



Medication Management of Opioid Dependence

3 CE hours

By: Kathryn Brohl, MA, LMFT

Learning objectives

- ♦ Define opioid dependence.
- ♦ Understand the diagnosis of opioid dependence.
- ♦ Describe opioid withdrawal.
- ♦ Understand the history of opioid use in the United States and related legal implications.
- ♦ Understand what opioid-dependent populations benefit from methadone and buprenorphine medical management.
- ♦ Understand why methadone provides effective medical management for opioid dependence.
- ♦ Understand why methadone can be used with pregnant women.
- ♦ Understand how buprenorphine is used with opioid dependence.
- ♦ Understand different research that validates medical management for opioid dependence.
- ♦ Provide treatment information in early recovery with health care and counseling professionals.

Jeff's story

Jeff was the third child born to professionals who adored their son. A rambunctious and curious child from birth, Jeff was not an A-student, but he was exceedingly bright, with interests in music and literature as well as a love for baseball. Sports came easily to him, and at the age of 10 he was the lead pitcher on a traveling baseball team. Jeff's dream was to get into the Major League and play for the Mets. His parents were diligent supporters and often traveled with the team, lending their support and encouragement.

Sadly, a shoulder injury sidelined the young man at age 16, and he was told an operation could fix the problem. Jeff, with his usual straight-ahead attitude, went for it. The operation proved to be more painful than the teen had anticipated, but the doctor prescribed pain medication, OxyContin, and it greatly helped Jeff's discomfort. As a matter of fact, it actually made Jeff feel good, so good, in fact, that when it came time to wean himself off the meds, he was not willing. He'd never experienced this feeling before, and while he told his parents he'd stopped his use, it continued after he returned to playing baseball.

Jeff didn't have any trouble getting the painkillers; there were plenty of people selling them. The once well-intended, benign use to relieve pain began to turn into abuse and then an addiction/dependence. Jeff became more concerned about getting the medication than getting to school on time, or practicing baseball, and he felt terribly guilty. A couple times he tried stop, but then he would get sick, and sought the pills to feel better.

His addiction was turning into a nightmare, and he was ashamed to tell his parents. They came upon the truth when they learned that Jeff had taken all of the money out of his savings account, but not before he began to behave erratically. Jeff's folks had a difficult time thinking that their son could have a drug problem because they thought they had done everything to prevent it from occurring. They watched him carefully throughout his childhood and adolescence, and never failed to mention the danger of using drugs.

Yet, the idea of pain medication as an addiction had never entered their minds. Didn't young people generally smoke marijuana, drink alcohol, or take ecstasy, they wondered?

After several days and much questioning, Jeff finally admitted to his addiction/dependence, and with even greater trepidation, his parents guiltily admitted him into a detox unit at local hospital. But while Jeff was getting medical attention and counseling during this time, his parents and he still had to decide what he was going to do when he was released from detox. The physician at the facility suggested that Jeff might have a very difficult time in early recovery without some form of medication management, coupled with counseling, and a suggested methadone maintenance regimen. He also referred him to a licensed mental health professional.

At this point, Jeff and his parents thought that this would simply extend his addiction, but the doctor told them that with careful supervision and counseling, Jeff's chances of sobriety long-term were good.

Introduction

In recent years, opiate dependence has become a catastrophic problem in the United States, causing thousands, especially younger people, to lose their lives, and leaving loved ones behind to question these senseless losses. People included in this grave epidemic come from the full spectrum of socio-economic backgrounds. Sadly, approximately 9 percent of the population is believed to misuse opiates over the course of their lifetimes, including illegal drugs like heroin and prescription pain medications such as Oxycontin. (Opiate drugs include heroin, morphine, codeine, Oxycontin, Dilaudid, methadone, and others.) It is an addiction, where, truly, no one gets left behind.

Prescription and OTC drugs and the brain

Taken as intended, prescription and OTC drugs safely treat specific mental or physical symptoms. But when taken in different quantities or when such symptoms aren't present, they may affect the brain in ways very similar to illicit drugs. For example, stimulants such as Ritalin increase alertness, attention, and energy the same way cocaine does – by boosting the amount of the neurotransmitter dopamine.

Opioid pain relievers like OxyContin attach to the same cell receptors targeted by illegal opioids like heroin. Prescription depressants produce sedating or calming effects in the same manner as the club drugs GHB and rohypnol by enhancing the actions of the neurotransmitter GABA (gamma-aminobutyric acid). When taken in very high doses, dextromethorphan acts on the same glutamate receptors as PCP or ketamine, producing similar out-of-body experiences.

When abused, all of these classes of drugs directly or indirectly cause a pleasurable increase in the amount of dopamine in the brain's reward pathway. Repeatedly seeking to experience that feeling can lead to addiction.

Opioids can produce drowsiness, cause constipation, and depending upon the amount taken, depress breathing. The latter effect makes opioids particularly dangerous, especially when they are snorted or injected or combined with other drugs or alcohol.

CNS depressants slow down brain activity and can cause sleepiness and loss of coordination. Continued use can lead to physical dependence and withdrawal symptoms if discontinuing use. Dextromethorphan can cause impaired motor function, numbness, nausea or vomiting, and increased heart rate and blood pressure. On rare occasions, hypoxic brain damage – caused by severe respiratory depression and a lack of oxygen to the brain – has occurred from the combination of dextromethorphan with decongestants often found in the medication.

Deaths from opioid pain relievers exceed those from illegal drugs. Opioid pain relievers have the potential for addiction, and this risk is amplified when they are abused. Also, as with other drugs, abuse of prescription and OTC drugs can alter a person's judgment and decision making, leading to dangerous behaviors such as unsafe sex and drugged driving.

Drug abuse and addiction/dependence changes the way the brain works, resulting in compulsive behavior focused on drug seeking and use, despite often devastating consequence. These behaviors are the essence of addiction. Consequently, drug abuse/addiction treatment must address these brain changes, both in the short and long term.

When people addicted to opioids first stop, they undergo withdrawal symptoms, which may be severe pain, diarrhea, nausea and vomiting. (Note: Throughout this course, “addiction” and “dependence” will be used interchangeably to describe the same condition.)

Medications can be helpful in this detoxification stage to ease craving and other physical symptoms, which often prompt relapse. However, this is just the first step in treatment. Medications may also become an essential component of an ongoing treatment plan, enabling opioid-addicted persons to regain control of their health and their lives.

Medications developed to treat opioid addiction work through the same receptors as the addictive drug, but are safer and less likely to produce the harmful behaviors that characterize addiction.

Three types include:

1. Agonists that activate opioid receptors.
2. Partial agonists that also activate opioid receptors but produce a diminished response.
3. Antagonists that block the receptor and interfere with the rewarding effects of opioids.

Physicians prescribe a particular medication based on a patient's specific medical needs and other factors. Effective medications include:

- **Methadone** (Dolophine or Methadose), a slow-acting, opioid agonist. Methadone is taken orally, so that it reaches the brain slowly, dampening the “high” that occurs with other routes of administration while preventing withdrawal symptoms. Methadone has been in use since the 1960s to treat heroin addiction and is still an excellent treatment option, particularly for patients who do not respond well to other medications; however, it is only available through approved outpatient treatment programs, where it is dispensed to patients on a daily basis.
- **Buprenorphine** (Subutex, Suboxone), a partial opioid agonist. Buprenorphine relieves drug cravings without producing the “high” or dangerous side effects of other opioids. Suboxone is a novel formulation taken orally that combines buprenorphine with naloxone (an opioid antagonist) to ward off attempts to get high by injecting the medication. If an addicted patient were to inject Suboxone, the naloxone would induce withdrawal symptoms, which are averted when taken orally as prescribed. The FDA approved buprenorphine in 2002, making it the first medication eligible to be prescribed by certified physicians through the Drug Addiction Treatment Act. This approval eliminates the need to visit specialized treatment clinics, expanding treatment access.

- **Naltrexone** (Depade, Revia) an opioid antagonist. Naltrexone is not addictive or sedating and does not result in physical dependence; however, poor patient compliance has limited its effectiveness. Recently an injectable long-acting formulation of naltrexone called Vivitrol received FDA approval for treating opioid addiction. Given as a

monthly injection, Vivitrol should improve compliance by eliminating the need for daily dosing. To avoid withdrawal symptoms, Vivitrol should be used only after a patient has undergone detoxification. Vivitrol provides an effective alternative for individuals who are unable to or choose not to engage in agonist-assisted treatment.

Benefits of medication-assisted treatment

Scientific research has established that medication-assisted treatment of opioid addiction increases patient retention and decreases drug use, infectious disease transmission, and criminal activity. For example, studies among criminal offenders, many of whom enter the prison system with drug abuse problems, showed that methadone treatment begun in prison and continued in the community upon release extended the time parolees remained in treatment, reduced further drug use, and produced a three-fold reduction in criminal activity.

Research has also demonstrated that methadone maintenance treatment is beneficial to society, cost-effective, and pays for itself in basic economic terms. A study of the cost benefits of methadone maintenance treatment showed that the costs to society of the criminal activities related to active heroin use can run as high as four times more than the costs for methadone maintenance treatment (Harwood et al., 1988).

Through the New York State Department of Substance Abuse Services, NIDA researchers have estimated the yearly costs to maintain an opioid addict in New York are:

- Untreated and on the street (\$43,000).
 - In prison (\$34,000).
 - In a residential drug-free program (\$11,000).
 - In methadone maintenance treatment (\$2,400).
- (New York State Committee of Methadone Program Administrators, 1991).

As early as the 1960s, methadone gained recognition as an effective treatment for heroin addiction. Naltrexone, an opioid receptor blocker, joined the medications treatment inventory in 1984. It proved to be highly effective in reversing the effects of opiate overdose, but poor treatment adherence has hampered its utility to promote abstinence.

Buprenorphine, the newest medication, is a long-acting partial agonist that acts on the same receptors as heroin and morphine, relieving drug cravings without producing the same intense “high” or dangerous side effects. These medications, along with effective behavioral treatments and outreach efforts, have not only reduced injection drug use in this country, but have also helped reduce the spread of HIV/AIDS from a peak of more than 25,000 new cases in 1993 to fewer than 10,000 cases in 2003.

This course will focus on medication maintenance treatment for substance abuse and addiction, as well as its medication management and treatment implications. Related, validating research on its use for opioid addiction will further be described. An additional section of the course will explain why methadone is used successfully with pregnant women, a seemingly counter-intuitive medication management intervention.

UNDERSTANDING THE CLASS OF DRUGS KNOWN AS OPIOIDS

Heroin, morphine, and some prescription painkillers (e.g., OxyContin, Vicodin, and Fentanyl) belong to the class of drugs known as opiates. They act on specific (opiate) receptors in the brain, which also interact with naturally produced substances known as endorphins or enkephalins, which are important in regulating pain and emotion.

And while prescription painkillers are highly beneficial medications when used as prescribed, opiates as a general

class of drugs have significant abuse liability. Currently, approximately 1 million people in the United States are addicted to heroin (Office of National Drug Control Policy, 2000), and more than 3 million people over the age of 12 have used heroin at least once (National Survey on Drug Use and Health, NSDUH, 2004). And an estimated 1.4 million people are dependent on or abusing other opiate drugs, including prescription painkillers (NSDUH, Ibid).

Opioid dependence

Opioid dependence falls under the DSM-IV-TR Criteria for Substance Dependence (American Psychiatric Association, 2000).

DSM-IV-TR

It is a maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

1. Tolerance, as defined by either of the following:

- a. A need for markedly increased amounts of the substance to achieve intoxication or desired effect.
 - b. Markedly diminished effect with continued use of the same amount of the substance.
2. Withdrawal, as manifested by either of the following:
 - a. The characteristic withdrawal syndrome for the substance (refer to Criteria A and B of the criteria sets for withdrawal from the specific substances).

- b. The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms.
- 3. The substance is often taken in larger amounts or over a longer period than was intended.
- 4. There is a persistent desire or unsuccessful efforts to cut down or control substance use.
- 5. A great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects.
- 6. Important social, occupational, or recreational activities are given up or reduced because of substance use.
- 7. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

ICD-10 Clinical Description (World Health Organization, 2006)

A cluster of physiological, behavioral, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviors that once had greater value. A central descriptive characteristic of the dependence syndrome is the desire (often strong, sometimes overpowering) to take psychoactive drugs (which may or may not have been medically prescribed), alcohol, or tobacco. There may be evidence that return to substance use after a period of abstinence leads to a more rapid reappearance of other features of the syndrome than occurs with nondependent individuals. (World Health Organization, 2006)

A definite diagnosis of dependence should usually be made only if three or more of the following have been present together at some time during the previous year:

- A strong desire or sense of compulsion to take the substance.
- Difficulties in controlling substance-taking behavior in terms of its onset, termination, or levels of use.
- A physiological withdrawal state when substance use has ceased or been reduced, as evidenced by the characteristic withdrawal syndrome for the substance or use of the same (or closely related) substance with the intention of relieving or avoiding withdrawal symptoms.
- Evidence of tolerance, such that increased doses of the psychoactive substance are required in order to achieve effects originally produced by lower doses (clear examples of this are found in alcohol- and opiate-dependent individuals who may take daily doses sufficient to incapacitate or kill non-tolerant users).
- Progressive neglect of alternative pleasures or interests because of psychoactive substance use and increased

amount of time necessary to obtain or take the substance or to recover from its effects.

- Persisting with substance use despite clear evidence of overtly harmful consequences, such as harm to the liver through excessive drinking, depressive mood states consequent to periods of heavy substance use, or drug-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm.

ICD-10 Diagnostic Criteria for Research (World Health Organization, 2006)

Three or more of the following manifestations should have occurred together for at least one month or, if persisting for periods of less than one month, should have occurred together repeatedly within a 12-month period:

- A strong desire or sense of compulsion to take the substance.
- Impaired capacity to control substance-taking behavior in terms of its onset, termination, or levels of use, as evidenced by the substance often being taken in larger amounts or over a longer period than intended, or by a persistent desire or unsuccessful efforts to reduce or control substance use.
- A physiological withdrawal state when substance use is reduced or ceased, as evidenced by the characteristic withdrawal syndrome for the substance or by use of the same (or closely related) substance with the intention of relieving or avoiding withdrawal symptoms.
- Evidence of tolerance to the effects of the substance, such that there is a need for significantly increased amounts of the substance to achieve intoxication or the desired effect, or a markedly diminished effect with continued use of the same amount of the substance.
- Preoccupation with substance use, as manifested by important alternative pleasures or interests being given up or reduced because of substance use; or a great deal of time being spent in activities necessary to obtain, take, or recover from the effects of the substance.
- Persistent substance use despite clear evidence of harmful consequences, as evidenced by continued use when the individual is actually aware, or may be expected to be aware, of the nature and extent of harm.

The spectrum of prescription drug abuse includes:

1. Taking someone else's prescription to self-medicate.
2. Taking a prescription medication in a way other than prescribed.
3. Taking a medication to get high.

A brief history of opioid addiction

1860-1910 – Although opioids have been used as pain medications and anti-anxiety drugs throughout recorded history, it was not until the U.S. Civil War of 1861-1865 that widespread prevalence of opioid addiction was documented in the United States (Hentoff, 1965). The synthesis of heroin

in 1874 and its commercial marketing as a “wonder drug” contributed to a pattern of iatrogenic addiction that continued into the early 1900s, with physicians, pharmacists, and patent medicine salesmen dispensing narcotics freely to patients who were primarily middle-aged, middle-class women (Courtwright,

1992; United Nations Department of Social Affairs, 1953; Acker, 2002). The Institute of Medicine estimated that by 1900, perhaps 300,000 Americans were addicted to opiates (Courtwright, 1992).

1910-1950 – Between 1910 and 1950, opioid addiction was rarely prevalent among U.S. patients inadvertently addicted to a medical cure. The Institute of Medicine describes how successive waves of immigration and urbanization contributed to a population of opioid abusers who were in their teens or early 20s, unmarried, poor, primarily male, ethnic minorities who experimented with drugs for nonmedical purposes (Courtwright, 1992).

1950-Present – Intravenous use of heroin intensified in the United States after WWII, reaching epidemic proportions in urban centers during the 1950s and 1960s (Joseph, Stancliff,

and Langrod, 2000). In 1967, the National Survey on Drug Use and Health (NSDUH) began collecting data on heroin use. The survey documents dramatic increases in the initiation of heroin use during the early 1970s and between 1995 and 2002 (Substance Abuse and Mental Health Services Administration, 2005), when the annual number of new heroin users ranged from 121,000 to 164,000. The National Institute on Drug Abuse (NIDA) reports that, during this period, most new users were age 18 or older (on average, 75 percent) and most were male (National Institute on Drug Abuse, 2005a). The 2003 NSDUH found that an estimated 3.7 million Americans had used heroin at some time in their lives and 314,000 in the past year. The group that represented the highest number of those users was age 26 or older (National Institute on Drug Abuse, 2005a). NIDA also reports that heroin use in 2003 was stable at low levels (National Institute on Drug Abuse, 2005b).

Opiates create physical dependence

People rely on the drug to prevent symptoms of withdrawal. Over time, greater amounts of the drug become necessary to produce the same effect. And the time it takes to become physically dependent varies with each individual.

Prescription and OTC drugs may be abused in one or more of the following ways:

- **Taking a medication that has been prescribed for somebody else.** Unaware of the dangers of sharing medications, people often unknowingly contribute to this form of abuse by sharing their unused pain relievers with their family members. Most teenagers who abuse prescription drugs are given them for free by a friend or relative.
- **Taking a drug in a higher quantity or in another manner than prescribed.** Most prescription drugs are dispensed orally in tablets, but abusers sometimes crush the tablets and snort or inject the powder. This hastens the entry of the drug into the bloodstream and the brain and amplifies its effects.
- **Taking a drug for another purpose than prescribed.** All of the drug types mentioned can produce pleasurable effects at sufficient quantities, so taking them for the purpose of getting high is one of the main reasons people abuse them. ADHD drugs like Adderall are also often abused by students for their effects in promoting alertness and concentration.

Opioid intoxication

Opioid intoxication is a condition caused by use of opioid-based drugs, which include morphine, heroin, oxycodone, and the synthetic opioid narcotics. Prescription opioids are used to treat pain. Intoxication or overdose can lead to a loss of alertness, or unconsciousness. Symptoms of opioid intoxication can include breathing problems, and breathing may stop; extreme sleepiness or loss of alertness, and small pupils.

Some people even withdraw from opiates after being given such drugs for pain while in the hospital without realizing what is happening to them. They think they have the flu, and because they don't know that opiates would fix the problem, they don't crave the drugs.

The opioid-dependent person generally uses opioids several times each day. Each use causes an elevation in mood, and the user feels "high." This high is followed by a rapid decline in mood and functional state. The user no longer feels high and may begin to feel sick. At the end of the day, or in the morning, the user feels quite sick as a result of opioid withdrawal.

Overall, a typical day includes several cycles of elevated and depressed mood and function state. As an opioid dependent person uses opioids for a period of time – weeks or months – the person's level of physical dependence makes it less likely that he or she will experience the "high." Continued drug use results from a desire to avoid the depressions and physical symptoms associated with opioid withdrawal. In the story shared earlier about Jeff, he was literally unable to stop his opioid use on his own because of this withdrawal cycle.

Opiate withdrawal refers to the wide range of symptoms that occur after stopping or dramatically reducing opiate drugs after heavy and prolonged use (several weeks or more). When the person stops taking the drugs, the body needs time to recover, and withdrawal symptoms result. Withdrawal from opiates can occur whenever any chronic use is discontinued or reduced.

Early symptoms of withdrawal include:

- Anxiety.
- Muscle aches.
- Increased tearing.
- Insomnia.
- Runny nose.
- Sweating.
- Yawning.
- Agitation.

Late symptoms of withdrawal include:

- Abdominal cramping.
- Diarrhea.
- Dilated pupils.
- Goose bumps.
- Nausea.
- Vomiting.

Prescription Opioids (Abuse): Hydrocodone, Oxycodone, Codeine

Health Effects

Acute	Pain relief, drowsiness, nausea, constipation, euphoria in some. When taken by routes other than as prescribed (e.g., snorted, injected), increased risk of depressed respiration, leading to coma, death. CDC reports marked increases in unintentional poisoning deaths since late the 1990s, due mainly to opioid pain reliever overdose (often in combination with alcohol or other drugs).
Long-term	Tolerance, addiction.
In combination with alcohol	Dangerous slowing of heart rate and respiration, coma, or death.
Withdrawal symptoms	Restlessness, muscle and bone pain, insomnia, diarrhea, vomiting, cold flashes with goose bumps (“cold turkey”), and leg movements.

Associated Special Vulnerabilities/Populations

Youth	8-10 percent of high school seniors have used Vicodin non-medically in the past year; ~5 percent have abused OxyContin.
Pregnancy	Spontaneous abortions; low birth weight.
Older Adults	The higher prevalence of pain in this population renders a greater number of prescriptions written for opioid medications. Unintentional misuse or abuse could have more serious health consequences for elderly patients because of comorbid illnesses (and multiple prescriptions), potential for drug interactions, and age-related changes in drug metabolism.

Treatment options

Medications	• Methadone. • Buprenorphine. • Naltrexone (short and long-acting).
Behavioral Therapies	Behavioral therapies that have proven effective for treating addiction to illicit opioid drugs, such as heroin, may be useful in addressing prescription opioid addiction.

Opioid withdrawal reactions are very uncomfortable but are not, in general, life-threatening. Symptoms usually start within 12 hours of last heroin usage and within 30 hours of last methadone exposure. The Addiction Severity Index (ASI) (McLellan, Kushner, Metzger, et al., 1992) is an instrument designed to assess the impact of a patient’s addiction on his or her function. Although this instrument is typically used in research, it has been adapted for clinical use and illustrates the various aspects of a patient’s life that should be assessed at each patient visit to determine the impact of active addiction or the benefits of abstinence.

The ASI evaluates patient function in the areas of:

- Drug use.
- Alcohol use.
- Psychiatric function.
- Medical function.

- Employment.
- Social/family functioning.
- Legal problems.

In addition to patient self-report, urine testing can be a useful practice in monitoring patient progress in treatment. In some countries, urine testing is mandated as part of the treatment plan.

A variety of substances can be detected in urine testing. Testing can occur for naturally occurring opioids (e.g., codeine, morphine) or synthetic or semi-synthetic opioids (e.g., oxycodone, methadone). Testing also can occur for benzodiazepines, cocaine, marijuana, or other drugs that are used and abused by the patient population. The period of detection of each of these substances varies with the laboratory technique that is used, and the extent of drug use and can range from days to weeks.

METHADONE MAINTENANCE TREATMENT

U.S. opiate addiction regulations and methadone maintenance treatment

U.S. regulations about treatment for heroin addiction have evolved from strict prohibition of medical prescription of heroin to treat addiction, which began in 1914 and continued into the 1960s. Initial pilot studies testing methadone maintenance treatment for heroin addiction began in 1964, and

methadone maintenance treatment was formally approved in 1972. Scientific advances prompted major reviews of Federal regulations by the Institute of Medicine in 1995 (Substance Abuse and Mental Health Services Administration, 2000b) made significant changes in U.S. regulations about treatment

for heroin addiction, reducing Federal regulations and paving the way for new pharmacotherapies to treat heroin addiction.

1860-1909: Minimal government Involvement - The Institute of Medicine documents U.S. narcotics policies from the 19th century through 1992, (Courtwright, 1992). In the first years following widespread use of heroin in the United States, there were no Federal regulations about the manufacture, distribution, or use of heroin, and the few State or municipal laws that existed were enforced sporadically. Physicians, pharmacists, and opportunists were free to prescribe opioids—and treat subsequent opioid addiction—in whatever manner they chose, which contributed to widespread addiction and sometimes unscrupulous practices. Inadvertent addiction to early over-the-counter medications prompted enactment of the 1906 Pure Food and Drug Act, which first authorized Federal regulations on any medication.

1909-1924: Increasing Federal Government Role - In the United States, heroin was first placed under Federal control by the 1914 Harrison Narcotic Act, which required anyone who sold or distributed narcotics—importers, manufacturers, wholesale and retail druggists, and physicians—to register with the Federal Government and pay an excise tax. The United Nations Bulletin on Narcotics documents early international efforts to address opioid addiction (United Nations Department of Social Affairs, 1953). The United States was among the organizers of the 1909 International Opium Commission in Shanghai, China, and a signatory of the 1912 Hague Opium Convention, the first international treaty to make heroin a controlled substance.

1924-1960: Criminalization of Narcotics Use - Between 1924 and 1960, the United States approved a series of progressively stiffer narcotics policies, first establishing mandatory sentences for possession and sale of opioids in 1951 (Courtwright, 1992). Internationally, the United States was a signatory to two more

international treaties to limit the manufacture of narcotics: the Geneva Convention of 1925 and the Limitation Convention of 1931 (United Nations Department of Social Affairs, 1953).

1960-Present: Combined Medical-Criminal Approach - Scientific advances in the 20th century revolutionized our understanding of addiction and contributed to a medical approach to drug abuse treatment coupled with criminal sanctions for drug traffickers. The 1962 White House Conference on Narcotic Drug Abuse first recommended more flexible sentencing, wider latitude in medical treatment, and more emphasis on rehabilitation and research. By 1971, the Special Action Office of Drug Abuse Prevention (SAODAP), established within the White House, was responsible for drug treatment and rehabilitation, prevention, education, training, and research.

Currently, heroin is regulated under the Controlled Substances Act. Federal policies and regulations about heroin are coordinated by the following agencies:

- The Office of National Drug Control Policy (ONDCP) operates within the White House to establish policies, priorities, and objectives for the Nation's drug control program.
- The U.S. Department of Health and Human Services to promote and regulate addiction treatment services.
- The Drug Enforcement Administration (DEA) operates within the Department of Justice to prevent diversion and illicit use of controlled substances and administer criminal sanctions for drug traffickers.

In 2004, the World Health Organization (WHO), the United Nations Office on Drugs and Crime (UNODC), and the Joint United Nations Program on HIV/AIDS (UNAIDS) adopted a joint position paper on substitution maintenance therapy for opioid dependence, calling substitution maintenance therapy one of the most effective treatment options.

Law and methadone maintenance

From 1914 through 1972, although heroin became a controlled substance under the Harrison Act of 1914, the law did not expressly prohibit the medical prescription of heroin to treat addiction. The U.S. Government concluded that the Harrison Act intended to prohibit such medical uses of controlled substances, prosecuting individual doctors who prescribed the drugs. In 1919, the U.S. Supreme Court upheld the Government's position in *Webb v. United States*. In response, about 40 localities opened municipal narcotic clinics to treat addiction using a variety of methods, including medical prescription of narcotics, but by the mid-1920s, these clinics had all been closed by the Federal Government (Joseph, Stanciliff, and Langrod, 2000). After 1972 until 2000, Methadone maintenance treatment for heroin addiction was first approved by the U.S. Food and Drug Administration in 1972, subject to three levels of Federal regulation:

- Food and Drug Administration rules that pertained to all prescription drugs.
- Drug Enforcement Administration rules that governed all controlled substances.
- Unique Department of Health and Human Services rules limiting methadone maintenance treatment to strictly controlled opioid treatment programs, which also were subject to additional State or local rules.

Methadone was approved for office-based dispensing by the Food and Drug Administration in 2002. Administered daily, methadone treatment is currently regulated so that only specialized clinics can provide it.

Methadone maintenance programs must go through an accreditation process in order to operate. The Substance Abuse and Mental Health Services Administration address each critical legal, clinical, safety, and program management area related to the treatment of patients using methadone maintenance therapy.

All accredited methadone programs operate under the authority of the Drug Enforcement Agency (DEA) regulations that govern the dispensing of controlled substances. The DEA regulations (www.deadiversion.usdoj.gov/pubs/manuals/narcotic/narcotic.pdf) stipulate requirements for the type of registration required, qualifications for physicians who dispense methadone, and rules for physician record-keeping.

Methadone treatment dosage

Patients' illicit opioid use declines, often dramatically, during methadone maintenance treatment. However, adequate methadone dosage and basic psychosocial services are essential for treatment effectiveness.

Methadone is provided in various forms, including diskettes, tablets, oral solution, liquid concentrate, and powder. In the United States, methadone used in medically assisted treatment is almost always administered orally in liquid form. Parenteral administration is prohibited in opioid treatment programs. Parenteral abuse of methadone is not widespread, and people rarely inject the methadone dispensed in U.S. programs because it is mixed with substances (e.g., flavored drinks) that make injection unattractive (Treatment Improvement Protocol 43, Chapter 3: <http://www.ncbi.nlm.nih.gov/books/NBK25695/#A82783>).

The acceptable initial dose for methadone treatment is 30 mg daily, unless a reason for a higher dose can be evidenced, which could increase the initial dose to no more than 40 mg a day. Based on the judgment of the program physician and careful

observation of the patient, dosing can go up to 60 mg a day prior to stabilization (http://dpt.samhsa.gov/pdf/draft_accred_guidelines.pdf) (267KB).

In the Ball and Ross studies (1991), patients reduced their use of injected heroin by 71 percent compared with preadmission levels. Illicit opioid use was directly related to methadone dosage: in patients on doses above 71 mg per day, no heroin use was detected, whereas patients on doses below 46 mg per day were 5.16 times more likely to use heroin than those receiving higher doses.

The impact of methadone dose has been demonstrated consistently across studies and countries. Higher (e.g., greater than 50 mg) doses of methadone are associated with better treatment retention and decreased illicit drug use (Faggiano, Vigna-Taglianti, Versino, et al., 2003).

A meta-analysis (Faggiano et al., 2003) of 21 studies concluded that methadone dosages ranging from 60 to 100 mg per day were more effective than lower dosages in retaining patients and in reducing use of heroin and cocaine during treatment.

Research and methadone treatment

Methadone is a rigorously well-tested medication that has been safely used to treat opioid addiction in the United States for more than 40 years. Methadone:

- Suppresses the symptoms of opioid withdrawal for 24 to 36 hours.
- Blocks the effects of administered heroin.
- Does not cause euphoria, intoxication, or sedation.
- Blocks the craving for opioids that is a major factor in relapse.

For 40 years, methadone maintenance treatment has been used successfully to treat heroin addiction in the United States. From the first pilot project in 1964, when Drs. Vincent P. Dole and Marie E. Nyswander established that methadone maintenance treatment was an effective medical intervention for heroin addiction, rigorous scientific research has documented the safety and effectiveness of methadone maintenance to treat heroin addiction. Through the extensive research grant programs administered by the National Institutes of Health, the Federal Government funds most major medical research conducted in the United States, including research on methadone maintenance treatment. In addition, some of the research on methadone maintenance treatment has been conducted by the Federal Government itself at research facilities like the U.S. Public Health Service Hospital in Lexington, Kentucky, where methadone was first shown to be effective in treating the symptoms of heroin withdrawal.

Research has demonstrated that methadone maintenance treatment is an effective treatment for heroin and prescription narcotic addiction when measured by:

- Reduction in the use of illicit drugs.
- Reduction in criminal activity.
- Reduction in needle sharing.
- Reduction in HIV infection rates and transmission.
- Cost-effectiveness.
- Reduction in commercial sex work.

- Reduction in the number of reports of multiple sex partners.
- Improvements in social health and productivity.
- Improvements in health conditions.
- Retention in addiction treatment.
- Reduction in suicide.
- Reduction in lethal overdose.

For example the following research demonstrates the efficacy methadone treatment:

- Recent meta-analyses have supported the efficacy of methadone for the treatment of opioid dependence. These studies have demonstrated across countries and populations that methadone can be effective in improving treatment retention, criminal activity, and heroin use (Marsch, 1998).
- An overview of 5 meta-analyses and systematic reviews, summarizing results from 52 studies and 12,075 opioid-dependent participants, found that when methadone maintenance treatment was compared with methadone detoxification treatment, no treatment, different dosages of methadone, buprenorphine maintenance treatment, heroin maintenance treatment, and L-a-acetylmethadol (LAAM) maintenance treatment, methadone maintenance treatment was more effective than detoxification, no treatment, buprenorphine, LAAM, and heroin plus methadone. High doses of methadone are more effective than medium and low doses (Amato, Davoli, Perucci, et al., 2005).
- Patients receiving methadone maintenance treatment exhibit reductions in illicit opioid use that are directly related to methadone dose, the amount of psychosocial counseling, and the period of time that patients stay in treatment. Patients receiving methadone doses of 80 to 100 mg have improved treatment retention and decreased illicit drug use compared with patients receiving 50 mg of methadone (Simpson, 1993).
- A systematic review conducted on 28 studies involving 7,900 patients has demonstrated significant reductions

in HIV risk behaviors in patients receiving methadone maintenance (Metzger, Woody, McLellan, et al., 1993).

- A randomized clinical trial in Bangkok, Thailand, included 240 heroin-dependent patients, all of whom had previously undergone at least 6 detoxification episodes. The patients were randomly assigned to methadone maintenance versus 45-day methadone detoxification. The study found that the methadone maintenance patients were more likely to complete 45 days of treatment, less likely to have used heroin during treatment, and less likely to have used heroin on the 45th day of treatment (Vanichseni, Wongsuwan, Choopanya, et al., 1991).
- In the Treatment Outcome Prospective Study (TOPS), methadone maintenance patients who remained in treatment for at least 3 months experienced dramatic improvements during treatment with regard to daily illicit opioid use, cocaine use, and predatory crime. These improvements persisted for 3 to 5 years following treatment, but at reduced levels (Hubbard, Marsden, Rachal, et al., 1989).
- In a study of 933 heroin-dependent patients in methadone maintenance treatment programs, during episodes of methadone maintenance, there were (1) decreases in

narcotic use, arrests, criminality, and drug dealing; (2) increases employment and marriage; and (3) diminished improvements in areas such as narcotic use, arrest, criminality, drug dealing, and employment for patients who relapsed (Powers and Anglin, 1993).

- In a 2.5-year follow up study of 150 opioid-dependent patients, participation in methadone maintenance treatment resulted in a substantial improvement along several relatively independent dimensions, including medical, social, psychological, legal, and employment problems (Kosten, Rounsaville, and Kleber, 1987).
- A study that compared ongoing methadone maintenance with 6 months of methadone maintenance followed by detoxification demonstrated that methadone maintenance resulted in greater treatment retention (median, 438.5 vs. 174.0 days) and lower heroin use rates than did detoxification. Methadone maintenance therapy resulted in a lower rate of drug-related (mean [SD] at 12 months, 2.17 [3.88] vs. 3.73 [6.86]) but not sex-related HIV risk behaviors and a lower score in legal status (mean [SD] at 12 months, 0.05 [0.13] vs. 0.13 [0.19]) (Sees, Delucchi, Masson, et al., 2000).

Patient status before and after methadone maintenance treatment

A study by McGlothlin and Anglin (1981) examined patients from three methadone maintenance treatment programs. All three program results illustrate that methadone maintenance treatment is effective in improving patients' lives in terms of time spent (1) using narcotics daily, (2) unemployed, (3) involved in crime, (4) dealing drugs, and (5) incarcerated. The percentage of time using daily narcotics was much greater before methadone maintenance treatment than after. The percentage of time unemployed

decreased after methadone maintenance treatment. The percentage of days the patient was involved in crime decreased after methadone maintenance treatment. The percentage of time dealing drugs decreased after methadone maintenance treatment. The percentage of time incarcerated decreased after methadone maintenance treatment (McGlothlin and Anglin, 1981). A single oral dose of methadone in the morning promotes a relatively steady state of mood and function.

Treatment duration and outcomes

There is a relationship between reduction in illicit opioid use in recovery and treatment duration. And there is a relationship between how long patients remain in treatment and how well they function after treatment. The length of treatment is, in general, associated with abstinence from illicit drug use and an absence of crime. The longer patients stay in treatment, the more likely they are to remain crime free. For example, those who remained in methadone maintenance treatment for the entire 18-month study period, 3.5 percent became infected with HIV. However, among those who remained out of treatment, 22 percent became infected with HIV (Metzger et al., 1993).

In a 3-year field study of methadone maintenance treatment programs in New York, NY, Philadelphia, PA, and Baltimore, MD, methadone maintenance treatment was found to be effective in reducing injection drug use and needle sharing by

most heroin addicts. Of 388 patients who remained in treatment for 1 year or more, 71 percent had stopped injection drug use. Conversely, 82 percent of the 105 patients who left treatment relapsed rapidly to injection drug use (Ball et al., 1988).

In one study, 82 percent of 105 patients who discontinued methadone relapsed to intravenous drug use within 12 months (Payte and Khuri, 1993). And, Drug abuse reduction program studies of opioid-dependent patients 12 years following admission to treatment showed that illicit opioid use declined progressively over time until year 6, when it stabilized at about 40 percent for "any" use and 25 percent for "daily" use (Simpson, Joe, Lehman, et al., 1986). In studies, of long treatment duration was the strongest predictor of reduced heroin use among methadone maintenance patients.

HIV and methadone maintenance

The daily oral administration of adequate dosages of methadone reduces the need for opioid-dependent individuals to inject drugs. By decreasing injection drug use, methadone maintenance treatment helps reduce the spread of diseases transmitted

through needle sharing, such as human immunodeficiency virus (HIV) infection, hepatitis C virus (HCV), and other bloodborne infections (Sullivan, Metzger, Fudala, et al., 2005; Gowing, Farrell, Bornemann, et al., in press).

Research demonstrates decreased in HIV risk behaviors among methadone maintenance patients

A systematic review of 23 studies of 7,900 patients in diverse countries and settings reported significant decreases in the following HIV risk behaviors among patients receiving methadone maintenance treatment: (1) the proportion of opioid-dependent injection drugs, (2) the reported frequency of injection, (3) levels of sharing of injection equipment, (4) illicit opioid use, (5) reduction in the proportion of opioid-dependent injection drug users reporting multiple sex partners or exchanges of sex for drugs or money, and (6) reductions in cases of HIV infection among opioid-dependent injection drug users. However, it should be noted that methadone treatment had little or no effect on the use of condoms. The authors concluded that the provision of agonist treatment for opioid dependence should be supported in countries with emerging HIV and injection drug use problems as well as in countries with established populations of injection drug users (Gowing, Farrell, Bornemann, et al., 2004).

These results support an earlier meta-analysis of 11 studies that found a consistent, statistically significant relationship between methadone maintenance treatment and the reduction of HIV risk behaviors. This meta-analysis found that methadone maintenance treatment had a small-to-moderate effect in reducing HIV risk behaviors (Marsch, 1998).

- A study that evaluated HIV risk behavior in patients receiving ongoing methadone maintenance compared with patients receiving 6 months of methadone maintenance followed by detoxification demonstrated that those patients who received ongoing methadone maintenance treatment reported lower HIV drug (but not sex) risk behaviors after 6 and 12 months of treatment (Sees, Delucchi, Masson, et al., 2000).
- In New Haven, CT, 107 methadone-maintained injection drug users who were not in treatment were surveyed regarding their risk behaviors. The frequency of injections was found to be 50 to 65 percent ($p < .001$) higher among the out-of-treatment subjects (Meandzija, O'Connor, Fitzgerald, et al., 1994).
- In a 3-year field study of methadone maintenance treatment programs in New York, NY, Philadelphia, PA, and Baltimore, MD, treatment was found to be effective in reducing injection drug use and needle sharing by most heroin addicts. Of 388 patients who remained in treatment for 1 year or more, 71 percent had stopped injection drug use. Conversely, 82 percent of patients who left treatment relapsed rapidly to injection drug use (Ball, Lang, Meyers, et al., 1988).
- Abdul-Quader, Friedman, Des Jarlais, et al. (1987) reported that both the frequency of drug injection and the frequency of drug injection in shooting galleries were significantly reduced by the amount of time spent in methadone maintenance treatment.
- A study by Serpelloni, Carrieri, Rezza, et al. (1994) examined the effect of methadone maintenance treatment

on HIV infection incidence among injection drug users. The study found that the amount of time spent in methadone maintenance treatment was the major determinant in remaining HIV-free, which confirms the effectiveness of long-term programs in reducing the risk of HIV infection. Indeed, the risk of HIV infection increased 1.5 times for every 3 months spent out of methadone treatment in the past 12 months immediately preceding seroconversion. The study noted that higher daily methadone doses were associated with a reduction in HIV infection.

- A study by Weber, Ledergerber, Opravil, et al. (1990) examined the role of methadone maintenance treatment in reducing the progression of HIV infection among 297 current and former injection drug users with asymptomatic HIV infection. The study showed that HIV infection progresses significantly more slowly in those who receive methadone maintenance treatment and those who are drug free than in active injection drug users.
- In Philadelphia, PA, a longitudinal study of HIV infection and risk behaviors among 152 injection drug users in methadone maintenance treatment and 103 out-of-treatment injection drug users found significantly lower rates of risk behavior, including needle sharing, injection frequency, shooting gallery use, and visits to crack houses among the methadone-maintained users. While 70 percent of the out-of-treatment cohort reported sharing needles during the 6 months before entry into the study, only 30 percent of those in treatment reported sharing needles during this same interval.
- At entry into this study, 18 percent of the out-of-treatment subjects and 11 percent of the methadone-maintained clients tested positive for antibodies to HIV. After 18 months of study, 33 percent of the out-of-treatment cohort were infected, whereas 15 percent of the methadone clients tested positive ($p < 0.01$). The incidence of new infection was strongly associated with the level of participation in methadone treatment. Among those who remained in methadone treatment for the entire 18-month study period, 3.5 percent became infected. Among those who remained out of treatment, 22 percent became infected with HIV (Metzger, Woody, McLellan, et al., 1993).
- Another study of HIV seroconversion followed 56 patients who were continuously enrolled in methadone maintenance and compared them with 42 patients who had intermittent methadone treatment. Subjects in continuous treatment had a seroconversion rate of 0.7 per 100 person years (95 percent CI = 0.1, 5.3), and those with interrupted treatment had a rate of 4.3 per 100 person years (95 percent CI = 2.2, 8.6) (Williams, McNelly, Williams, et al., 1992).
- A relatively short-term study of methadone maintenance versus control in a prison system in Australia found reductions in opioid use but no changes in HIV or HCV incidence (Dolan, Shearer, MacDonald, 2003).

Methadone maintenance and criminal activity

Patients are less likely to become involved in criminal activity while in methadone maintenance treatment.

- Patients who remain in methadone maintenance treatment for long periods of time are less likely to be involved in criminal activity than patients in treatment for short periods.

- The availability of methadone maintenance treatment in a community is associated with a decrease in that community's criminal activity, particularly theft.

Research

- In a meta-analysis of 24 studies, results indicate an overall small-to-medium effect of $r = -0.25$ (un-weighted) of the impact of methadone maintenance on criminal activity. A large effect size of $r = 0.70$ (un-weighted) was seen in those studies that investigated the efficacy of methadone maintenance treatment in reducing drug-related criminal behaviors. A small-to-moderate effect of $r = 0.23$ (un-weighted) was obtained when both drug and property-related criminal activities were evaluated. Finally, a small effect of $r = 0.17$ (un-weighted) was demonstrated when drug- and nondrug-related criminal behaviors were combined (Marsch, 1998).
- In the Treatment Outcome Perspective Study (TOPS), 32 percent of the methadone maintenance patients acknowledged committing one or more predatory crimes in the year before treatment, but only 10 percent continued these activities during treatment. By 3 to 5 years after leaving treatment, only 16 percent of the patients reported predatory criminal activity—a reduction of one-half the pretreatment level (Hubbard, Marsden, Rachal, et al., 1989).
- Among the 617 patients studied by Ball and Ross (1991), there was a 70.8-percent decline in crime-days within the 4-month methadone maintenance treatment period. This decline was followed by continuing, but less dramatic, declines in mean crime-days among those in treatment for 1 to 3 years. Those in treatment for 6 or more years had the lowest rate of crime-days per year (14.5).
- The Powers and Anglin (1993) retrospective study of 933 heroin addicts demonstrated that rates of criminality, arrests, and drug dealing decreased during episodes of methadone maintenance treatment when compared with addicts not in treatment.
- In the National Treatment Outcome Research Study, acquisitive criminal behavior decreased in the majority of

the 333 patients except those ($n = 88$) who were felt to have a poor treatment response. In these patients, there was no change in this type of criminal activity (Gossop, Marsden, Stewart, et al., 2000).

- The meta-analysis by Mattick, Breen, Kimber, et al. (2003) revealed that criminal activity declined in consort with reductions in heroin use, although the advantage for methadone beyond control in reducing criminal activity was not statistically significant (3 studies, 363 patients: $RR = 0.39$, 95 percent CI: 0.12-1.25).

The Effects of Methadone Maintenance Treatment on Crime-Days

Ball and Ross study (1991) of 617 patients demonstrated that methadone maintenance treatment is associated with a dramatic decline in the average number of crime-days per year. The study revealed that the average number of crime days per year before treatment was 237. During the 4-month initial methadone maintenance treatment, the average number of crime days per years was 69. This represents about a 71 percent decline. The decline was followed by continuing, but less dramatic, declines in the average number of crime days among those in methadone maintenance treatment for one to three years. Patients who remained in methadone maintenance treatment for 6 or more years reported only 14.5 crime days per year, representing a 94 percent decline in average number of crime days.

Ball and Ross (1991) also found a dramatic decline in crime when comparing pretreatment crime-days per year and the number of crime-days per year after 6 months or more in methadone maintenance treatment. Although there are differences among programs, the dramatic decrease in crime days before and during methadone maintenance treatment occurs for all six programs. The average reduction in crime for those in methadone maintenance treatment was just over 91 percent.

Methadone maintenance and employment

Methadone maintenance has been associated with significant increases in full-time employment.

Research

- In an early study of 100 chronic heroin users who were admitted to methadone maintenance treatment, the employment rate increased from 21 percent at admission to 65 percent 1 year later (Maddux and Desmond, 1979).
- A study of 92 males admitted to methadone maintenance treatment programs from 1971 through 1973 demonstrated that, following methadone maintenance treatment, employment increased about 18 percent (Harlow and Anglin, 1984).
- In a 10-year followup study, 95 chronic opioid users who spent at least 1 cumulative year in methadone maintenance treatment were compared with 77 chronic opioid users who spent less than 1 cumulative year in methadone maintenance treatment. Those who were on methadone maintenance treatment for more than 1 year had a higher average time employed (mean of 42 months) than those who were in treatment for less than 1 year (mean of 35 months) (Maddux and Desmond, 1992).

- The Powers and Anglin (1993) study of 933 heroin addicts in methadone maintenance treatment demonstrated that rates of employment (and marriage) increased during treatment.
- Methadone maintenance patients in the Treatment Outcome Perspective Studies (TOPS) had small changes in employment rates during and following treatment compared with pretreatment rates. Although 24 percent of the patients reported full-time employment in the year before admission, this rate did not increase significantly during treatment. It declined abruptly in the 3 months following discharge, improved to 29 percent by year 2, and dropped off again to less than pretreatment rates by years 3 to 5 following treatment (Hubbard, Marsden, Rachal, et al., 1989).
- In a study that compared ongoing methadone maintenance with 6 months of methadone maintenance followed by detoxification, no difference was seen in employment, although nearly 50 percent of patients were employed at entry into the study (McLellan, Arndt, Metzger, et al., 1993).

Methadone maintenance treatment and general drug abuse

Research outcomes are mixed regarding the effect of methadone maintenance treatment on the use of illicit drugs other than opioids. In other words, some research indicates that methadone maintenance treatment is associated with decreases in the use of alcohol, cocaine, and marijuana; other research indicates increases in the use of these drugs. It is important to note that the medication methadone has no direct effect and is not intended to have an effect on rates of alcohol and other drug use. Patients receiving methadone maintenance who disengage from interactions with others who are actively using drugs are less likely to engage in these behaviors.

In addition, reductions in alcohol and drug use result from the counseling services included in methadone maintenance treatment. When these services are specifically designed to reduce alcohol and other drug use, such reductions are likely.

Research

- In the Drug Abuse Reporting Program (DARP) studies, there were reductions in non-opioid drug use (except marijuana) among 895 methadone maintenance patients, comparing the 2-month period before admission and the year following discharge. The reduction in non-opioid use was 13 percent—from 54 percent of patients who reported any use before admission to 41 percent at the 1-year follow-up point (Simpson and Sells, 1982).
- In the 12-year DARP follow-up study, “heavy drinking” was reported by 21 percent of the sample in the month before treatment; it rose to 31 percent during the first year afterward and then declined to 22 percent by year 12. One-half of the patients reported substituting alcohol for opioids after stopping daily illicit opioid use (Lehman, Barrett, and Simpson, 1990).
- In a study comparing buprenorphine maintenance with methadone maintenance for patients with opioid dependence and cocaine abuse, both treatments resulted in significant declines in opioid use but were indistinguishable in terms of their effect on comorbid cocaine use (Schottenfeld, Pakes, Oliveto, et al., 1997).

Among three cohorts of new-admission patients in methadone maintenance treatment, Ball and Ross (1991) found that the use of all illicit drugs, except marijuana, decreased markedly in relation to time in treatment. These three cohorts had been in treatment 6 months, 4.5 years, or more than 4.5 years.

In the Treatment Outcome Perspective Study (TOPS), 90 percent of methadone maintenance treatment patients who reported drug use at intake reported a reduction in use during the first 3 months of treatment. For 80 percent, this reduction is large. In the year before treatment, less than 10 percent of methadone maintenance treatment patients were minimal drug users. During treatment, more than 50 percent of the patients were minimal drug users. During the 3 to 5 years after discharge, less than 32.5 percent were minimal drug users (Hubbard, Marsden, Rachal, et al., 1989).

In the National Treatment Outcome Research Study (NTORS), of 333 patients receiving methadone maintenance in the United Kingdom, overall declines were seen in the use of heroin, barbiturates, amphetamines, cocaine, and crack cocaine among patients receiving methadone maintenance. Alcohol use, however, did not change over time (Gossop, Marsden, Stewart, et al., 2000).

In another evaluation of 513 heroin users in methadone treatment in TOPS, a decline was observed in the use of cocaine, amphetamines, illegal methadone, tranquilizers, and marijuana, but not alcohol (Fairbank, Duntzman, and Condelli, 1993).

The Powers and Anglin study (1993) of 933 heroin addicts in methadone maintenance programs demonstrated that during episodes of methadone maintenance treatment, illicit opioid use decreased, but alcohol and marijuana levels increased moderately. Kreek (1991) observed that by 1990, alcoholism was identified in 40 or 50 percent of new admissions to methadone maintenance treatment programs, and cocaine abuse was found in 70 to 90 percent. She also estimated that 20 to 46 percent of patients in effective methadone maintenance treatment programs continue using cocaine, and 15 to 20 percent of methadone maintenance treatment patients regularly inject cocaine.

Methadone maintenance treatment and cocaine use

Among the TOPS patients who remained in methadone maintenance treatment at least 3 months, 26.4 percent had used cocaine regularly the year before treatment. This rate fell to 10 percent during the first 3 months of treatment but returned to 16 percent by 3 to 5 years after discharge. Altogether, 40 percent of methadone maintenance treatment patients who regularly used cocaine before treatment and stayed in treatment for at least 3 months abstained from cocaine use in the year after treatment (Hubbard et al., 1989).

In the TOPS studies, although 70 percent of heroin abusers had frequently used cocaine the year before treatment, it was the primary drug of choice for only 2 percent of methadone maintenance treatment patients (Hubbard et al., 1989).

In the new admissions group of a six-program study ($n = 345$), 46.8 percent of 126 patients had used cocaine in the past 30 days.

Among the average-stay group (up to 4.5 years in treatment), 27.5 percent still used cocaine; this rate dropped to 17.2 percent among the long-term group of 146 patients who had been in continuous treatment for more than 4.5 years (Ball and Ross, 1991).

A study evaluating the effect of methadone dose on treatment outcomes noted that patients receiving 50 mg of methadone, compared with those receiving 20 mg or 0 mg, had a reduced rate of opioid-positive urine samples (56.4 percent vs. 67.6 percent and 73.6 percent, respectively; $p < 0.05$) and cocaine-positive urine samples (52.6 percent vs. 62.4 percent and 67.1 percent, respectively; $p < 0.05$) (Strain, Stitzer, Liebson, et al., 1993).

A systematic review examined the impact of methadone dose on cocaine use and found three studies that addressed the question. Results from the one study in which cocaine use was based on self-reported use showed no significant excess of use

of cocaine among subjects treated with higher doses compared with subjects treated with lower doses. Pooled results from the two studies that used urine analysis and looked at an abstinence period longer than 3 weeks showed that higher methadone

doses increased the probability that patients would stay abstinent from cocaine, compared with lower doses (RR = 1.81 [1.15, 2.85]) (Faggiano, Vigna-Taglianti, Versino, et al., 2003).

Methadone maintenance and marijuana use

Among TOPS subjects, marijuana use was common: 55 percent of methadone maintenance patients who stayed in treatment for 3 months reported regular use in the year before admission. This decreased to 47 percent during the first 3 months of treatment, continued to decline immediately posttreatment, and decreased even more to 36.4 percent in the 3- to 5-year period after discharge. However, marijuana use appeared more resistant to change than other illicit substances (Hubbard et al., 1989). It should be considered that the treatment programs likely did not clinically address marijuana or other drug use.

Ball and Ross (1991) found that marijuana continued to be used quite regularly (an average of 13 to 16 days per month) by high percentages of all patient groups in methadone maintenance treatment: 48.4 percent of the new admissions, 47.7 percent of the average-stay group, and 37.2 percent of the patients in treatment more than 4.5 years.

In one study of 132 opioid addicts participating in methadone maintenance treatment programs, it was noted that during episodes of methadone maintenance treatment, levels of alcohol and marijuana use increased modestly (Powers and Anglin, 1993).

Methadone maintenance and the non-medical use of prescription drugs

In the TOPS studies, the regular nonmedical use of psychoactive prescription drugs by methadone maintenance treatment patients during the first post-treatment year decreased by one-third from the pretreatment period. Although 30.3 percent of this methadone maintenance group reported regular nonmedical use of prescription drugs (i.e., barbiturates, amphetamines, tranquilizers, sedatives, and hypnotics), nonmedical prescription drug use was a primary problem for only 1.9 percent of these patients at admission (Hubbard et al., 1989).

In the NTORS study, a decline was seen in the use of benzodiazepines among patients receiving methadone

maintenance (Gossop et al., 2000). In the TOPS studies, nonmedical prescription drug use declined during methadone maintenance treatment, increased immediately following discharge, and declined again to 10 percent of patients 3 to 5 years following discharge (Hubbard et al., 1989).

Ball and Ross (1991) found that although the nonmedical use of sedatives other than barbiturates was acknowledged by 31.8 percent of new admissions to methadone maintenance treatment, the percentage of sedative-using patients who had been in treatment for more than 4.5 years was less than half that of the new admission group (14.5 percent).

Methadone maintenance treatment and alcohol and other drug use

In the TOPS studies, improvements in the use of illicit and nonprescription drugs follow a pattern of (1) a dramatic reduction during treatment, (2) a sharp increase immediately after discharge, and (3) a leveling off at an impressively reduced rate for up to 5 years of follow-up contacts (Hubbard et al., 1989). In the TOPS study of 4,184 patients, methadone maintenance treatment was associated with reductions in: 1. Any illicit opioid use 2. Any cocaine use 3. Any marijuana

use, and 4. Alcohol abuse. (Hubbard et al., 1989) “Any opioid use” declined from 63 percent pretreatment to 17 percent 1 year post-treatment. This was the most dramatic decline. “Any cocaine use” declined from 26 percent to 18 percent. “Any marijuana use” declined from 55 percent pretreatment to 46 percent 1 year post-treatment. Alcohol abuse remained almost steady, declining slightly from 25 percent to 24 percent.

Women and methadone maintenance

Since the earliest methadone maintenance treatment programs in the United States, women have been treated successfully with methadone through all phases of their lives, including pregnancy. There is consensus that the major outcomes of the effectiveness of methadone maintenance treatment, especially cessation of illicit drug use and lifestyle stabilization, apply to both men and women. However, gender-specific issues, which are often related to the social status of women, are important to treatment effectiveness for female injection drug users.

Compared with men, women are more likely to:

- Have total responsibility for child care.
- Have lower socioeconomic status.

- Encounter greater barriers to treatment entry, retention in treatment, and economic independence.
- Have different psychological, counseling, and vocational training needs.
- Have difficulty with transportation to treatment.

Research

- In the past, little emphasis was placed on gender-specific bio-psychosocial problems in drug treatment. One reason was the predominance of drug-addicted men, estimated in the United States to be three males to every female. Although mild forms of psychoactive substance use show converging usage rates and patterns for males and females,

opioid addiction and other forms of chemical dependency continue to show a male predominance (Kandel, 1992).

- Drug Abuse Reporting Program (DARP) studies showed that 19 to 28 percent of admissions to drug treatment programs from 1969 to 1973 were women. In 12 years of follow-up of 84 females and 91 males in methadone maintenance, there were no differences between men and women in overall reduction of opioid use. Women required more government financial assistance and had lower rates of employment than men. Compared with men, women were more likely to enter treatment for health reasons (Marsh and Simpson, 1986).
- A study of 567 methadone-maintained patients in California found overall shorter duration of time from first entry to first discharge from treatment for women compared with men (Murphy and Irwin, 1992).
- A study of white, Latina, and African American women in methadone maintenance found that, in general, Latinas were more likely to report familial influences and to display evidence of low self-esteem and self-efficacy, inconsistent condom use, and high-risk injection behavior. White women reported the highest levels of regular condom use at follow-up; however, they were the least likely to report safer injection practices. African American women expressed the highest levels of self-esteem, yet they reported more alcohol use at intake and crack cocaine use both before and after treatment entry. African American women showed the greatest gains in adopting safer injection practices and were the least likely to report multiple sex partners after treatment entry (Grella, Annon, and Anglin, 1995).
- Drug-using women are likely to experience clinical depression, anxiety disorders, and low self-esteem to a much greater degree than their male counterparts. Women entering treatment have experienced unique gender-specific life events. In particular, female drug users often have been abused physically, sexually, and emotionally. Experiences of sexual violence, especially during childhood, have profound, lifelong psychological effects and often underlie addiction, complicating successful recovery. Methadone maintenance treatment of women requires awareness of these issues and appropriate counseling. Confrontational styles of therapy and counseling are not effective for most women in treatment (Hartel, 1989/1990). Therefore, key treatment issues include:
 - Social isolation.
 - Poor self esteem.
 - Clinical depression and anxiety disorders.
 - Physical and sexual abuse.

There is a strong need for:

- Child care.
- Transportation to treatment.
- Non-confrontational therapy and counseling.
- Vocational job skills training and education designed specifically for women.

In research conducted in New York, NY, among 452 methadone-recruited injection drug users early in the HIV epidemic, having an injection drug user as a sex partner was associated with HIV infection status independent of or in addition to injection risk behavior. In this same study, women reported a higher level of sexual risk behavior than men: 57

percent of women compared with 45 percent of men reported one or more injection drug users as sex partners since 1978. In addition, women were more likely than men to have engaged in sex work: 23 percent of women compared with 5 percent of men (Schoenbaum, Hartel, Selwyn, et al., 1989).

Research

Since the early 1970s, methadone maintenance treatment has been used successfully with pregnant women. There is consensus that methadone can be safely administered during pregnancy with little risk to mother and infant. Maintenance on methadone is necessary to prevent relapse to illicit opioid use and thus to maintain optimal health during pregnancy.

A systematic review revealed that randomized controlled studies of methadone treatment in pregnancy demonstrate an approximate threefold reduction in heroin use and a threefold increase in retention in treatment relative to non-pharmacologic treatment (Rayburn and Bogenschutz, 2004).

- All drug-using women are considered to be at higher-than-normal risk for medical and obstetrical complications. Methadone-maintained women show a far greater improvement in obstetrical health than untreated women. Hepatitis types A, B, and C and other sexually transmitted diseases; bacterial endocarditis; septicemia; and cellulites are common among active injection drug users, particularly those who share needles. Women maintained on methadone who have stopped illicit drug use and injection before pregnancy are less likely to experience these and other medical complications during pregnancy. Obstetrical complications such as spontaneous abortion, placental insufficiency, and other conditions also occur at a lower rate among methadone-maintained women than among opioid-dependent women not enrolled in treatment. When compared with opioid-addicted women not in treatment, women in methadone maintenance treatment have been observed to maintain better overall health and nutritional status during pregnancy because of stability provided through treatment. In addition, methadone clinics can provide onsite prenatal services or link patients to these services in nearby clinics, coordinating addiction treatment and prenatal care to optimize both (Kaltenbach, Silverman, and Wapner, 1993).
- Some women in methadone maintenance treatment are infected with HIV before pregnancy. Treatment programs that link women to appropriate medical care during pregnancy may reduce the burden of illness suffered by HIV-infected women. In a study of 191 methadone-maintained women in a New York City clinic with extensive medical linkages, medical and obstetrical complications did not differ among women with and without HIV infection. HIV infection occurred among 37 percent of women, most of whom were asymptomatic for HIV disease and AIDS before pregnancy. Adverse birth outcomes were relatively infrequent and occurred at approximately the same rates as observed in studies of methadone-maintained women before the HIV epidemic (Selwyn, Schoenbaum, Davenport, et al., 1989).
- U.S. research in the 1970s demonstrated that methadone does cross the placenta. Passive exposure to methadone in utero can result in neonatal abstinence syndrome among exposed infants. The syndrome varies considerably and depends on

a number of factors, including the use of other drugs during pregnancy, anesthesia during delivery, the maturational and nutritional status of the infant, and other aspects of maternal health that affect the fetal environment. The relationship of maternal methadone dose in the last trimester of pregnancy has been explored in a number of studies, but results have not consistently delineated a dose-response relationship between maternal dose and severity of infant abstinence syndrome. For those neonates experiencing withdrawal, the length and severity of the withdrawal vary greatly; however, pharmacotherapy for neonatal methadone abstinence syndrome is simple and effective. Methadone maintenance treatment affords protection of the fetus from erratic maternal opioid levels and repeated episodes of withdrawal typically seen in users of illicit opioids (Finnegan, 1991).

- The majority of infants exposed to methadone in utero are healthy and have fewer adverse outcomes than infants exposed to heroin and other illicit drugs. Methadone maintenance treatment for pregnant women can reduce in utero growth retardation and neonatal morbidity and mortality, in comparison with women not in treatment (Kaltenbach and Finnegan, 1984).

A review of the literature on methadone and lactation reveals that the amount of methadone in breast milk is very small and depends on the dose of methadone that a mother is receiving. The amount of methadone received by an infant from breast milk is not enough to prevent neonatal abstinence syndrome. Therefore, even though a mother is receiving methadone, her infant may require additional opiate treatment of neonatal abstinence syndrome (Jansson, Velez, and Harrow, 2004).

Methadone safety for pregnant women and their infants

Methadone for pregnant women and their infants:

- Reduces adverse pregnancy outcomes.
- Reduces adverse birth outcomes.
- Infant withdrawal is treatable.
- Shows no long-term adverse neurobehavioral consequences to *in utero* exposure.

Women have been safely maintained on stable methadone dosage during pregnancy without adverse long-term effects on their health and the health of their infants. Withdrawal of medication during pregnancy leads to opioid abstinence syndrome, which is harmful to the pregnancy and often leads to relapse to illicit drug use. Dosage change in pregnancy must be carefully evaluated on an individual basis. Some women experience lowered blood levels of the methadone during pregnancy and may need an increase in dosage or split (e.g., twice daily) dosing. It is important to determine the relapse risk for each woman when considering a dosage change because a woman steadily maintained on methadone is more likely to have a healthy pregnancy and infant than a woman who uses alcohol and other drugs. The intermittent periods of withdrawal that typically occur with illicit opioid use and can adversely affect the fetus do not occur when methadone is individually determined and properly administered.

Research

- Optimal methadone dosage for pregnant women in methadone maintenance treatment should be based on careful consideration of risks and benefits to both mother and fetus on an individual basis. Individual dose should be evaluated, taking into account the stage of pregnancy, the relapse risk potential of the mother, pre-pregnancy methadone dose, previous experience with methadone, and history of addiction recovery. When the mother does not relapse to illicit drug use, short-term

reductions in maternal dose have been effectively administered during the last stage of pregnancy. However, many women in treatment have been successfully maintained on a constant dose and, in some cases, on an increased dose to keep blood levels stable throughout pregnancy (Finnegan, 1991).

- Some women in treatment experience decreased blood levels of methadone during pregnancy, causing withdrawal symptoms. This decrease in blood levels of methadone during pregnancy can be accounted for by an increased fluid space, a large tissue reservoir that can store methadone, and drug metabolism by both the placenta and the fetus. Pregnant women in treatment with low blood levels of methadone frequently experience a high level of discomfort, withdrawal symptoms, and drug craving and anxiety and may be at high risk of relapse to opioid use and treatment dropout. Determination of methadone blood levels and possibly raising the methadone dosage to maintain sufficient blood levels may be warranted in such cases but must be carefully evaluated. Dosages should be evaluated in conjunction with ongoing medical monitoring of the pregnancy. Since the greatest risks to maternal and infant health occur when women in treatment relapse to illicit drug use, it is important to promote methadone dosage stability during and after pregnancy to optimize both maternal and child health (Kreek, Schecter, Gutjahr, et al., 1974; Pond, Kreek, Tong, et al., 1985).

Methadone dosage adjustment during pregnancy

Three main considerations regarding dosage for pregnant women in methadone maintenance treatment:

- Pregnancy can lower methadone blood levels.
- Lower blood methadone levels can increase relapse-risk.
- Dosage levels should be evaluated and individually tailored to reduce risk of relapse and to stabilize both mother and fetus.

Long-term administration of methadone

Studies of the long-term administration of methadone confirm that it is a medically safe drug. Long-term methadone maintenance treatment at doses of 80 to 120 mg per day is not toxic or dangerous to any organ system after continuous treatment for 10 to 14 years in adults and 5 to 7 years in adolescents.

Research

- Methadone has few adverse biological effects. There appear to be no dangerous or troubling psychological effects from long-term administration (Verdejo, Toribio, Orozco, et al., 2005).

- Methadone sometimes causes minor side effects, such as sweating, constipation, temporary skin rashes, weight gain, water retention, and changes in sleep and appetite (Lowinson et al., 1992).
- Methadone prescribed in high doses for a long period of time has no toxic effects and only minimal side effects for adult patients maintained in treatment for up to 14 years and for adolescent patients treated for up to 5 years (Kreek, 1978).
- Although early studies demonstrated no persisting abnormalities directly attributable to methadone in the functioning of five organ systems (pulmonary, cardiovascular, renal, ophthalmologic, and liver) (Krantz, Lewkowicz, Hays, et al., 2002).
- Patients maintained on methadone have no impairment in driving and have no more frequent motor vehicle accidents than people not receiving methadone maintenance treatment (Schindler, Ortner, Peternell, et al., 2004).
- The most common and enduring complaints after 6 months to 3 years of continuous methadone treatment are sweating, constipation, abnormalities in libido and sexual functioning, sleep abnormalities (insomnia and nightmares), and altered appetite (mild anorexia, weight gain) (Kreek, 1979). A study of 92 methadone-maintained patients found that the rate of global sexual dysfunction in methadone-treated men was similar to the general population but that orgasm dysfunction may respond to methadone dose reduction.
- Although euphoria and drowsiness, with occasional nausea and vomiting, can occur before tolerance develops, these side effects are most noticeable when doses are increased too

rapidly. Conversely, if a heroin habit has been particularly heavy, initial methadone doses may be too low to prevent the onset of early withdrawal symptoms (Kreek, 1979).

- Life-threatening interactions of methadone with other drugs have not been identified. Drugs found to affect the metabolism of methadone include phenytoin (Dilantin) and rifampin. Opioid antagonists such as pentazocine (Talwin) and buprenorphine can cause withdrawal symptoms in methadone patients and should not be prescribed (Kreek, 1978).

Methadone maintenance patients, in the early stages of treatment, can experience several minor side effects that include: constipations, organism abnormalities, alternations of sexual interest, alternations of sleep and appetite, nausea, drowsiness, nervousness, headaches, body aches and pains, and chills. Many of these side effects almost disappear with long-term, high-dose methadone maintenance treatment. (Hartel, 1989/1990)

Patient characteristics associated with treatment success include the following:

- Age.
- Age of first heroin use.
- Overall drug-use history.
- Severity and duration of drug use.
- Emotional health.
- Psychiatric health.
- Social health.
- Vocational stability.
- Criminal history.

Methadone maintenance retention in treatment

Retention in methadone is related to the dose of methadone but not the provision of ancillary services. In a study of 351 daily or weekly heroin users who were admitted to 1 of 17 publicly funded methadone treatment programs, predictors of retention in methadone maintenance treatment programs included (1) positive patient evaluations of the quality of social services received during the first month after admission (e.g., family, legal, educational, employment, financial services); (2) positive patient ratings of how easily accessible the program was; and (3) participation in programs that informed patients of their

methadone dosage levels (Condelli, 1993). Mandated methadone maintenance treatment (being forced to attend treatment by the criminal justice system) is as effective as voluntary treatment. Patients who are legally coerced into methadone maintenance treatment experience treatment success at about the same rate as patients who participate voluntarily in treatment.

A study by 36) had moderate legal pressure to participate in methadone maintenance treatment (medium coercion). A third group had mild legal pressure to participate in methadone maintenance treatment (low coercion).

Methadone abuse

Methadone can be diverted for oral or intravenous use (Fiellin and Lintzeris, 2003; Green, James, Gilbert, et al., 2000). Some diverted methadone can result in fatal overdoses; however, the rate of overdose among patients enrolled in methadone maintenance is low. A meta-analysis revealed a relative risk of death of 0.25 (95 percent CI: 0.19-0.33) for patients receiving methadone maintenance (Capelhorn et al., 1996). A study of nearly 10,000 individuals inducted onto methadone determined that the mortality rate was 7.1 deaths per 10,000 inductions (95 percent CI: 1.8± 12.4). In this same study, 51 percent of methadone-related deaths occurred in people who were not registered in methadone maintenance (Zador and Sunjic, 2002).

In addition, while methadone may be detected in drug-related deaths, it is often not the causative agent. In one study in the west of Scotland, during the period 1991–2001, methadone alone was judged to be the causative agent in only 29 percent (56) of drug-related deaths (Seymour, Black, Jay, et al., 2003).

Similarly, with the increased use of methadone as a treatment for chronic pain, the majority of methadone-related deaths in Australia and the United States are believed to be associated with the use of this medication for pain treatment instead of treatment of opioid dependence (Center for Substance Abuse Treatment, 2004).

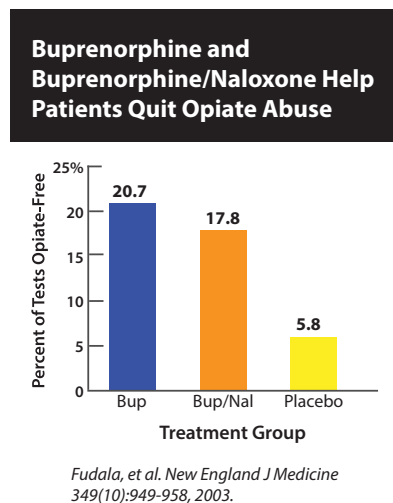
Both methadone and buprenorphine can be diverted from their intended recipients. This diversion occurs in countries that provide these medications via supervised dispensing (e.g., pharmacies) and by prescription. Oftentimes, this diversion is by individuals who are seeking a therapeutic benefit (e.g., unobserved treatment). Other times, this diversion results in abuse. The extent of these two types of diversion varies, although most studies note that the benefits of providing the treatment outweigh the risks associated with diversion. For instance, the efficacy of methadone has been demonstrated over the past 40 years (O'Connor and Fiellin, 2000).

The provision of methadone and buprenorphine treatment was associated with a 75-percent decrease in fatal heroin overdoses in France (Lepere, Gourarier, Sanchez, et al., 2001; Auriacombe, Fatseas, Dubernet, et al., 2004).

In studies that have compared death rates from heroin overdose among those who are untreated and those who receive methadone, deaths are higher among untreated opioid-dependent individuals (Capelhorn, Dalton, Haldar, et al., 1996; Zanis and Woody, 1998).

BRUPRENOPHINE AND BUPRENOPHINE/NALOXONE MEDICATION MANAGEMENT

NIDA-supported basic and clinical research led to the development of buprenorphine, which culminated in a large NIDA-sponsored, multisite clinical trial demonstrating its effectiveness. The trial showed that, alone or in combination with naloxone, buprenorphine significantly reduced opiate drug abuse and cravings and was a safe and acceptable addiction treatment (figure).



While these products were being developed in concert with industry partners, Congress passed the Drug Addiction Treatment Act (DATA 2000) permitting qualified physicians to prescribe narcotic medications (Schedules III to V) for the treatment of opioid addiction. This legislation created a major paradigm shift by allowing access to opiate treatment in a medical setting rather than limiting it to federally approved Opioid Treatment Programs.

The FDA approved Subutex (buprenorphine) and Suboxone tablets (buprenorphine/naloxone) in October 2002, making them the first medications to be eligible for prescribing under the DATA 2000. To date, nearly 10,000 physicians have taken the training needed to prescribe these two medications, and nearly 7,000 have registered as potential providers.

Buprenorphine is approved for use in the treatment of opioid dependence in a large number of countries, including Australia, Belgium, Canada, Croatia, Germany, Iran, England, France, the United Kingdom, and the United States. Buprenorphine is a partial agonist at the opioid receptor, as opposed to a full agonist such as methadone or heroin. This means that buprenorphine has a unique pharmacologic profile leading to a lower likelihood

of overdose or respiratory depression. Like methadone, buprenorphine has the ability to suppress opioid craving and withdrawal, block the effects of self-administered opioids, retain patients in treatment, and decrease illicit opioid use. Because it is a partial agonist, buprenorphine maintains patients in a milder degree of physical dependence and is associated with milder withdrawal syndrome following cessation.

Clinical trials comparing the efficacy of buprenorphine to methadone on the outcomes of retention and illicit opioid use have demonstrated similar results when compared with low doses of methadone (20 to 30 mg) (Kosten, Schottenfeld, Ziedonis, et al., 1993).

Patients receiving buprenorphine can be either (1) discontinued without significant withdrawal, (2) maintained, or (3) transferred to opioid antagonist treatment, such as naltrexone. Patients with a higher level of physical dependence and whose needs cannot be met by buprenorphine can be transferred to an opioid agonist, such as methadone or L-alpha-acetyl-methadol, (LAAM).

Research

- Mello and Mendelson showed that buprenorphine suppresses heroin self-administration by opioid-dependent primates and humans (Mello, Bree, and Mendelson, 1983).
- Findings from a subsequent dose-ranging study at the Los Angeles Addiction Treatment Research Center (LAATRC) suggest that the median doses of buprenorphine for adequate clinical stabilization may be in the 12- to 16-mg range (Compton, Ling, Charuvastra, et al., in press).
- A NIDA-sponsored, 12-site LAATRC/Veterans Administration/NIDA multicenter study compared doses of 1, 4, 8, and 16 mg of buprenorphine in 631 patients. The primary comparison between the 8-mg and the 1-mg groups shows that the 8-mg group used fewer illicit opioids and remained in treatment longer (Ling, Charvastra, Collins, et al., 1998).
- A clinical trial comparing buprenorphine, the buprenorphine/naloxone combination, and placebo was terminated early because buprenorphine and naloxone in combination and buprenorphine alone were found to have greater efficacy than placebo. Opioid-negative urine samples were found more frequently in the buprenorphine and buprenorphine/naloxone groups (17.8 percent and 20.7 percent, respectively) than in the placebo group (5.8 percent, $p < 0.001$ for both comparisons) (Fudala, Bridge, Herbert, et al., 2003).

Potential Benefits of Buprenorphine

Research on buprenorphine has shown that it has the potential to be a feasible alternative to methadone maintenance treatment. One potential benefit of buprenorphine compared with methadone that needs further investigation is a lower prevalence of medication interactions between buprenorphine and highly active antiretroviral treatment used to treat patients with HIV. Potential benefits of buprenorphine include:

- Low abuse potential
- Relatively mild withdrawal symptoms
- May facilitate transfer to opioid antagonist treatment
- High safety profile
- May attract broader range of addicts

Buprenorphine Abuse

As a partial agonist, buprenorphine has less potential for abuse than most full agonists. However, there is a reinforcing effect that subjects can experience with buprenorphine administration, especially via the injection route. This reinforcement is less likely if the subject has recently used a full agonist compound; in fact, buprenorphine can lead to a painful and uncomfortable precipitated withdrawal under this scenario. In addition, the development of a tablet that combines buprenorphine with naloxone, in a 4 to 1 ratio, has demonstrated decreased abuse potential and the ability to precipitate withdrawal in patients

who are receiving a full opioid agonist (Mendelson, Jones, Welm, et al., 1999).

When the buprenorphine/naloxone combination tablet is taken sublingually, as prescribed, naloxone is poorly absorbed, and the patient receives a buprenorphine effect. However, if the tablet is dissolved and injected, the naloxone will antagonize the buprenorphine, resulting in a range of reactions, including blockade of opioid effects and precipitation of an immediate withdrawal. In this way, the combination gives the therapeutic benefit but greatly reduces opportunities for abuse by injection.

Buprenorphine's Pioneering Contributions to Addiction Treatment

- Buprenorphine's novel formulation with naloxone, an opioid antagonist, limits abuse and diversion potential. Scientific breakthroughs led to this formulation, which produces severe withdrawal symptoms in those who inject it to get "high" but no adverse effects when taken orally, as prescribed.
- Buprenorphine represents a health services delivery innovation. The development of buprenorphine and its authorized use in physicians' offices gives opiate-addicted patients more medical options and extends the reach of addiction medication to remote populations. Its accessibility may even prompt earlier attempts to obtain treatment.

Outreach

SAMHSA, NIDA is developing and disseminating protocols to educate multidisciplinary treatment professionals about buprenorphine (<http://www.ctndisseminationslibrary.org/display/85.htm>External link, please review our disclaimer.). Blending Teams of NIDA researchers, treatment practitioners, and trainers have completed two buprenorphine training packets:

- To increase overall awareness of buprenorphine therapy, and

- To instruct physicians and treatment practitioners in implementing a 13-day detoxification intervention for opiate-dependent patients.

Through these efforts, buprenorphine has helped change the mindset of many community treatment providers previously unwilling to consider the use of medications to treat drug addiction. Some of these programs now regularly use buprenorphine to assist in opiate detoxification and treatment maintenance.

Next steps

- NIDA will continue to test the safety and efficacy of buprenorphine in other affected populations, including pregnant women, adolescents, and patients addicted to opiate analgesics.
- Working with SAMHSA's Addiction Technology Transfer Centers (ATTCs), State Directors, and other stakeholders, these agencies are continuing to spread the word about buprenorphine to more proactively address the urgent needs of drug addiction. They are striving to increase the use of this and other addiction medications in different settings and locales, including in the U.S. criminal justice system and in countries where injection drug use is still a primary mode of HIV transmission.

NIDA continues to be committed to supporting research to improve opioid addiction treatment, including behavioral therapies, which can be an important component of long-term recovery. Equally important is ensuring that these improvements reach all affected communities.

Improved medications

Probuphine is a long-acting version of buprenorphine that is showing promise in clinical trials. An implant inserted under the skin, Probuphine can deliver medication continuously for

6 months. Like Vivitrol, it aims to prevent abuse and diversion and increase treatment adherence by eliminating the need for daily dosing.

Vaccine research

Vaccines are being developed to help combat a variety of addictions including heroin. A heroin vaccine, currently under development, would corral heroin in the bloodstream and prevent it from reaching the brain and exerting its euphoric effects. This approach could guard against relapse and be an effective addition to a comprehensive treatment plan for heroin addiction.

This brief intervention gives patients a chance to learn about their drug use—especially as it pertains to their health—from an objective third party with medical training. It relies on the premise that advice from an expert has been shown to promote change.^{11,12}

TREATMENT

Research validates the use of both health care and counseling predicts better outcomes for sustaining sobriety and engagement with long-term recovery.

The mental health professional will, in general, first meet their prospective opioid dependent client, shortly after he or

she has been examined by a health care provider and started the medication induction process. Often, the first contact will include a brief introduction and handing the client written information pertaining to opioid recovery treatment.

The role of the health care provider

The health care provider will measure and monitor the patient's vital signs, including temperature, pulse, breathing rate, and blood pressure. Symptoms will be treated as appropriate. The patient may receive:

- Breathing support.
- Tube placed through the mouth into the lungs (endotracheal intubation).
- Medicine called naloxone, which helps block the effect of the drug on the central nervous system (such medicine is called a narcotic antagonist).
- Toxicology screening.

In most cases, the health care team will monitor the patient for 4 to 6 hours in the emergency room, although the optimal observation time after opioid intoxication has not been defined for most opioids. Those with moderate-to-severe intoxications will likely be admitted to the hospital for 24 to 48 hours.

The health care provider may also indicate a psychiatric evaluation is needed for all exposures with suicidal intent. For example, a new analysis of data from a trial in which “intensive case management” or (ICM) outperformed usual care among women receiving welfare indicates that comorbid depression played a significant role in the outcomes. Dr. Alexis Kuerbis and colleagues at Columbia University [External link](#), please review our disclaimer. found that both assignment to ICM and the presence of high levels of depression symptoms

independently enhanced participants' likelihood of engaging in substance abuse treatment and attending more treatment sessions during the 2-year study. Surprisingly, ICM proved to be more effective among depressed participants than among non-depressed ones in improving two outcomes: treatment engagement and reducing alcohol consumption. A higher level of depression symptoms at the start of the study also predicted more days of abstinence over a 2-year period. The researchers had hypothesized that ICM would be less, rather than more, effective for depressed women, as it did not include any specialized focus on comorbid psychiatric disorders. To explain their contrary findings, the researchers note previous research that showed that depression increases readiness to change. They suggest that ICM participants' copious ongoing contact with case managers and help in overcoming practical barriers to treatment capitalizes on such readiness.

Complications from withdrawal include vomiting and breathing in stomach contents into the lungs. This is called aspiration, and can cause lung infection. Vomiting and diarrhea can cause dehydration and body chemical and mineral (electrolyte) disturbances.

The biggest complication is return to drug use. Most opiate overdose deaths occur in people who have just withdrawn or detoxed. Because withdrawal reduces a person's tolerance to the drug, those who have just gone through withdrawal can overdose on a much smaller dose than they used to take.

Exams, Tests and long-term health care maintenance

A doctor can often diagnose opiate withdrawal after performing a physical exam and asking questions about your medical history and drug use.

Urine or blood tests to screen for drugs will be utilized.

Treatment involves supportive care and medications. The most commonly used medication, clonidine, primarily reduces anxiety, agitation, muscle aches, sweating, runny nose, and cramping.

Other medications can treat vomiting and diarrhea. Buprenorphine (Subutex) has been shown to work better than other medications for treating withdrawal from opiates, and it can shorten the length of detox. It may also be used for long-term maintenance like methadone.

People withdrawing from methadone may be placed on long-term maintenance. This involves slowly decreasing the dosage of methadone over time. This helps reduce the intensity of withdrawal symptoms.

Some drug treatment programs have widely advertised treatments for opiate withdrawal called detox under anesthesia or rapid opiate detox. Such programs involve placing you under anesthesia and injecting large doses of opiate-blocking drugs, with hopes that this will speed up the return the body to normal opioid system function. There is no evidence that these programs actually reduce the time spent in withdrawal. In some cases, they may reduce the intensity of symptoms. However, there have been several deaths associated with the procedures, particularly when it is done outside a hospital. Because opiate withdrawal produces vomiting, and vomiting during anesthesia significantly increases death risk, many specialists think the risks of this procedure significantly outweigh the potential (and unproven) benefits.

Patient progress should be monitored via clinical evaluation (e.g., patient self-report) and objective measures (e.g., urine toxicology testing).

Mental health professional intervention

The mental health professional's role, often includes "case management" jobs, and in general, includes:

- Advising the client about drug use.
- Assessing client's readiness to quit.
- Facilitating client changes.
- Arranging other types of treatment or follow-up care.

Providers should be aware that many States mandate reporting of drug use during pregnancy and that failure to do so may be a prosecutable offense.

Mental health professionals, during the course of their initial sessions will assess their clients' readiness to quit opioid use

Utilizing the ASI results

When administering and reporting on the ASI results begin by reviewing screening results with the client by:

- Asking permission to have a short discussion about the screening results.
- Report back the types and amounts of use reported:
 - Allow the client to correct omissions so you get the full picture of use.
 - Prompt the patient: *"Tell me more about your use of drug X and Y"* (for each drug the patient reported).

The Addiction Severity Index (ASI) (McLellan, Kushner, Metzger, et al., 1992), mentioned earlier in this course, is an instrument designed to assess the impact of a patient's addiction on his or her function. Although this instrument is typically used in research, it has been adapted for clinical use and illustrates the various aspects of a patient's life that should be assessed at each patient visit to determine the impact of active addiction or the benefits of abstinence. The ASI evaluates patient function in the areas of:

- Drug use
- Alcohol use
- Psychiatric function
- Medical function
- Employment
- Social/family functioning
- Legal problems

Stated earlier, in addition to patient self-report, urine testing can be a useful practice in monitoring patient progress in treatment. In some countries, urine testing is mandated as part of the treatment plan. A variety of substances can be detected in urine testing. Testing can occur for naturally occurring opioids (e.g., codeine, morphine) or synthetic or semi-synthetic opioids (e.g., oxycodone, methadone). Testing also can occur for benzodiazepines, cocaine, marijuana, or other drugs that are used and/or abused by the patient population. The period of detection of each of these substances varies with the laboratory technique that is used and the extent of drug use and can range from days to weeks.

while establishing a therapeutic alliance. The professional wears many hats during this process by utilizing the ASI, checking in with the client's healthcare professional, and informing clients about medical management, and possible side effects, and normal withdrawal cycles.

It is important to establish rapport by:

- Avoiding a tone that your client might think is judgmental or confrontational.
- Show an interest in your client's life.
- Acknowledge your client's current view of his/her drug use.
- Signal to the client that having mixed feelings about a drug use problem is normal.
- Highlight client's confidentiality (and its limitations).

Reminder: The ASI screen is only one indicator of a client's potential drug use problem. It is not a substitute for clinical judgment, which you should use to determine when an intervention is warranted.

When appropriate, educate clients on the following:

- Use of even small amounts of drugs or tobacco may negatively impact health and performance (e.g., driving or operating machinery).
- Because drug intoxication can lead to impaired judgment and risky behaviors, refer all sexually active clients for confidential testing for HIV and other sexually transmitted

diseases or provide an onsite testing opportunity, if they do not know their status or have not been tested recently. Encourage all clients to practice safe sex.

- Refer all clients with past or current injection drug use for HIV and Hepatitis B/C testing if they have not been tested twice over a 6-month span following their last injection.
- Make referrals to evaluate suspected co-occurring conditions (e.g., psychiatric consultation for depressed, inattentive, or anxious clients or pain specialist consultation for patients seeking narcotic prescriptions for chronic nonmalignant pain).
- Provide recommendations based on risk level that includes:

High Risk - A strong recommendation to change substance use is essential. Consider making a statement such as: “Based on the screening results, you are at high risk of having or developing a substance use disorder. It is medically in your best interest to stop your use of (insert specific drugs here). I am concerned that if you do not make a change quickly, the consequences to your health and well-being may be serious.” Include a referral for additional assessment (the NIDA-Modified ASSIST provides a risk level, but not a diagnosis of abuse or dependence). Let the client know that the assessment will determine whether they have a diagnosis of substance abuse or dependence and if substance abuse treatment is indicated. Whether to attend treatment will be the patient’s decision.

- Specific examples of harm for different problem drug categories may be helpful.
- Emphasize that there are many ways to change substance use behavior (e.g., community treatment programs, self-help groups, medications, etc.).
- Emphasize that treatment is often on an outpatient basis and programs are often accommodating of concerns like maintaining employment, insurance reimbursement, child care, etc., depending on the patient’s concerns.

Moderate Risk - Consider beginning the discussion by saying, “Based on the screening results, you are at moderate risk of having or developing a substance use disorder. It is medically in your best interest to change your use of (insert specific drugs here).”

- Add information that is specific to the drugs the client uses.
- Express your concern about specific ways drugs might negatively impact your patient’s life (e.g., health, relationships, work, etc.).
- Emphasize that there are many ways to change substance use behavior (e.g., community treatment programs, self-help groups, medications, etc.).

Assessing client’s readiness to quit

When assessing your client’s readiness to quit consider these suggestions:

- Have a conversation about whether the client is ready to quit. For example, you might say something like, “*Given what we’ve talked about, do you want to change your drug use?*”
- If the client is unwilling to quit, raise awareness about drugs as a health problem. Let clients who are not ready know that you will revisit the issue at future visits and have resources available when he/she decides to pursue making a change.

Lower Risk - Consider having a discussion about acceptable levels of use and the potential for future problems. You may begin the discussion by saying, “Your screening results show you are unlikely to have a substance use disorder. However, people with any history of substance use can be at some risk of adverse consequences and developing a disorder especially in times of stress or if they have just started to use recently. It is impossible to know in advance whether or not a person will become addicted. As your physician I encourage you to only use alcohol moderately and responsibly and to avoid using other substances.”

- Intervention duration may be minimal.
- Use your clinical judgment based on the medical status of the patient and drug being used. For example, pregnant women,* youth, people with histories of substance use disorders, and others for whom any drug use could potentially pose a serious risk may benefit from a complete intervention regardless of apparent risk level.

At follow-up, make targeted recommendations to moderate-, high- and select lower-risk clients accordingly:

High Risk—Targeted Recommendations:

- Determine whether the client followed through with the referral.
- Offer additional brief intervention for clients who did not attend the referral.
- Make additional referrals for clients who missed referral.
- Obtain records of assessment and/or treatment for clients who attended referral and/or treatment.
- Discuss ways to help support recommendations of referral source.

Moderate Risk—Targeted Recommendations:

- Determine whether the client reduced or abstained from use.
- For clients who did not make progress with change efforts, acknowledge change is hard, repeat brief intervention, and discuss additional ways to support the clients’ efforts.
- For clients who have made changes, reinforce efforts and encourage additional goal-setting.
- Follow up at subsequent visits.

Lower Risk—Targeted Recommendations:

- If the client indicated that he/she wanted to make a change, ask what, if anything, the client decided to do about substance use.
- Encourage abstinence from tobacco and illicit drugs and advise low-risk alcohol users to remain within acceptable drinking levels.
- On evidence of escalation of use, conduct brief intervention.

Facilitating your client's change

- Jointly complete a progress note form with the client to document the screening results and create a follow-up plan.
- Help set concrete (and reasonable) goals for making a change:
 - Ask interested clients to complete a change plan during session.
 - Make a copy without their name or the name of your office on it, give it to them to take home, and tell them you will check in on their progress at the next visit.
 - For clients who do not complete a change plan, schedule a second appointment to continue the discussion and to complete the change plan. You may provide a blank copy for them to take home and ask them to return with it, but some clients may need to start again with a fresh copy during their second session.
 - For clients **not** interested in completing a change plan, encourage them to set a few brief change goals (e.g., cutting back, trying a self-help group); record the goals to check progress at the next visit.

Longer-term treatment is recommended for most people following withdrawal. This can include self-help groups, like Narcotics Anonymous or SMART Recovery, outpatient counseling, intensive outpatient treatment (day hospitalization), or inpatient treatment.

Professional counseling is strongly recommended, particularly in early recovery. Those withdrawing from opiates should be checked for depression and other mental illnesses. Appropriate treatment of such disorders can reduce the risk of relapse. Antidepressant medications should NOT be withheld under the assumption that the depression is only related to withdrawal, and not a pre-existing condition.

Treatment goals should be discussed with the patient and recommendations for care made accordingly. If a person continues to withdraw repeatedly, methadone maintenance is strongly recommended.

Follow-up

As a licensed mental health professional it is necessary to evaluate your strengths when counseling substance abuse clients; specifically opioid dependent persons. Continue to assess your client for need for additional services such as specialty assessments, residential drug treatment, and long-term care.

Remember to:

- Refer clients as appropriate.

Support Groups - Support groups, such as Narcotics Anonymous and SMART Recovery, can be enormously helpful to people addicted to opiates.

- Schedule follow-up on a consistent basis.
- Offer continuing support at follow-up with regard to additional book recommendations, materials, blogs, etc.
- Because the screening does not provide a diagnosis of abuse or dependence, refer high-risk clients for a full assessment. For moderate-risk clients and low-risk patients with special concerns (e.g., pregnant women, past injection drug users), use clinical judgment to determine whether additional

assessment is necessary. Use SAMHSA's treatment locator (see additional resources, <http://findtreatment.samhsa.gov/>) or NIDA's National Drug Abuse Treatment Clinical Trials Network List of Associated Community Treatment Programs (see additional resources, www.drugabuse.gov/about-nida/organization/cctn/ctn) to locate assessment resources.

- If nearby treatment resources are not available, consider providing support group contact information and self-change materials, as well as other counseling resources—clergy or mental couples counselors.
- Obtain a written information release to send the screening results to all providers who will receive referrals.
- Schedule a follow-up session within 1–2 weeks for moderate and high-risk clients and low-risk clients in certain groups.
- Offer continuing support at follow-up sessions.
 - Annual rescreening is indicated for clients who report any drug use at baseline (even with scores of 0–3) and for any other clients about whom you remain concerned. For moderate- and high-risk patients, rescreen at next appointment.

Treatment Benefits

Many benefits of medication management combined with counseling for opioid dependence have been discussed in this course. But in addition, intensive case management (ICM) can help substance-abusing women who receive welfare benefits stay off drugs and make strides in employment, report Dr. Jon Morgenstern and colleagues at Columbia University. In a study of 302 applicants for Temporary Assistance for Needy Families in New Jersey, the researchers assigned roughly half to an ICM intervention that included weekly visits from a case manager, help in overcoming treatment barriers, assistance in identifying and meeting other patient service needs, and voucher incentives for remaining in treatment. The rest of the trial participants received the care welfare agencies typically provide to

substance-abusing clients, which consists of screening and referral for treatment.

When interviewed after 24 months, 47 percent of the women receiving ICM had been abstinent from drugs for the past 30 days, compared with 24 percent of those in the usual care group. At that same time, 22 percent of the women in the ICM group—but only 9 percent of those in the usual care group—were employed full-time. For comparison, the full-time employment rate was 34 percent among 150 female welfare recipients who did not abuse drugs.

The researchers are now conducting a cost-benefit analysis of ICM. If their promising results are replicated in future

evaluations, welfare agencies may have an effective tool to help some of their most vulnerable clients. (*American Journal*

of Public Health 28(53):14372–14378, 2008 (AbstractExternal link, please review our disclaimer.))

Preventing opioid dependence in the future

Healthcare providers have long wrestled with how best to treat patients who suffer from chronic pain, roughly 116 million in this country. Their dilemma stems from the potential risks involved with long-term treatment, such as the development of drug tolerance (and the need for escalating doses), hyperalgesia (increased pain sensitivity), and addiction. Patients themselves may even be reluctant to take an opioid medication prescribed to them for fear of becoming addicted. Estimates of addiction among chronic pain patients vary widely - from about 3 percent to 40 percent. This variability is the result of differences in treatment duration, insufficient research on long-term outcomes, and disparate study populations and measures used to assess abuse or addiction.

To mitigate addiction risk, physicians should screen patients for potential risk factors, including personal or family history of

drug abuse or mental illness. Monitoring patients for signs of abuse is also crucial, and yet some indicators can signify multiple conditions, making accurate assessment challenging. Early or frequent requests for prescription pain medication refills, for example, could represent illness progression, the development of drug tolerance, or the emergence of a drug problem.

The development of effective, non-addicting pain medications is a public health priority. A growing elderly population and an increasing number of injured military only add to the urgency of this issue. Researchers are exploring alternative medications that can alleviate pain but have less abuse potential. More research is needed to better understand effective chronic pain management, including identifying factors that predispose some patients to addiction and developing measures to prevent abuse.

Summary

Taken as intended, prescription and OTC drugs safely treat specific mental or physical symptoms. But when taken in different quantities or when such symptoms aren't present, they may affect the brain in ways very similar to illicit drugs. For example, stimulants such as Ritalin increase alertness, attention, and energy the same way cocaine does—by boosting the amount of the neurotransmitter dopamine.

Drug abuse and dependence changes the way the brain works, resulting in compulsive behavior focused on drug seeking and use, despite often devastating consequence. These behaviors are the essence of addiction. Consequently, drug abuse/addiction treatment must address these brain changes, both in the short and long term. When people addicted to opioids first stop, they undergo withdrawal symptoms, which may be severe pain, diarrhea, nausea and vomiting.

Medications can be helpful in this detoxification stage to ease craving and other physical symptoms, which often prompt relapse. However, this is just the first step in treatment. Medications may also become an essential component of an ongoing treatment plan, enabling opioid-addicted persons to regain control of their health and their lives. Physicians prescribe a particular medication based on a patient's specific medical needs and other factors. Effective medications include:

Methadone (Dolophine or Methadose), a slow-acting, opioid agonist. Methadone is taken orally, so that it reaches the brain slowly, dampening the “high” that occurs with other routes of administration while preventing withdrawal symptoms. Since the earliest methadone maintenance treatment programs in the United States, women have been treated successfully with methadone through all phases of their lives, including pregnancy.

Buprenorphine (Subutex, Suboxone), a partial opioid agonist. Buprenorphine relieves drug cravings without producing the “high” or dangerous side effects of other opioids. Suboxone is a novel formulation, taken orally, that combines buprenorphine with naloxone (an opioid antagonist) to ward off attempts to get high by injecting the medication.

Naltrexone (Depade, Revia) an opioid antagonist. Naltrexone is not addictive or sedating and does not result in physical dependence; however, poor patient compliance has limited its effectiveness.

Research validates the use of both health care and counseling predicts better outcomes for sustaining sobriety and engagement with long-term recovery with opioid dependent persons.

References

- Abbott PJ, Moore B, Delaney H, Weller S. Retrospective analyses of additional services for methadone maintenance patients. *Journal of Substance Abuse Treatment* 1999;17(1-2):129-37.
- Abdul-Quader OS, Friedman SR, Des Jarlais DC, Marmor MM, Maslansky R, Bartelme S. Methadone maintenance and behavior by intravenous drug users that can transmit HIV. *Contemporary Drug Problems* 1987;14:425-33.
- Amato L, Davoli M, Perucci C, Ferri M, Faggiano F, Mattick RP. An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. *Journal of Substance Abuse Treatment* 2005;28(4):321-29.
- Amato L, Minozzi S, Davoli M, Vecchi S, Ferri M, Mayet S. Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. *The Cochrane Database of Systematic Reviews*, Issue 4, 2004.
- Anglin D, Hser Y, Booth M. Sex differences in addict careers. *American Journal of Drug and Alcohol Abuse* 1987;13(3):253-80.
- Auriacombe M, Fatseas M, Dubernet J, Daulouede JP, Tignol J. French field experience with buprenorphine. *American Journal on Addictions* 2004;13(Suppl 1):S17-28.
- Ball JC, Lange WR, Meyers CP, Friedman SR. Reducing the risk of AIDS through methadone maintenance treatment. *Journal of Health and Social Behavior* 1988;29:214-226.
- Ball JC, Ross A. *The Effectiveness of Methadone Maintenance Treatment*. New York, NY: Springer-Verlag Inc., 1991.

- Ball JC, Ross A. The Effectiveness of Methadone Maintenance Treatment: Patients, Programs, Services, and Outcomes. New York: Springer-Verlag, 1991.
- Beschner G, Reed B, Mondanaro J. Treatment Services for Drug Dependent Women. Rockville, MD: National Institute on Drug Abuse, 1981.
- Capelhorn JR, Dalton MS, Haldar F, Petrenas AM, Nisbet, JG. Methadone maintenance and addicts' risk of fatal heroin overdose. *Substance Use and Misuse* 1996;31:177-96.
- Capelhorn JRM, Bell J, Kleinbaum DG, Gebiski VJ. Methadone dose and heroin use during maintenance treatment. *Addiction* 1993;88:119-24.
- Capelhorn JRM, Bell J. Methadone dosage and retention of patients in maintenance treatment. *The Medical Journal of Australia* 1991;154:195-99.
- Center for Substance Abuse Treatment. Methadone-Associated Mortality: Report of a National Assessment, May 8-9, 2003. CSAT Publication No. 28-03. Rockville, MD: Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, 2004.
- Centers for Disease Control and Prevention, National Center for HIV, STD and TB Prevention. Methadone Maintenance Treatment. Atlanta, GA: CDC, 2000. Available online at: www.cdc.gov/odp/oc/facts/MethadoneFin.pdf. [Accessed March 23, 2006.]
- Compton P, Ling W, Charuvastra C, Wesson DR. Buprenorphine as a pharmacotherapy for opioid addiction: what dose provides a therapeutic response? *American Journal of the Addictions*, in press.
- Condelli WS, Duntzman GH. Exposure to methadone programs and heroin use. *American Journal of Drug and Alcohol Abuse* 1993;19:65-78.
- Courtwright D. A century of American narcotic policy. In: *Institute of Medicine. Treating Drug Problems: Volume 2*. Washington, DC: IOM, 1992, pp. 1-62. Available online at: books.nap.edu/openbook.php?isbn=0309043964. [Accessed March 23, 2006.]
- Dolan KA, Shearer J, MacDonald M, Mattick RP, Hall W, Wodak AD. A randomized controlled trial of methadone maintenance treatment versus wait list control in an Australian prison system. *Drug & Alcohol Dependence* 2003;72(1):59-65.
- Dole VP, Nyswander ME, Kreek MJ. Narcotic blockade. *Archives of Internal Medicine* 1966;118:304-09.
- Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. Methadone maintenance at different dosages for opioid dependence. *The Cochrane Database of Systematic Reviews*, Issue 3, 2003.
- Fairbank JA, Duntzman GH, Condelli WS. Do methadone patients substitute other drugs for heroin? Predicting substance use at 1-year follow-up. *American Journal of Drug & Alcohol Abuse* 1993;19(4):465-74.
- Fiellin DA, Lintzeris N. Methadone syrup injection in Australia: a sentinel finding? *Addiction* 2003;98:385-386.
- Finnegan L. Treatment issues for opioid-dependent women during the perinatal period. *Journal of Psychoactive Drugs* 1991;23:191-201.
- Fudala PJ, Bridge TP, Herbert S, Williford WO, Chiang CN, Jones K, et al. Buprenorphine/Naloxone Collaborative Study Group. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *New England Journal of Medicine* 2003;349(10):949-58.
- Gossop M, Marsden J, Stewart D, Rolfe A. Patterns of improvement after methadone treatment: 1 year follow-up results from the National Treatment Outcome Research Study. *Drug & Alcohol Dependence* 2000;60(3):275-86.
- Gowing L, Farrell M, Bornemann R, Ali R. Substitution treatment of injecting opioid users for prevention of HIV infection. *The Cochrane Database of Systematic Reviews*, Issue 4, 2004.
- Gowing LR, Farrell M, Bornemann R, Sullivan L, Ali, R. Methadone treatment of injecting opioid users for prevention of HIV infection. *Journal of General Internal Medicine*, in press.
- Green H, James RA, Gilbert JD, Harpas P, Byard RW. Methadone maintenance programs—a two-edged sword? *American Journal of Forensic Medicine & Pathology* 2000;21(4):359-61.
- Grella CE, Annon JJ, Anglin MD. Ethnic differences in HIV risk behaviors, self-perceptions, and treatment outcomes among women in methadone maintenance treatment. *Journal of Psychoactive Drugs* 1995;27(4):421-33.
- Harlow LL, Anglin MD. Time series design to evaluate effectiveness of methadone maintenance intervention. *Journal of Drug Education* 1984;14(1):53-72.
- Hartel D. Cocaine use, inadequate methadone does increase risk of AIDS for IV drug users in treatment. *NIDA Notes* 1989/1990;5(1).
- Hentoff N. The treatment of patients - I. *The New Yorker* 1965;June 26:32-77.
- Hubbard RL, Marsden ME, Rachal JV, Harwood HJ, Cavanaugh ER, Ginzburg HM. *Drug Abuse Treatment: A National Study of Effectiveness*. Chapel Hill: University of North Carolina Press, 1989.
- Hubbard RL, Marsden ME, Rachal JV, Harwood HJ, Cavanaugh ER, Ginzburg HM. *Drug Abuse Treatment: A National Study of Effectiveness*. Chapel Hill: University of North Carolina Press, 1989.
- Jaffe JH, Martin WR. Opioid analgesics and antagonists. In: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. New York: Pergamon Press, 1985.
- Jansson LM, Velez M, Harrow C. Methadone maintenance and lactation: a review of the literature and current management guidelines. *Journal of Human Lactation* 2004;20(1):62-71.
- Johnson RE, Jaffe JH, Fudala JP. A controlled trial of buprenorphine treatment for opioid dependence. *JAMA* 1992;267(20):2750-55.
- Joseph H, Stancliff S, Langrod J. Methadone maintenance treatment (MMT): a review of historical and clinical issues. *The Mount Sinai Journal of Medicine* 2000;67(5 & 6):347-64. Available online at: http://mountsinai.site-ym.com/?page=Journal_of_Medicine/67/6756.shtml. [Accessed March 23, 2006.]
- *Journal of Studies on Alcohol and Drugs* 72(2):297-307, 2011. Abstract AvailableExternal link, please review our disclaimer.
- Kaltenbach K, Finnegan L. Developmental outcome of children born to methadone maintained women: a review of longitudinal studies. *Neurobehavioral Toxicology and Teratology* 1984;6:271-75.
- Kaltenbach K, Silverman N, Wapner R. Methadone maintenance during pregnancy. In: *State Methadone Treatment Guidelines*. Rockville MD: U.S. Department of Health and Human Services, 1993.
- Kandel D. Epidemiological trends and implications for understanding the nature of addiction. In: O'Brien D, Jaffe J (eds.). *Addictive States*. New York: Raven Press, 1992.
- Kleber HD, Mezritz M, Slobetz F. *Medical Evaluation of Long-Term Methadone-Maintained Clients*. Rockville, MD: National Institute on Drug Abuse, 1980.
- Kosten TR, Rounsaville BJ, Kleber, HD. Multidimensionality and prediction of treatment outcome in opioid addicts: a 2.5-year follow-up. *Comprehensive Psychiatry* 1987;28:3-13.
- Kosten TR, Schottenfeld R, Ziedonis D, Falcioni J. Buprenorphine versus methadone maintenance for opioid dependence. *Journal of Nervous and Mental Disease* 1993;181(6):358-64.
- Kraft KM, Rothbard AB, Hadley TR, McLellan AT, Asch DA. Are supplementary services provided during methadone maintenance really cost-effective? *American Journal of Psychiatry* 1997;154:1214-19.
- Krantz MJ, Lewkowicz L, Hays H, Woodroffe MA, Robertson AD, Mehler PS. Torsade de pointes associated with very-high-dose methadone. *Annals of Internal Medicine* 2002;137(6):501-04.
- Kreek M, Schecter A, Gutjahr C, Bowen D, Field F, Queenan J, et al. Analyses of methadone and other drugs in maternal and neonatal body fluids: use in evaluation of symptoms in a neonate of mother maintained on methadone. *American Journal of Drug and Alcohol Abuse* 1974;1:409.
- Kreek MJ. Medical complications in methadone patients. *Annals of the New York Academy of Science* 1978;311(29):110-34.
- Kreek MJ. Methadone in treatment: physiological and pharmacological issues. In: DuPont RL, Goldstein A, O'Donnell J, Brown B (eds.). *Handbook on Drug Abuse*. Rockville, MD: National Institute on Drug Abuse, 1979.
- Kreek MJ. Using methadone effectively: achieving goals by application of laboratory, clinical, and evaluation research and by developing of innovative programs. In: Pickens RW, Leukefeld CG, Schuster CR (eds.). *Improving Drug Abuse Treatment*. NIDA Research Monograph Series 196. Rockville, MD: National Institute on Drug Abuse, 1991.
- Lehman WEK, Barrett ME, Simpson DD. Alcohol use by heroin addicts 12 years after drug abuse treatment. *Journal of Studies in Alcohol* 1990;51(3):233-44.
- Lenne MG, Dietze P, Rumbold GR, Redman JR, Triggs TJ. The effects of the opioid pharmacotherapies methadone, LAAM and buprenorphine, alone and in combination with alcohol, on simulated driving. *Drug & Alcohol Dependence* 2003;72(3):271-78.
- Lepere B, Gourarier L, Sanchez M, Adda C, Peyret E, Nordmann F, et al. Reduction in the number of lethal heroin overdoses in France since 1994. Focus on substitution treatments. *Annales de Medecine Interne* 2001;152:5-12.
- Ling W, Charuvastra C, Collins JF, Batki S, Brown LS, Kintaudi P, et al. Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. *Addiction* 1998;93(4):475-86.
- Ling W, Wesson DR, Charuvastra C, Klett CJ. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. *Archives of General Psychiatry* 1996;53(5):401-47.
- Lowinson JH, Marion IJ, Joseph H, Dole VP. Methadone maintenance. In: Lowinson JH, Ruiz P, Millman RB (eds.). *Substance Abuse: A Comprehensive Textbook*. Second Edition. Baltimore, MD: Williams & Wilkins, 1992.
- Maddux JF, Desmond DP. Crime and treatment of heroin users. *The International Journal of the Addictions* 1979;14(7):891-904.
- Maddux JF, Desmond DP. Ten-year follow-up after admission to methadone maintenance. *American Journal of Drug and Alcohol Abuse* 1992;18(3):289-303.
- Maddux JF, McDonald LK. Status of 100 San Antonio addicts one year after admission to methadone maintenance. *Drug Forum* 1973;2:239-52.
- Maddux JF, Williams TR, Ziegler JA. Driving records before and during methadone maintenance. *American Journal of Drug and Alcohol Abuse* 1977;4(1):91-100.
- Marion IJ. Methadone treatment at forty. *NIDA Science & Practice Perspectives* 2005;3(1):25-31. Available online at: <http://archives.drugabuse.gov/perspectives/vol3no1.html>. [Accessed March 23, 2006.]
- Marsch LA. The efficacy of methadone maintenance interventions in reducing illicit opiate use, HIV risk behavior and criminality: a meta-analysis. *Addiction* 1998;93(4):515-32.
- Marsh J, Miller N. Female clients in substance abuse treatment. *International Journal of the Addictions* 1985;20:995-1019.
- Marsh K, Simpson D. Sex differences in opioid addiction careers. *American Journal of Drug and Alcohol Abuse* 1986;12:309-29.
- Martell BA, Arnsten JH, Krantz MJ, Gourevitch MN. Impact of methadone treatment on cardiac repolarization and conduction in opioid users. *American Journal of Cardiology* 2005;95(7):915-18.
- Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *The Cochrane Database of Systematic Reviews*, Issue 2, 2003.
- McGlothlin WH, Anglin MD. Shutting off methadone: cost and benefits. *Archives of General Psychiatry* 1981;38:885-92.
- McLellan AT, Arndt IO, Metzger DS, Woody GE, O'Brien CP. The effects of psychosocial services in substance abuse treatment. *JAMA* 1993;269(15):1953-59.
- McLellan AT, Kushner H, Metzger D, Peters R, Smith I, Grissom G, et al. The Fifth Edition of the Addiction Severity Index. *Journal of Substance Abuse Treatment* 1992;9(3):199-213.
- Meandzija B, O'Connor PG, Fitzgerald B, Rounsaville BJ, Kosten TR. HIV infection and cocaine use in methadone maintained and untreated intravenous drug users. *Drug & Alcohol Dependence* 1994;36(2):109-13.

- Mello NK, Bree MP, Mendelson JH. Comparison of buprenorphine and methadone effects on opioid self-administration in primates. *Journal of Pharmacological Experimental Therapy* 1983;225:378-86.
- Mello NK, Mendelson JH, Kuehnle JC. Buprenorphine effects on human heroin self-administration: an operant analysis. *Journal of Pharmacological Experimental Therapy* 1982;223:30-39.
- Mello NK, Mendelson JH. Buprenorphine suppresses heroin use by heroin addicts. *Science* 1980;207:657-59.
- Mendelson J, Jones RT, Welms S, Baggott M, Fernandez I, Melby AK, et al. Buprenorphine and naloxone combinations: the effects of three dose ratios in morphine-stabilized, opiate-dependent volunteers. *Psychopharmacology* 1999;141(1):37-46.
- Metzger DS, Woody GE, McLellan AT, O'Brien CP, Druley P, Navaline H, et al. Human immunodeficiency virus seroconversion among intravenous drug users in- and out-of-treatment: an 18-month prospective follow-up. *Journal of Acquired Immune Deficiency Syndrome* 1993;6:1049-56.
- Mondanaro J. Strategies for AIDS prevention: motivating health behavior in drug dependent women. *Journal of Psychoactive Drugs* 1987;19:143-49.
- Murphy S, Irwin J. Living with the dirty secret: problems of disclosure for methadone maintenance clients. *Journal of Psychoactive Drugs* 1992;24:257-64.
- National Institutes of Health. Effective Medical Treatment of Opiate Addiction: Consensus Development Conference Statement. Bethesda, MD: NIH, 1998. Available online at: <http://consensus.nih.gov/1997/1998TreatOpiateAddiction108html.htm>. [Accessed March 22, 2006.]
- O'Connor PG, Fiellin DA. Pharmacologic treatment of heroin-dependent patients. *Annals of Internal Medicine* 2000;133:40-54.
- Payte JT, Khuri ET. Treatment duration and patient retention. In: *State Methadone Treatment Guidelines*. Rockville, MD: Center for Substance Abuse Treatment, 1993.
- Pond S, Kreek M, Tong T, Raghunath J, Benowitz NL. Altered methadone pharmacokinetics in methadone-maintained pregnant women. *Journal of Pharmacology and Experimental Therapeutics* 1985;233:1-6.
- Powers KI, Anglin MD. Cumulative versus stabilizing effects of methadone maintenance. *Evaluation Review* 1993;17(3):243-70.
- Rayburn WF, Bogenschutz MP. Pharmacotherapy for pregnant women with addictions. *American Journal of Obstetrics & Gynecology* 2004;191(6):1885-97.
- Rettig R, Yarmolinsky A (eds.). *Federal Regulation of Methadone Treatment*. Washington, DC: Institute of Medicine, 1995, pp. 1-16. Available online at: books.nap.edu/catalog.php?record_id=4899. [Accessed March 22, 2006.]
- Rosenbaum M. Sex roles among deviants; the women addict. *International Journal of the Addictions* 1981;16:859-77.
- Schindler SD, Ortner R, Peterzell A, Eder H, Opgenoorth E, Fischer G. Maintenance therapy with synthetic opioids and driving aptitude. *European Addiction Research* 2004;10(2):80-87.
- Schottenfeld RS, Pakes JR, Oliveto A, Ziedonis D, Kosten TR. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Archives of General Psychiatry* 1997;54(8):713-20.
- Sees KL, Delucchi KL, Masson C, Rosen A, Clark HW, Robillard H, et al. Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence. A randomized controlled trial. *JAMA* 2000;283:1303-10.
- Sells SB, Simpson DD (eds.). *The Effectiveness of Drug Abuse Treatment*. Cambridge, MA: Ballinger, 1976.
- Selwyn P, Schoenbaum E, Davenny K, Robertson VJ, Feingold AR, Shulman JF, et al. Prospective study of human immunodeficiency virus infection and pregnancy outcomes in intravenous drug users. *JAMA* 1989;261:1289-94.
- Serpelloni G, Carrieri MP, Rezza G, Morganti S, Gomma M, Binkin N. Methadone treatment as a determinant of HIV risk reduction among injecting drug users: a nested case-control study. *AIDS Care* 1994;6:215-20.
- Seymour A, Black M, Jay J, Cooper G, Weir C, Oliver J. The role of methadone in drug related deaths in the west of Scotland. *Addiction* 2003;98(7):995-1002.
- Simpson DD, Joe GW, Lehman WEK, Sells SB. Addiction careers: etiology, treatment, and 12-year follow-up outcomes. *Journal of Drug Issues* 1986;16(1):107-21.
- Simpson DD, Sells SB (eds.). *Opioid Addiction and Treatment: A 12-Year Follow-Up*. Malabar, FL: Krieger Publishing Company, 1990.
- Simpson DD, Sells SB. Effectiveness of treatment for drug abuse: an overview of the DARP research program. *Advances in Alcohol and Substance Abuse* 1982;2(1):7-29.
- Simpson DD. Drug treatment evaluation research in the United States. *Psychology of Addictive Behaviors* 1993;7(2):120-28.
- Simpson DD. Longitudinal outcome patterns. In: Simpson DD, Sells SB (eds.). *Opioid Addiction and Treatment: A 12-Year Followup*. Malabar, FL: Krieger Publishing, 1990.
- Strain EC, Bigelow GE, Liebson IA, Stitzer ML. Moderate- vs high-dose methadone in the treatment of opioid dependence. A randomized trial. *JAMA* 1999;281:1000-05.
- Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Buprenorphine versus methadone in the treatment of opioid-dependent cocaine users. *Psychopharmacology (Berl)* 1994;116(4):401-06.
- Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Dose-response effects of methadone in the treatment of opioid dependence. *Annals of Internal Medicine* 1993;119:23-37.
- Substance Abuse and Mental Health Services Administration. *About Buprenorphine Therapy*. Rockville, MD: SAMHSA, 2000a. Available online at: <http://buprenorphine.samhsa.gov/about.html>. [Accessed March 23, 2006.]
- Substance Abuse and Mental Health Services Administration. *Drug Addiction Treatment Act of 2000*. Rockville, MD: SAMHSA, 2000b. Available online at: <http://buprenorphine.samhsa.gov/data.html>. [Accessed March 23, 2006.]
- Substance Abuse and Mental Health Services Administration. *Medication Assisted Treatment*. Rockville, MD: SAMHSA, 2005. Available online at: www.dpt.samhsa.gov/404error.aspx?404; <http://www.dpt.samhsa.gov/treatment.htm>. [Accessed March 27, 2006.]
- Sullivan LE, Fiellin DA. Buprenorphine: its role in preventing HIV transmission and improving the care of HIV infected patients with opioid dependence. *Clinical Infectious Diseases* 2005;41(6):891-96.
- Sullivan LE, Metzger DS, Fudala PJ, Fiellin DA. Decreasing international HIV transmission: the role of expanding access to opioid agonist therapies for injection drug users. *Addiction* 2005;100(2):150-58.
- Vanichseni S, Wongsuwan B, Choopanya K, Wongpanich K. A controlled trial of methadone maintenance in a population of intravenous drug users in Bangkok: implications for prevention of HIV. *International Journal of the Addictions* 1991;26(12):1313-20.
- Verdejo A, Toribio I, Orozco C, Puente KL, Perez-Garcia M. Neuropsychological functioning in methadone maintenance patients versus abstinent heroin abusers. *Drug & Alcohol Dependence* 2005;78(3):283-88.
- Wang D, Teichtahl H, Drummer O, Goodman C, Cherry G, Cunningham D, et al. Central sleep apnea in stable methadone maintenance treatment patients. *Chest* 2005;128(3):1348-56.
- Weber RB, Ledergerber M, Opravil M, Siegenthaler W, Luthy R. Progression of HIV infection in misusers of injected drugs who stop injecting or follow a programme of maintenance treatment with methadone. *British Medical Journal* 1990;301:1362-5.
- Williams AB, McNelly EA, Williams AE, D'Aquila RT. Methadone maintenance treatment and HIV type 1 seroconversion among injecting drug users. *AIDS Care* 1992;4(1):35-41.
- Williamson PA, Foreman KJ, White JM, Anderson G. Methadone-related overdose deaths in South Australia, 1984-1994. How safe is methadone prescribing? *Medical Journal of Australia* 1997;166(6):302-05.
- Zador DA, Sunjic SD. Methadone-related deaths and mortality rate during induction into methadone maintenance, New South Wales, 1996. *Drug & Alcohol Review* 2002;21(2):131-36.
- Zanis DA, Woody GE. One-year mortality rates following methadone treatment discharge. *Drug & Alcohol Dependence* 1998;52:257-60.

MEDICATION MANAGEMENT OF OPIOID DEPENDENCE

Final Examination Questions

Select the best answer for each question and then proceed to www.EliteCME.com to complete your final examination.

1. Scientific research has established that medication-assisted treatment of opioid addiction:
 - a. Suppresses patient retention.
 - b. Interrupts patient retention.
 - c. Increases patient retention.
 - d. Decreases patient retention.
2. Methadone (Dolophine or Methadose) is:
 - a. Neural inhibitor.
 - b. A slow-acting, opioid agonist.
 - c. A fast-acting opioid agonist.
 - d. A partial opioid agonist.
3. Buprenorphine (Subutex, Suboxone) is:
 - a. A partial opioid agonist.
 - b. A slow-acting opioid agonist.
 - c. A fast-acting opioid.
 - d. None of the above.
4. Opioid intoxication is a condition caused by:
 - a. Use of Xanax.
 - b. Taking more than 10 mg. a day.
 - c. Drinking alcohol.
 - d. Use of opioid-based drugs.
5. The acceptable initial dose for methadone treatment is:
 - a. 30 mg daily.
 - b. 130 mg daily.
 - c. 10 mg daily.
 - d. None of the above.
6. Ball and Ross study (1991) of 617 patients demonstrated that methadone maintenance treatment is associated with a dramatic decline in the average number of:
 - a. Days missed at work per year.
 - b. Crime-days per year.
 - c. Employee complaints.
 - d. Days in treatment.
7. As a partial agonist, buprenorphine has:
 - a. Less potential for abuse than addiction.
 - b. Greater potential for abuse than most partial agonists.
 - c. Less potential for abuse than most full agonists.
 - d. None of the above.
8. The ASI screen is:
 - a. The only proven indicator of a client's potential drug use problem.
 - b. Still being tested as a viable assessment instrument.
 - c. A very long assessment instrument that takes several hours to complete.
 - d. Only one indicator of a client's potential drug use problem.
9. Providers should be aware that many States mandate reporting of drug use during pregnancy and that failure to do so may be:
 - a. A sign of future problems for the mother and child.
 - b. A problematic issue for the States.
 - c. An ethics issue.
 - d. A prosecutable offense.
10. The mental health professional's role, often includes "case management" jobs, and in general, includes:
 - a. Advising the client about drug use.
 - b. Assessing client's readiness to quit.
 - c. Facilitating client changes.
 - d. All of the above.