these medications, including general and family practitioners, internal medicine physicians, and nurse practitioners, typically receive very little training on treating chronic pain or substance abuse disorders. The FDA is developing Risk Evaluation and Mitigation Strategies (REMS), to be implemented by pharmaceutical manufacturers, which will entail mandatory prescriber education and a certificate of competency for all practitioners who prescribe opioids.

Pharmacotherapeutic Approaches to Prescription Opioid Abuse: Historical Perspectives and Current Research

Historically, three major medications have been developed to treat prescription opioid abuse: methadone, naltrexone, and buprenorphine. These medications were the end result of a scientific approach to opioid addiction that began in the early part of the 20th century. Before this time, treatment of drug addicts was highly punitive and depended heavily on law enforcement agencies. In the late 1920s, researchers began to investigate the chemical and pharmacologic properties of opioids as well as the clinical aspects of opioid addiction, in an effort to define rules for safer use of opioids, design non-addictive substitutes, and improve pain therapy.

However, it was not until the 1960s that methadone, the first drug to be developed for this purpose, was accepted as legitimate medical practice for treating opioid addiction. Moreover, until recently, federal laws also set in place in the early 20th century prohibited physicians from prescribing opioids to opioid addicts except under highly controlled conditions in clinics known as Opioid Treatment Programs (OTPs). In the year 2000, the Drug Addiction Treatment Act (DATA) greatly expanded the ability of individual physicians to prescribe opioids for opioid addiction outside of the OTPs, allowing office-based treatment with FDA approved medications

for maintenance or detoxification, including prescription of schedule III, IV, or V opioids. Under the act, physicians must obtain specific credentials and are limited in the number of patients they can treat. Currently over 17,000 health care providers are registered, greatly expanding medication-assisted treatment capacity for opioid addiction, as an important response to the prescription opioid addiction epidemic.

Methadone. By the 1940s, research had established methadone as an orally active, long acting opiate that produced physical dependence. This compound gained importance in the 1960s with increasing societal acceptance that solving the problem of drug addiction requires a medical treatment approach in addition to law enforcement activities. Methadone maintenance therapy was developed, primarily for heroin addiction, as a means of relieving addicts' cravings and inducing opioid tolerance that blocked heroin-induced euphoria. This approach was shown to improve psychosocial outcomes for opioid addicts, however, a societal backlash against this form of treatment led to increasingly stringent regulations. Over time, these regulations have given way somewhat to the use of guidelines set in place by professional medical organizations and to accreditation programs.

Until the passage of DATA, all methadone was dispensed in the US in the approximately 1,100 OTPs, under the aegis of the federal Substance Abuse and Mental Health Services Administration (SAMHSA). With the rise of prescription opioid addiction, the population enrolling in these clinics has changed considerably. Most patients enrolling now in suburban and rural areas are addicted to prescription opioids rather than heroin, and about 70% of these prescription opioid abusers are enrolling for the first time. The overall population is younger, whiter, and more likely to be employed. Prescription opioid abusers are also more likely to suffer from chronic pain and to have a psychiatric co-morbidity such as anxiety or depression. Many of these new enrollees have never injected drugs so they have do not suffer from the high rates of bloodborne diseases, such as HIV and hepatitis, found among those who inject illicit drugs. Although methadone prescriptions are now available at individual physicians' offices, there appears to be a patient population that prefers, and may do better in, the highly structured clinic environment. Some providers prefer to give this care within the OTP structure as well.

Naltrexone. Naltrexone, which was first synthesized in 1967, is an orally available opioid receptor antagonist that is chemically related to morphine. Naltrexone was developed for the treatment of opioid addiction in the 1970s by the National Institute on Drug Abuse (NIDA) in

partnership with the Dupont company. Naltrexone has been shown to be safe to take for long periods. The FDA first approved naltrexone in 1984, but the availability of this medication has not had a large impact on the treatment community because of compliance issues.

Naltrexone is not physically reinforcing like methadone and withdrawal symptoms are mild, so there are no adverse consequences to discontinuing treatment. For this reason, naltrexone therapy requires very high motivation on the part of the patient, and compliance is a major problem. The high level of psychosocial support that is required to keep patients on naltrexone therapy adds greatly to the expense of treatment, but has been shown to improve outcomes. Naltrexone therapy can be overridden by a high dose of an opioid agonist, and there is a high potential for opioid overdose, particularly during the first two weeks after discontinuing naltrexone therapy. Naltrexone does not provide pain relief. Oral naltrexone can be highly effective in motivated patients, for example in addicted health care professionals, but most studies have shown poor outcomes.

Sustained release formulations of naltrexone, such as Depotrex or Vivitrol, have been tested for alcohol dependence and may help to alleviate the compliance issues associated with this medication in opioid dependence as well. Proof of concept studies have shown that opioid addicted patients with higher plasma levels of the active metabolite of naltrexone stay in treatment longer. These formulations may make naltrexone a good choice for patients with milder opioid abuse disorders, but they are unlikely to be helpful for patients who need an opioid for the treatment of chronic pain.

Buprenorphine. Buprenorphine was originally developed in the 1960s as an analgesic medication. Buprenorphine is a partial opioid receptor agonist that fits between methadone, a full agonist, and naltrexone, an antagonist. Buprenorphine is thought to be less liable to abuse than other synthetic opioids, has less overdose risk compared to full agonists, and carries fewer withdrawal symptoms, characteristics that suggested its use as a treatment for opioid addiction. It was developed for this purpose through a collaboration between NIDA and Reckitt Benckiser Pharmaceuticals. Pivotal studies were performed in the 1990s, leading to US approval of sublingual buprenorphine tablets as a treatment for opioid addiction in 2002. Buprenorphine is available as a monotherapy (Subutex) and in combination with the abuse deterrent compound naloxone (Suboxone). Buprenorphine prescriptions have risen steadily since its approval.

Buprenorphine was used as a treatment in the largest study to date of prescription opioid dependence, the Prescription Opioid Addiction Treatment Study (POATS), sponsored by McLean Hospital in collaboration with University of California. POATS compared buprenorphine-naloxone therapy of varying durations, combined with counseling of varying intensities, in 653 patients with prescription opioid addiction. These patients were psychiatrically stable, reported little or no heroin use, and about 40% experienced chronic pain.

This study has produced important data on the relationship between patient characteristics and success in treatment for opioid addiction. In the general study population, successful outcomes were associated with older age, the presence of depression, lack of prior treatment, and oral or sublingual abuse of prescription opioids rather than injection use. Chronic pain patients were just as likely as non-chronic pain patients to succeed in treatment, and many had significant pain improvement. Chronic pain patients who had the highest levels of pain relief were more likely to succeed in treatment.

These results strongly suggest that there are clinically meaningful subgroups of opioid abusers who may benefit from different treatment paradigms. This concept may particularly apply to chronic pain patients who, the study showed, for the most part had different reasons for taking opioids compared with “recreational” users. Further research is needed into the most effective treatment protocols for specific patient subgroups. For example, it is unknown how to choose among buprenorphine, methadone, and particularly naltrexone, where there is very little data, for specific types of patients. It is also unknown why it is easier for some individuals than others to escape addiction. Such differences could relate to underlying differences in pharmacology or physiology, varying social structures, and differences in patients’ subjective experiences of addiction, addiction treatment, and/or pain, among other factors.

Buprenorphine and Methadone as Pain Therapies

As mentioned above, buprenorphine was initially developed for pain but was first approved as a maintenance therapy for the treatment of opioid addiction. As a potent analgesic that lasts for about 6 to 8 hours, buprenorphine was increasingly used off-label as a treatment for pain after its approval. In 2010, the FDA approved a 7-day buprenorphine transdermal patch for the management of moderate to severe chronic pain in patients who require continuous opioid analgesia. Buprenorphine has a reasonably good safety profile that makes it an attractive possibility for pain in appropriate patients. However its half-life is highly variable, as are

withdrawal symptoms once it is stopped. There are no long term safety data on buprenorphine in pain patients, and there is some potential for abuse. Clinical studies have shown that it is effective compared to placebo for low back pain, chronic cancer pain, and chronic non-cancer pain. Buprenorphine is expensive, which may limit its use as an analgesic.

Methadone is also an effective analgesic, especially for neuropathic pain. The first clinical trials of methadone for pain were performed in Germany in the 1940s but revealed undesirable side effects. Methadone reduces tolerance to other opioids and stabilizes opioid levels. It is produced as a racemic mixture, and the two enantiomers have different pharmacologic effects, which makes dosing highly variable between patients and even within a single patient. The elimination half-life of methadone is also highly variable. These characteristics have given methadone a reputation for unpredictability. Methadone can kill patients as the result of a single overdose, as the result of accumulated toxicity due to its long and variable half-life, or as the result of drug-drug interactions. Studies have shown some efficacy in the treatment of pain but significant clinical experience or careful mentoring is needed to use methadone safely in this context.

Buprenorphine and Methadone as Drugs of Abuse

As opioid compounds, buprenorphine and methadone are also potential drugs that can be abused. Data from the National Forensic Laboratory Information System shows that these drugs are increasingly found at crime scenes. Methadone was second only to oxycodone and hydrocodone in seizures of narcotic analgesics in the US in the period from 2005 to 2010. Illicit methadone use has risen considerably in recent years, as have overdose deaths. Most illicit methadone comes from individual prescriptions rather than the Opioid Treatment Programs, suggesting that “doctor shopping” and multiple prescriptions are being used to divert these drugs, similar to pain prescriptions. Many of the Florida pain clinics (“pill mills”) that are major sources of misused pain medications had also identified themselves as addiction treatment centers, in order to be able to offer buprenorphine and methadone prescriptions. Recently enacted legislation in Florida has shut down many of these operations, and opioid medication prescriptions of all types are facing greatly increased scrutiny in that state.

Current Management of Patients with Both Chronic Pain and Substance Abuse Disorders

Management of these dual diagnosis patients is difficult, but a few best practices have been established, and others are under investigation.

Pain management in patients receiving pharmacotherapy for addiction. Several lines of evidence suggest that individuals who are dependent on opioids have an altered experience of pain. Studies show that such individuals have less pain tolerance than: their peers who are in remission, control subjects, or siblings who do not have a history of addiction. It is unknown whether this is a pre-existing characteristic that raises the risk for developing addiction, or whether an increased sensitivity to pain occurs as a result of opioid addiction. In either case, it is likely that pain management should be tailored to the specific needs of these individuals.

Although clinical evidence is lacking in many areas, best practices are available for some aspects of pain management in individuals being treating for opioid addiction. In patients on methadone maintenance who experience acute pain, such as surgical or trauma pain, it is thought that the risk of relapse to active drug abuse associated with inadequate pain control may be higher than that associated with the use of opioid analgesics. Methadone maintenance patients with acute pain thus should be treated with opioids, but will require higher doses to overcome the “opioid debt” created by their physical dependence on methadone. Methadone maintenance patients with chronic pain can also be treated with opioids, but must be monitored very closely due to the risk of diversion. Methadone blocks the euphoric effects of opioid pain relievers in these individuals, which may limit their reinforcing effects. Careful coordination with the addiction treatment program is an important aspect of this approach.

In buprenorphine maintenance patients, the most effective approach to acute pain is still in question. For surgical patients, many institutions follow a “Five Day” rule, in which buprenorphine is discontinued five days prior to surgery and the patient is transitioned to a short acting opioid for pain. However, there is no evidence to support this approach to pain management in these patients, and the risks of disrupting the patient’s recovery from opioid addiction are high. Other options might be to continue the buprenorphine and add a short acting opioid at the same time, or to use supplemental doses or divide doses so patients are receiving pain relief via buprenorphine every six to eight hours. There is currently no evidence supporting a specific approach to acute pain management in these individuals.

Buprenorphine maintenance patients who have chronic pain may not benefit from concurrent opioid analgesics, due to the high mu opioid receptor occupancy rate of buprenorphine. Here again, the pain relieving effects of buprenorphine could be utilized by giving buprenorphine every six to eight hours to treat opioid dependence and pain at the same time. This approach is

on-label for opioid addiction but involves an off-label use of sublingual buprenorphine for pain. However, buprenorphine has been shown to provide substantial pain relief with minimal side effects when given this way.

In patients on naltrexone maintenance, very little is known about the most effective means of managing either acute or chronic pain. These patients represent a very complex situation due to the long acting nature of currently used naltrexone formulations, and the need to override mu receptor blockade by naltrexone. Non-opioid pain relievers may be the best option for these individuals but much is still unknown.

Transitioning pain patients to treatment for substance abuse disorders. Chronic pain is a highly complex condition, but as for other chronic conditions there is considerable literature to guide its management. Important concepts, such as promoting patient self-care and using a team-centered approach, are highly applicable to the treatment of opioid addiction as well. Thus practitioners who are already providing careful management of chronic pain should be able to manage addiction effectively as well if it becomes necessary.

Experienced practitioners have identified a number of factors that are likely to promote successful outcomes from addiction treatment. It is important that the primary care physician remain involved in addiction treatment, to provide a broad longitudinal perspective on the patient as an individual, and to ensure that specialty care is integrated most effectively. The choice of pharmacotherapy for opioid addiction should be based on patient characteristics, including the availability of social support and scheduling constraints, such as job or school commitments. Patients in treatment for addiction should be supported with both psychological counseling and urine drug testing, and should be under some form of supervision, whether by a professional or a family member. Many patients benefit from cognitive behavioral therapy that improves their ability to provide self-care. Overall, it is important to have realistic goals for addiction therapies, and to assist patients in taking personal responsibility for their condition and their treatment.

Clinical studies suggest that adequate time and attention to management can prevent full fledged addiction from developing in patients being treated with opioids for chronic pain. However, patients who do become addicted should not be treated with an *ad hoc* approach, but will require an opioid-based therapy and a structured program of care. For this reason, physicians should be prepared to take on the difficult task of having a conversation with patients

if their opioid usage has become problematic, and should know how to assist patients in transitioning to an appropriate treatment program if it becomes necessary.

Possibilities for Future Pharmacotherapeutic Approaches

A number of new pharmacotherapies are in development that may widen the field of therapeutic choices for opioid-addicted individuals.

Probuphine. Probuphine is a subcutaneously implantable 6-month formulation of buprenorphine that is intended to reduce the risk of diversion and improve patient compliance. The implantable formulation releases a constant amount of medication into the bloodstream, and thus may reduce patient drug exposure compared to conventional dosing, and cause fewer side effects. A randomized placebo-controlled trial in 163 patients showed that probuphine was superior to placebo with no significant increase in adverse events, although it is important to note that most of those enrolled were heroin abusers (63%) rather than prescription drug abusers (37%). Probuphine was superior to placebo in a number of outcomes including illicit opioid use, treatment retention, withdrawal symptoms, and several other parameters.

Buprenorphine film. This recently released formulation of buprenorphine is designed to be child resistant so that it reduces the risk of accidental exposure. The film, which is interchangeable with buprenorphine sublingual tablets, dissolves faster and tastes better than the tablets. This formulation has met with limited acceptance and mixed results regarding patient preference. This formulation does not assist with patient compliance or prevent diversion.

Lofexidine. Lofexidine is a non-opioid therapy that is currently available in the United Kingdom. Lofexidine is an alpha-2-adrenergic receptor agonist related to clonidine. It is used for opioid detoxification since it suppresses acute symptoms of withdrawal. Because it is not an opioid, there are no abuse concerns and no need for special regulation. This medication may be attractive to patients who want to get away from the perceived stigma of taking an opioid. A recent open label placebo-controlled study of lofexidine was stopped early due to its highly significant effects over placebo. However, at least one more clinical study is needed before this therapy can be considered for approval in the US.

Vivitrol. Vivitrol is an injectable, extended release form of naltrexone that is given once a month. It was approved for the treatment of alcohol addiction in 2006, and for the treatment of addiction

to heroin or narcotic painkillers in 2010. There is very little evidence for its use in opioid addiction, aside from a randomized, double-blind placebo-controlled trial that was conducted in Russia. This trial showed positive effects on opioid use, drug craving, treatment retention, and other outcomes. Vivitrol is expensive and it blocks pain relief with narcotic pain relievers. It has yet to be widely adopted.

Ibudilast. Ibudilast, also known as AV411, is a novel agent that acts on glial cells to enhance morphine analgesia, reduce opioid tolerance, and suppress opioid withdrawal symptoms. This compound is still in very early development.

Regulatory aspects of developing new medications for opioid addiction. Most studies of new pain medications for registration with the FDA exclude patients with substance abuse disorders, even though these individuals make up 15 to 40% of the chronic pain patient population. Thus there is a high public health need for therapies that are approved for use and shown to be effective in patients with both chronic pain and substance abuse disorders. Pharmaceutical companies might be motivated to perform studies in these patients if they were able to seek a dual indication, for pain and co-morbid addiction, for new medications. There is a scientific rationale for this approach, since pain and addiction, as well as mood disorders and addiction, are likely to share common underlying pathways in the central nervous system. There is also a potential regulatory pathway, because current FDA guidance strongly encourages the use of narrow subpopulations of patients in drug development, encouraging studies focused on individuals with specific genetic characteristics, for example, or differences in drug metabolism. Companies may be able to test therapies that have already been approved for one indication in a sub-population with a specific co-morbidity—for example, chronic pain patients who have developed addiction, or patients with addiction who require pharmacotherapy for pain. This strategy would open up new patient populations for existing medications and might encourage increased use by physicians, thus providing the market incentive that companies need to justify the expense involved in the development of new indications for existing medications.