Opioid Dependence Backgrounder

Newspaper articles and news programs frequently highlight the negative effects of drug dependence, particularly dependence on opioids such as prescription painkillers and heroin. Opioid dependence creates havoc in people's lives, usually causing grave financial, social, and medical burdens for patients and their families, friends and employers, and often fraying the very fabric of society.

Many people have known someone who has been hurt by opioid dependence. But what do we really understand about this disease? How many Americans suffer from opioid dependence, and how did they come to be dependent? How can the condition be treated?

The hopeful news is that there is now an office-based medical treatment modality for people who suffer from this chronic brain disease. The most recent additions to the medical armamentarium are Suboxone® (buprenorphine/naloxone) and Subutex® (buprenorphine), the only FDA-approved medications that any certified doctor may use to treat opioid-dependent patients in an office-based setting. Introduced by Reckitt Benckiser Pharmaceuticals in early 2003, Suboxone is helping treat opioid-dependent patients across the country who suffer from what the World Health Organization categorizes as a chronic, relapsing brain disease.

What are opioids?

Opioids are drugs with opium-like qualities, and they are either derived from opiates (drugs created directly from opium, such as morphine or codeine) or are chemically related to, but not directly derived from, opiates or opium.[1] Opioids include such drugs as methadone; some prescription painkillers, including oxycodone and hydrocodone; buprenorphine; and the illegal drug heroin.

Opioids' Mechanism of Action

Opioids act by attaching to specific proteins called opioid receptors, which are found in the brain, spinal cord, and gastrointestinal tract. When these drugs attach to the opioid receptors, they block the transmission of pain messages to the brain, which is why opioids are highly effective analgesics in relieving chronic and/or acute pain. Opioids can also cause euphoria by affecting certain brain regions that mediate what we perceive as pleasure. Depending on how much of the drugs are taken, opioids can cause an array of side effects, such as drowsiness, constipation, and respiratory depression. Acute respiratory depression resulting from an overdose of opioids can be fatal.[2]

Not all opioids have the same onset of analgesic activity, a fact that is associated with an opioid's abuse potential. Typically, those with a fast onset of action are more likely to be misused and are highly prized on the black market.[3]

History of Opiates

The medicinal properties of opium, which is derived from the juice of the opium poppy, have been known for thousands of years; a grieving Odysseus is served a drink containing opium by a daughter of Zeus in Homer's *Odyssey*, and an early reference to opium in medical writings appeared in those of the Greek philosopher Theophrastus in the 3rd Century BC.[4] In China, opium was widely smoked for centuries and accepted as an aspect of everyday life.

Originally opiates were not the pure compounds that we think of today; it was not until 1806 that a German scientist, Serteuner, synthesized morphine directly from the opium poppy and created the first opiate (he later received a Nobel Prize for this medical breakthrough).[5,6] Other opiates were discovered shortly thereafter, and morphine, codeine and heroin became available as over-the-counter medicines in the U.S. in the early 20th century. Their use was commonly accepted as a remedy for numerous medical conditions, and opiates were also often credited with enhancing the artistic sensibilities of writers and other artists. This easy availability stopped when Congress passed the Harrison Narcotics Act in 1914. This Act made opiate use and distribution illegal,

created the Bureau of Narcotics, set the stage for the arrest and successful prosecution of tens of thousands of prescribing doctors, and essentially created the conditions for a criminal subculture involving opioids. Although initially the Act established a variety of "heroin clinics" to treat addicts, they were all closed during the 1920s due to negative publicity and shifting attitudes concerning heroin and medicine.[7,8]

Today, the manufacture and distribution of narcotics, stimulants, depressants, hallucinogens, anabolic steroids, and chemicals used in the manufacture of controlled substances is regulated by the Controlled Substances Act, Title II of the Comprehensive Drug Abuse Prevention and Control Act, passed by Congress in 1970. This Act, which remains the legal foundation of narcotic use and control today, segregates controlled substances into five "schedules" based on the compounds' medicinal value, harmfulness, and potential for abuse and addiction. These classifications range from Schedule V, the least stringently controlled substances, to the most strictly regulated Schedule I drugs such as heroin and LSD that have no recognized medical value. The 1970 Act also replaced the Bureau of Narcotics with the Drug Enforcement Administration (DEA) to oversee legal compliance with the requirements of the Act. Subsequent legislation over the next several years added the government infrastructure within the U.S. Department of Health and Human Services that currently addresses the many aspects of substance abuse – chief among them are the National Institute on Drug Abuse (NIDA), the Substance Abuse and Mental Health Services Administration (SAMHSA), and the Center for Substance Abuse Treatment (CSAT).[9]

In 2000, Congress passed another seminal piece of legislation affecting treatment for opioid-dependent patients. The Drug Addiction Treatment Act (DATA) allows certified physicians to prescribe Schedule III-V drugs to treat opioid dependence in an office-based setting. To date, buprenorphine, formulated as Suboxone (buprenorphine/ naloxone) and Subutex (buprenorphine), is uniquely qualified under "office-based opioid treatment" (OBOT), and Suboxone is the only medication with FDA approval to treat opioid dependence both in a doctor's office and with take-home maintenance prescriptions. To prescribe Suboxone, doctors must take an 8-hour CME course offered

by the medical societies, notify the government of their intent to treat opioid-dependent patients, and obtain a DEA waiver to become certified to prescribe Suboxone.[10]

What is opioid dependence?

Addiction to a drug is not the same as physical dependence on it. Chronic administration of an opioid, such as may be required for appropriate treatment of pain, can be expected to cause physical dependence. Addiction, however, is associated with extreme behavior that continues, even to the detriment of the individual.

Excessive use of opioids can eventually cause physiological changes in the brain's function and chemistry, resulting in the chronic brain disease of opioid dependence. After long-term use, these changes persist even after the patient has stopped using the drug; it is for this reason that opioid dependence is properly characterized as a chronic, relapsing disease.[11] Dependence is a condition that involves a physical, psychological and behavioral need for the opioid drug that is unrelated to medical necessity for analgesia. More specifically, opioid dependence is defined as the co-occurrence of three or more of the following symptoms:

- Drug tolerance;
- Withdrawal symptoms;
- Use of the drug in larger amounts or for longer periods than required for medical necessity;
- Repeated unsuccessful attempts to decrease or discontinue use;
- Significant time spent obtaining the substance or recovering from its effects;
- Drug use to avoid withdrawal; and
- Foregoing of important activities, or willingness to accept severe physical, social, or professional negative consequences, due to drug use.[12]

How do drug tolerance, dependence, and addiction differ?

Opioid tolerance, dependence, and addiction refer to progressively more severe forms of the disease state caused by excessive use of opioids. Tolerance means that the patient

must use increasingly higher doses of a drug in order to obtain the desired effect, or that a constant dose will give the patient increasingly less effect. Physical dependence is typically associated with tolerance, and also with withdrawal, an adverse physiological effect that occurs when blood/tissue concentrations of a drug decline. Symptoms of withdrawal include extreme nausea, generalized pain, sweating, headache, irritability, and shaking. Psychological dependence involves continued drug use for reasons other than tolerance and withdrawal, such as the experience from a drug's pleasurable effects or to block out or to escape from reality. Addiction describes the most severe form of dependence, under which the patient has uncontrollable cravings for the drug, is willing to risk any adverse consequences to obtain it, and requires ever-higher doses in order to ward off withdrawal and/or to obtain the pleasurable narcotic high associated with the drug.[13]

Causes of dependence

Substances such as opioids that produce euphoria are considered to have high reinforcement potential, which increases the likelihood that they will be taken repeatedly or abused, although most people who take these powerfully reinforcing drugs do not become dependent on them. Although the causes of opioid dependence vary from person to person, certain factors, such as the drug itself, genetics and the individual's environment, are known to be important in its development. Some people appear to be genetically predisposed to dependence, raising the possibility that susceptibility to the disease may be hereditary. Also, individual absorption levels of the drug into the blood can vary widely for different people, thus causing very different effects. Lastly, substance abuse, which can lead to dependence, is often highly influenced by societal norms and peer pressure.[14]

Opioid dependence in the U.S.

Opioid dependence is a chronic, relapsing brain disease that can, and does, affect people in all walks of life and at all sociodemographic levels. In particular, abuse of opioid prescription painkillers such as oxycodone, hydrocodone, and fentanyl is increasing rapidly, and in some parts of the country has become a significant medical and social

problem. There is no unique profile of people who become dependent on opioid drugs, nor does opioid dependence result from a character flaw.

During 2006, according to the *National Survey on Drug Use and Health* conducted by SAMHSA, approximately 5.2 million teenagers and adults used prescription painkillers for nonmedical purposes. This same survey also reported that the nonmedical use of painkillers drew the largest number of new users than any other illicit drug category - 2.2 million persons used pain relievers nonmedically for the first time within the past 12 months.[15]

Treatment for Opioid Dependence

Treating opioid dependence clearly offers many medical and personal benefits to patients and their families, as well as to society as a whole. Several forms of treatment are available, and until the advent of office-based opioid treatment with Suboxone in 2003, they included drug-free psychosocial counseling in an inpatient or outpatient setting, "12-step" programs, opioid pharmacotherapy with methadone in specialized treatment or rehab centers, and certain specialized "rapid detox" approaches. With office-based treatment, a new treatment approach exists, and it is now possible for any doctor to become certified to treat opioid dependence using Suboxone in the privacy of his or her office, just as other chronic diseases like diabetes or depression are treated.

Treatment has not always been so accessible. Prescribing one opioid to treat dependence on another has been the subject of much controversy, and for much of the 20th century office-based treatment was illegal and led to physicians being prosecuted and convicted for doing so.[16] Unfortunately, the consequence of such tight scrutiny was limited availability of treatment options for opioid-dependent patients.

Methadone

By the early 1960s, tremendous national concern arose about the societal consequences of heroin use. At that time, researchers were beginning to show successful results with methadone to treat heroin dependence, and early research showed great promise in

reducing heroin use and its associated criminal activity. Patients on methadone often recovered sufficiently to enter the workforce again with improved general health. Despite these successes, however, methadone as a treatment was highly stigmatized, and concerns about drug diversion, appropriate use, and potential harm to children were high among law enforcement officials, the general public, and advocates for drug-free treatment alternatives [17]

Finally, thanks to the efforts of the then-White House Action Office for Drug Abuse Prevention (SAODAP), in 1973 methadone was accepted by the FDA as a treatment for opioid addiction in special methadone clinics or rehab centers and hospital pharmacies.[18] Strict regulations governing its use are still in place today. While the introduction of this treatment modality was a major positive step forward for treatment of this disease, methadone – a Schedule II narcotic – carries disadvantages. With limited exceptions, methadone must be administered in a drug treatment clinic, which means that patients must visit a clinic for daily therapy. As a "full opioid agonist," overly high doses of methadone can cause severe, sometimes fatal, respiratory depression, and withdrawal from methadone has been reported to be very difficult.[19] Furthermore, the drug itself is highly addictive – the DEA classifies methadone as a Schedule II narcotic that requires stringent control – and it carries enough abuse potential that it has become a street drug of choice in some instances.

LAAM

The FDA approved another medical therapy, LAAM, in 1994 for the treatment of heroin addiction, but like methadone its use was also restricted to special treatment programs and clinics.[20] Due to subsequent concerns about its potential for creating cardiovascular problems, LAAM was reduced to a second-line treatment, and eventually withdrawn from the U.S. market.[21]

Office-Based Opioid Treatment

In October 2000, Congress passed the Drug Addiction Treatment Act (DATA) allowing certified physicians to prescribe Schedule III-V drugs to treat opioid dependence in an

office-based setting. Suboxone (buprenorphine/naloxone) and Subutex (buprenorphine) are uniquely qualified for office-based treatment under DATA, and are the only Schedule III-V medications with FDA approval to treat opioid dependence in a doctor's office and with take-home maintenance prescriptions. This is the first time in more than 80 years that physicians have been able to treat opioid-dependent patients in an office-based setting.[22] The fact that *any* doctor, including general practitioners and primary care doctors, can become certified to treat opioid dependence with Suboxone has already greatly expanded patient access to treatment. As office-based treatment with Suboxone gains wider use, this intervention modality carries the potential to make treatment available across the country, in rural areas and small towns as well as in large metropolitan areas.

Suboxone

Two molecules comprise Suboxone – buprenorphine and naloxone. Buprenorphine is unique among treatment options for opioid dependence in that it is a partial opioid agonist. What this means is that, like any other opioid agonist, the molecules of buprenorphine bind to the same opioid receptors in the brain that otherwise would bind to molecules of opioid painkillers or heroin. Buprenorphine binds tightly to the receptors and is not easily displaced by other opioids (like a parking space in the brain that has been taken, it blocks the activity of other opioids). But because buprenorphine is only a partial opioid agonist (rather than a full agonist, like methadone, heroin, or opioid painkillers), it does not activate the receptors to the same degree as full agonists do.

All of these features of buprenorphine mean that patients should derive less reinforcement from Suboxone, that any additional reinforcement from other opioids is greatly blunted if patients attempt to use them while being treated with Suboxone, that Suboxone effectively suppresses withdrawal symptoms and cravings, and that patients are likely to have less severe symptoms of physiological withdrawal when taken off the drug after chronic dosing. Perhaps most importantly, because it is a partial agonist, buprenorphine by itself does not lower respiration to the same extent as a full opioid agonist. However, as with all opioids, when buprenorphine is abused intravenously or in

combination with other Central Nervous System depressants, serious adverse events have been reported.

The molecule naloxone, an opioid antagonist, is added to Suboxone to discourage abuse and diversion. When Suboxone is used as prescribed, the naloxone in the tablets should have no perceived effect,[23] but if Suboxone is taken by injection by an opioid-dependent person, then the naloxone precipitates severe withdrawal symptoms. The deterrent effect of naloxone should lower Suboxone's abuse potential.

There is also a buprenorphine formulation called Subutex, which does not contain naloxone. In the U.S., Subutex may be used for initial "induction" to buprenorphine under a doctor's direct supervision and for patients allergic to naloxone. Subutex is not routinely recommended for at-home maintenance therapy in the U.S.

Phases of Pharmacotherapeutic Treatment

Whether patients receive Suboxone or methadone, they typically undergo four phases of treatment, which should generally be coupled with psychosocial counseling.

- Induction: During this first phase, patients are transferred from their opioid of abuse, such as prescription painkillers or heroin, to a pharmaceutically pure opioid such as Suboxone or methadone. The induction phase will vary in length according to patient need and response.
- Stabilization: After induction, the stabilization phase begins. During this time, the patient should have a reduction in cravings for the opioid of abuse and should have few or no side effects. Also during the stabilization phase the doctor modifies the patient's dose to find the most appropriate level to enable the patient to enter into the maintenance phase.
- Maintenance: During the maintenance phase, the patient does well on a constant dose of the drug while under medical supervision.
- Medically supervised withdrawal: In the final stage of treatment for opioid dependence, formerly referred to as detoxification, some patients may reach a point at which they can stop receiving treatment with opioids completely. During

this last phase, the doctor gradually reduces the patient's dose of medication until the patient is drug-free. This phase is highly variable in duration, and because of the chronic nature of this disease, some patients may require lifelong treatment.[24]

Clinical Information about Suboxone/Subutex[25]

Suboxone/Subutex are indicated for use in the treatment of opioid dependence in adults who are 16 years of age and older. They are not indicated for patients under the age of 16. Suboxone/Subutex are available in 2 mg and 8 mg sublingual tablets.

Determination of efficacy: The two drugs' indication is based on data from double-blind studies of buprenorphine sublingual tablets, with and without naloxone, and of buprenorphine sublingual solutions in conjunction with psychosocial counseling. In a double, placebo controlled study, patients who were treated with Suboxone/Subutex sublingual tablets (16 mg/day) demonstrated a greater reduction in their use of non-study opioids while in treatment compared to patients who received placebo. In a separate double-blind, double-dummy, parallel-group study comparing buprenorphine solution to a full agonist active control, treatment with the buprenorphine solution (8 mg/day) showed greater effectiveness in keeping patients in treatment and in reducing their use of opioids while in treatment than the active control group.

Furthermore, a dose-controlled, double-blind, parallel group of patients was treated with various doses of buprenorphine sublingual solutions (1 mg, 4 mg, 8 mg, and 16 mg/day). In this group, patients exhibited higher treatment retention rates and a greater reduction in their use of non-study opioids when treated with the three highest tested doses of the solution (4 mg, 8 mg, and 16 mg/day) compared to the 1 mg dose.

Safety data: In total, safety data included 3,214 opioid-dependent patients who were treated with buprenorphine. Clinical studies have shown that the most common side effects of buprenorphine include headache, pain, asthenia, infection, constipation, nausea, anxiety, depression, insomnia, rhinitis, sweating, and withdrawal syndrome. As with other opioid agonists, there is also the risk of respiratory depression, though because

buprenorphine is a partial opioid agonist, the risk with buprenorphine is less than that of full opioid agonists, such as prescription opioid painkillers, heroin, and methadone.

About Reckitt Benckiser Pharmaceuticals, Inc.

Reckitt Benckiser Pharmaceuticals Inc. is a specialty pharmaceutical company that markets Suboxone® (buprenorphine HCl/naloxone HCl dihydrate [2 mg/0.5 mg and 8 mg/2 mg]) C-III Sublingual Tablets and Subutex® (buprenorphine HCl [2 mg and 8 mg]) C-III Sublingual Tablets, formulations of buprenorphine used to treat opioid dependence in a medical office-based setting. Suboxone and Subutex, manufactured by Reckitt Benckiser Healthcare Ltd., are the only controlled medications under the Drug Addiction Treatment Act of 2000 approved by the FDA for office-based treatment of opioid dependence. Reckitt Benckiser Pharmaceuticals Inc. is committed to expanding access to medical therapies for patients suffering from the chronic, relapsing brain disease of opioid dependence. For more information, visit **suboxone.com** or **opioiddependence.com**. Reckitt Benckiser Pharmaceuticals Inc. is a wholly owned subsidiary of Reckitt Benckiser PLC, a publicly traded UK firm.

Statement of Fair Balance

SUBOXONE® (buprenorphine/naloxone sublingual tablets) is indicated for the treatment of opioid dependence.

Buprenorphine, usually by the intravenous route, in combination with benzodiazepines or other CNS depressants (including alcohol) has been associated with significant respiratory depression and death.

SUBOXONE has potential for abuse and produces dependence of the opioid type with a milder withdrawal syndrome than full agonists.

Cytolytic hepatitis and hepatitis with jaundice have been observed in the addicted population receiving buprenorphine.

There are no adequate and well controlled studies of SUBOXONE (a Category C medication) in pregnancy.

Caution should be exercised when driving cars or operating machinery.

Always store buprenorphine containing medications safely and out of the reach of children and destroy any unused medication appropriately.

The most commonly reported adverse events with SUBOXONE include headache (36%, placebo 22%), withdrawal syndrome (25%, placebo 37%), pain (22%, placebo 19%), insomnia (14%, placebo 16%), nausea (15%, placebo 11%), and constipation (12%, placebo 3%). Please see full prescribing information for a complete list.

[1] Information on file (Reckitt Benckiser, Suboxone Learning Series, Module 1, p.3)
[2] National Institute on Drug Abuse. Research Report Series – Prescription Drugs: Abuse and Addiction. http://165.112.78.61/ResearchReports/Presciption/presciption2.html
[3] Information on file (Reckitt Benckiser, Suboxone Learning Series, Module 1, p.16)
[4] Information on file (Reckitt Benckiser, Suboxone Learning Series, Module 1, p.3)
[5] Gustein, H.B. & Akil, H. Opioid analgesics. In Hardman, J.G., Limbird, L.E. & Gilman, A.G., eds. Goodman & Gilman. The Pharmacological Basis of Therapeutics. 10th ed. New York: McGraw- Hill: 2001. 529-619.
[6] Keel, R.O. University of Missouri at St. Louis, http://www.umsl.edu/~rkeel/180/drughistory.htm, 20 October 2004.
[7] Information on file (Reckitt Benckiser, Suboxone Learning Series, Module 1)
[8] Keel, R.O., *op. cit*.
[9] *Ibid*.
[10] Information on file (Reckitt Benckiser, Suboxone Learning Series, Module 1, p. 11)
[11] Information on file (Reckitt Benckiser, Suboxone Learning Series, Module 1)
[12] *Diagnostic and Statistical Manual of Mental Disorders.* 4th edition (DSM-IV-TR). American Psychiatric Association, 2000.
[13] Information on file (Reckitt Benckiser, Suboxone Learning Series, Module 1, pp. 17-19)
[14] Information on file (Reckitt Benckiser, Suboxone Learning Series, Module 1, p. 25)
[15] Substance Abuse and Mental Health Services Administration. (2007). *Results from the 2006 National Survey on Drug Use and Health: National Findings* (Office of Applied Studies, NSDUH Series H–27, DHHS Publication No. SMA 05–4061). Rockville, MD.
[16] Jaffe, J.H. & O'Keeffe. (2003). From morphine clinics to buprenorphine: regulating opioid agonist treatment of addiction in the United States. *Drug and Alcohol Dependence,* 70, S3-S11.
[17] *Ibid*
[18] *.Ibid*.
[19] White J.M. and Irvine, R.J. (1999). Mechanisms of fatal opioid overdose. *Addiction*. 94 (7): 961-72. Also, Information for health professionals data sheet, Methadone syrup. http://www.medsafe.govt.nz/Profs/Datasheet/m/Methadonesyr.htm. 4 December 2002.
[20] Information on file (Reckitt Benckiser, Suboxone Learning Series, Module 3, p. 10)
[21] Jaffe, J.H*., op. cit*
[22] Information on file (Reckitt Benckiser, Suboxone Learning Series, Module 3, p. 3)
[23] Information on file (Reckitt Benckiser, Suboxone Learning Series, Module 4, p.5)
[24] Information on file (Reckitt Benckiser, Suboxone Learning Series, Module 3, p. 7)
[25] Suboxone/Subutex Package Insert