

# Opiate Abuse and Dependence

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### Faculty

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### Faculty Disclosure

Contributing faculty, Mark Rose, BS, MA, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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### Division Planner Disclosure

The division planner has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

### Audience

This course is designed for dental care providers who may be involved in identifying or treating opiate dependence.

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#### **Disclosure Statement**

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#### **Course Objective**

The purpose of this course is to assist dental professionals in identifying, treating, and providing appropriate referrals to patients with opiate use disorders. Fear of creating new opiate addicts has influenced prescribing practices for decades, and this course will convey the actual risk of patient addiction to these pain-relieving drugs when used legitimately.

#### **Learning Objectives**

Upon completion of this course, you should be able to:

1. Define key terms associated with opiate abuse and dependence.
2. Outline the background and epidemiology of opiate use and abuse, including risk factors for misuse and dependence.
3. Describe the pharmacology and clinical effects of opioids.
4. Discuss characteristics of specific opiate drugs and opioid antagonists.
5. Review the natural history, pathophysiology, and effects of opiate abuse and dependence.
6. Identify signs and symptoms of opiate overdose and withdrawal.
7. List the issues associated with the abuse of or dependence on legitimately prescribed opiates.
8. Discuss the role of crisis intervention and harm reduction in the management of opiate abuse and dependence.
9. Identify methods of managing the detoxification and withdrawal associated with cessation of opiate abuse or dependence.
10. Discuss therapies used to maintain extended abstinence from opiates, including agonist replacement and abstinence therapies.
11. Identify common psychological comorbidities present in opiate-dependent patients and implications for treatment.
12. Outline the effects of opiate use on fetuses and neonates and appropriate interventions for opiate-dependent pregnant women.
13. Identify factors associated with favorable/unfavorable treatment outcome.



Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

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## INTRODUCTION

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The purpose of this course is to provide the reader with a current, evidence-based overview of opiate abuse and dependence and its treatment. Topics covered in this review include the history and demographics of illicit and prescription opiate abuse; risk factors, background characteristics, and comorbid conditions of opiate abusers; the pharmacology of opiate drugs; the biological and behavioral characteristics of opiate dependence; and management of opiate dependence, including treatment of overdose, detoxification and withdrawal, agonist replacement therapy, and drug-free approaches. Additional areas of the course will be devoted to the abuse liability of prescription opiates and the impact of abused opiates on the fetus.

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## DEFINITIONS

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A confusing aspect of the body of research on opiate abuse and dependence is the inconsistent use of important terminology that describes the nature and severity of involvement with therapeutic and illicit opiates. The following definitions have been proposed in an effort to encourage more correct usage of this terminology:

- **Misuse:** Patients' incorrect use of a medication, including use for an unintended purpose, exceeding the prescribed amount, or taking the drug more frequently or for longer than prescribed [1].
- **Abuse:** Definition varies widely depending on the context. The Drug Enforcement Agency (DEA) defines abuse as the use of a schedule II-V drug in a manner or amount inconsistent with the medical or social pattern of a culture [1]. Abuse is also defined as the use of prescription medications beyond "the scope of sound medical practice" [1]. Abuse and misuse often overlap when referring to prescription medication. The American Psychiatric Association defines

abuse as "a maladaptive pattern of substance use, leading to clinically significant impairment or distress as manifested by one or more behaviorally based criteria" [2].

- **Addiction:** Defined by the American Society of Addiction Medicine (ASAM) as "a primary chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing the development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving" [1]. Addiction is also referred to a psychological dependence.
- **Dependence:** This term has replaced the term "addiction" in some contexts. Opioid dependence, as defined in the latest *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)*, refers to both psychological dependence (or addiction) and physical dependence [2]. Physical dependence consists of neurobiological adaptation (development of tolerance) from chronic exposure.

The most widely used definition of opiate dependence syndrome is the *DSM-IV-TR* diagnostic criteria. The *DSM-IV-TR* defines opiate dependence as a maladaptive pattern of opiate use, leading to clinically significant impairment or distress. Opiate dependence may be diagnosed if a patient exhibits three or more of the following [2; 3]:

- Tolerance (need to increase the dose to achieve the desired effect)
- Withdrawal symptoms when use stops or abruptly declines
- Loss of control
- Persistent desire or unsuccessful attempts to cut down or control use
- Preoccupation with obtaining opiate medications (e.g., multiple doctors, trips to the emergency department)

- Important social, occupational, or recreational activities forfeited or reduced because of opiate use
- Use despite the awareness of adverse physical or psychological problems caused or worsened by opiates

In summary, the term dependence is used to describe two separate phenomena. Pharmacologically, drug dependence is characterized by the presence of tolerance and a withdrawal syndrome. Psychiatrically, drug dependence is characterized by compulsive use, inability to reduce use, preoccupation, drug-seeking behaviors, and a heightened vulnerability to relapse after abstinence [4].

Pseudoaddiction describes drug-seeking behaviors iatrogenically produced in pain patients by inadequate pain treatment. This is manifested as preoccupation with and pursuit of opiate medication driven by a desire for pain relief, not the drug's mood-altering effects. Pseudoaddiction develops in three phases. Initially, the patient receives an inadequate level of analgesia, which leads to the patient's escalation of analgesic demands and behavioral changes. This may be exaggerated to convince others of the pain severity and need for more medication, which results in a crisis of mistrust between the patient and the healthcare team. Pseudoaddiction is preventable when the patient's report of pain is accepted as valid [1].

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## BACKGROUND

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The first reference to opium is found in the third century BCE. The use of opium was well-understood by Arabic physicians, and Arabic traders introduced the drug to Asia, where it was utilized primarily for the control of dysentery [5].

The isolation of morphine from opium was achieved in 1806 and was named for Morpheus, the Greek god of dreams [5]. The discovery of other alkaloids in opium followed: codeine in 1832 and papaverine in 1848. By the mid-nineteenth century, pure alkaloids were used in medical practice in place of crude opium preparations [5].

In addition to the highly beneficial therapeutic effects, the toxic side effects and addictive potential of opiates have been known for centuries. These undesired effects have prompted a search for a potent synthetic opioid analgesic free of addictive potential and other complications. However, all synthetic opiates introduced into medical use share the same liabilities of the classical opioids. The search for new opioid therapeutics has resulted in the synthesis of opioid antagonists and compounds with mixed agonist-antagonist properties, such as buprenorphine, which has expanded therapeutic options and provided the basis of expanded knowledge of opioid mechanisms [5].

Nonmedical use of prescription opioids was reported in literature as early as 1880. A report in 1928 documented that injection of opiates contributed to the development of nonmedical use and misuses of prescription opioids. Before 1930, the prevalence of nonmedical opioid injecting in the U.S. was low. But by the mid-1940s, more than one-half the admissions to the National Institute of Mental Health's Lexington Hospital were for the misuse of prescription opioids [6].

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## EPIDEMIOLOGY OF OPIATE ABUSE AND DEPENDENCE

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The estimated worldwide annual prevalence of opiate use is 0.4%, and roughly 8 million people abuse opiates [7]. Substantial regional differences in opiate abuse patterns exist. In the majority of Europe, heroin is the most prevalent illegally consumed opioid. In North America, illegally diverted prescription opioids, including hydromorphone, oxycodone, codeine, meperidine, morphine, and hydrocodone, are increasingly the primary illegal opioids [8].

The Drug Abuse Warning Network (DAWN) provides estimates of the health consequences of non-medical use of individual drugs, including opiate medications. DAWN emergency department mentions are collected from affiliated hospital emergency departments to identify abused substances, assess associated adverse health consequences, and monitor drug misuse patterns and trends on local, state, and national levels [3]. The definition of drug abuse in the DAWN system is the nonmedical use of a substance for psychic effect, dependence, or suicide attempt or gesture [3].

Research has indicated that there were 164,572 heroin-related emergency department episodes in 2005 [85]. Opiate/opioid analgesic misuse was also encountered frequently in emergency departments. In 2005, hydrocodone and its combinations accounted for 51,225 emergency department visits, and oxycodone and its combinations resulted in 42,810 visits to the emergency department [85]. Research has indicated a significant increase in the number of emergency department mentions for hydrocodone and oxycodone between 1996 and 2000 [1; 18].

An estimated 3.7 million people in the U.S. have used heroin at least once in their lives; approximately 800,000 are addicted to the drug [9]. According to the 2003 National Survey on Drug Use and Health, the annual number of new heroin users from 1995 to 2002 ranged from 121,000 to 164,000. Most new users are older than 17 years of age and male. In 2003, 57.4% of past-year heroin users were believed to have developed heroin abuse or dependence, and an estimated 281,000 persons received treatment for heroin abuse. It is important to note that this survey underestimates heroin use, possibly to a substantial extent, as obtaining accurate statistics on illicit drug use is difficult [10].

According to the Monitoring the Future survey, NIDA's nationwide annual survey of drug use among the nation's 8th-, 10th-, and 12th-graders, heroin use remained relatively stable from 2003 to 2007. Lifetime heroin use (at least one use in an individual's lifetime) measured 1.3% among 8th-graders and 1.5% among 10th- and 12th-graders [11]. Lifetime heroin-only users are more likely to report a past year family income of less than \$20,000 (31.5%) than either lifetime oxycodone-only users (19.7%) or lifetime heroin and oxycodone users (24.9%) [12].

Nonmedical use of prescription opioids has caused increasing concern among law enforcement officials and regulatory, pain relief advocacy, and drug abuse organizations [13]. The prevalence of lifetime nonmedical oxycodone use increased from 11.8 million users (5%) in 2002 to 13.7 million users (5.8%) in 2003. In contrast, the estimated lifetime prevalence for heroin use is 1.8% [12]. Among high school seniors, an estimated 9.6% used hydrocodone/acetaminophen (Vicodin) non-medically. More than 85 million prescriptions were written for hydrocodone/acetaminophen in 2003, making it the most prescribed drug in the U.S. for that year [13].

An estimated 63 million individuals in the U.S. have used a prescription opiate for nonmedical purposes at least once during their lifetime; oxycodone accounts for 1.9 million of these cases [14]. In 2002, 4.7% (11 million) household residents older than 12 years of age abused an opioid medication. Almost 14% of those who had abused opiates, or 1.5 million Americans, displayed opioid use disorder [15]. In 2003, opioid analgesics were second only to marijuana as the most frequently abused illicit drugs among high school seniors. Escalation in use and associated problems indicate an expanded pathway to opioid dependence [15].

The number of new nonmedical users of the four major classes of prescription-type drugs (pain relievers, tranquilizers, stimulants, and sedatives) increased between 1991 and 2001; the largest increase occurred with pain relievers. In 1990 there were 628,000 initiates compared to 2.4 million in 2001 [12; 16]. Concurrently, the number of primary treatment admissions for opioid analgesic abuse increased 76% between 1997 and 2000 [12; 17].

Between 2002 and 2003, lifetime nonmedical use of pain relievers significantly increased among persons 12 years of age and older, from 29.6 million to 31.2 million. Opioids with statistically significant increases in lifetime use were [16]:

- Hydrocodone/acetaminophen (from 13.1 million to 15.7 million)
- Oxycodone/aspirin or acetaminophen (from 9.7 million to 10.8 million)
- Hydrocodone (from 4.5 million to 5.7 million)
- Oxycodone (from 1.9 million to 2.8 million)
- Methadone (from 0.9 million to 1.2 million)
- Tramadol (from 52,000 to 186,000)

While increases in nonmedical use of opioid analgesics have been observed in both rural and urban areas, treatment data suggest it may be more prevalent in rural areas. Research data also suggest a rising problem with injecting among rural opioid users, a problem more typically associated with urban drug users [6].

The increase in opioid analgesic abuse is particularly troubling because respiratory depression and death can result from the doses at which these agents are frequently abused, especially when mixed with other central nervous system depressants [15]. The two populations for whom prescription opiate abuse is especially problematic are adolescents, due to the uncertain implication of future dependence, and the elderly, due to the increased vulnerability to toxicity. Early exposure to opioids in adolescent users may cause neurobiological changes and behavioral consequences that differ from adults [15].

#### DEMOGRAPHICS OF PRESCRIPTION AND ILLICIT OPIATE USERS

Male-to-female ratios for lifetime heroin-only users and lifetime heroin and oxycodone users are similar. However, lifetime oxycodone-only users are more likely to be female (43.7%) than either of the other two groups [12].

Lifetime oxycodone-only users and lifetime heroin and oxycodone users are similarly distributed racially and ethnically, with both groups being predominantly white (91.3% and 90.6%, respectively). A small percentage of these users are black or African American and an even smaller percentage are other minority races/ethnicities. While the majority of lifetime heroin-only users are white (65.7%), a greater proportion are black (26.8%) or other races/ethnicities (7.5%) than the other two groups [12].

Lifetime heroin-only users and lifetime heroin and oxycodone users are predominantly 35 years of age or older (74% and 63.5%, respectively). Lifetime oxycodone-only users are more likely to be 12 to 34 years of age (56.6%) [12].

## RISK FACTORS FOR OPIATE ABUSE/DEPENDENCE

Persons at heightened risk for heroin experimentation include those who abuse alcohol or marijuana, those with first-degree relatives addicted to alcohol or other drugs, and those with friends and associates addicted to heroin or at high risk of heroin experimentation [4]. Of course, not all persons who ingest drugs regarded as having a high liability of abuse and dependence end up becoming addicted to the drug. Among persons who try heroin, an estimated 23% develop heroin dependence, a rate comparable to cocaine but greater than marijuana [19].

The expected drug effect and the setting of use (context of administration) play important roles in the social learning of drug use. Because opioids, like other drugs that increase dopamine turnover, lead to conditional responses, the use of opiates may become conditioned to the activities of daily living. As a result, environmental stimuli become powerfully associated with opiate use, which can trigger cravings for the drug [15]. The visibility of pharmaceutical marketing and advertising of medications may also play a role by changing the attitudes towards ingestion of these agents [15]. For youth, a social learning aspect to drug use is likely, based on the modeling of drug use by adults in their families and social networks [15].

Marked increases in prescriptions written for opioids in the U.S. and Internet access to prescription drugs may explain a portion of the increase in opiate abuse and dependence. However, although Internet access is a major problem and accounts for some of the increase in opioid drug abuse, the same rate of increase has not been observed for other prescription drugs, such as stimulants, suggesting that other factors are involved [15]. Changes in the way medicine is practiced also influence prescription practices. Primary care physicians provide a greater proportion of care for pain patients rather than pain specialists, increasing the potential of diversion and abuse [15].

The increase in emergency department mentions is not solely accounted for by an increase in prescriptions; for example, from 1994–2002, fentanyl mentions increased more than 50-fold while the number of prescriptions increased only 7.2-fold. Similar excessive increases in ED mentions relative to prescriptions have been observed with oxycodone but not morphine or hydrocodone [15].

### Risk Factors for Prescription Opiate Abuse Among Pain Patients

Predictors of dependence on opiate medications among pain patients include substance abuse-related diagnoses, positive toxicology for opiates, and other medical diagnoses. Other patients at risk include those with idiopathic pain (no clear etiology) or high levels of psychological distress or disability [3]. Alcoholism and other drug dependence are often viewed as contraindications for opiate medications in chronic noncancer pain.

### EPIDEMIOLOGY OF OVERDOSE

Overdose is a major cause of premature death among heroin users. Nonfatal opiate overdoses (defined as instances in which loss of consciousness and respiratory depression occur but are not fatal) are highly prevalent among heroin users, occurring in 50% to 70% of users [20].

### Risk Factors for Heroin/Opiate Overdose

Identified risk factors for fatal heroin overdose include male gender, single status, unemployment, history of heroin dependence, no current treatment for heroin dependence, intravenous (IV) use, and concomitant use of alcohol or benzodiazepines. An unexplained and consistent finding is that victims of fatal heroin overdose are generally older, experienced users. Also, at autopsy, a large proportion of overdose fatalities have relatively low blood morphine concentrations [20]. (Heroin is rapidly metabolized into morphine once administered.) Demographic patterns among overdose fatalities suggest that polydrug use and loss of tolerance are key factors, which partially explains low blood opiate concentrations. However, this does not explain the strong association of fatal overdose with age [20].

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## CLASSIFICATION

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Opioid broadly refers to all compounds related to opium. The term opium is derived from *opos*, the Greek word for “juice,” as the drug is derived from the juice of the opium poppy *Papaver somniferum*. Opiates are drugs derived from opium, including the natural products morphine, codeine, and thebaine, and numerous semisynthetic derivatives [5].

The narcotic analgesics can be categorized into three groups. The first group includes the natural opium derivatives (heroin, morphine, and codeine) and the semi-synthetic derivatives from this group, including hydromorphone, oxycodone, hydrocodone, oxycodone, dihydrocodeine, and buprenorphine. The two other groups are synthetic chemicals: the phenylpiperidines, including meperidine and fentanyl, and the pseudopiperidines, including methadone and propoxyphene [21].

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## OPIATE SYNTHESIS

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As noted, opium is obtained from the unripe seed capsules of the poppy plant *P. somniferum*. The sides of the unripe seed pod are slit, and the milky juice that emerges is dried to make powdered opium. Although raw opium contains numerous alkaloids, only a few, such as morphine, codeine, thebaine, and papaverine, have clinical utility. Because morphine synthesis is difficult, the drug is still primarily obtained from opium or extracted from poppy straw [5].

Heroin, or diacetylmorphine, is synthesized by collecting and converting powdered opium to heroin hydrochloride in clandestine laboratories [4]. Impurities in the processing, particularly in heroin from Mexico, result in some street heroin being brown in color. This type of heroin, often referred to as “black tar,” is the predominant type available in the western U.S. The purity of Colombian and Mexican heroin powder averages 40% to 60% [4].

From the point of entry in the U.S. to the consumer, heroin hydrochloride is adulterated by the addition of quinine, lactose, mannitol, dextrose, or talc at each level of distribution, to the point that bags costing \$10 (“dime bags”) may contain only 6% heroin hydrochloride [4].

The numerous synthetic derivatives of morphine and thebaine are made by relatively simple modifications of the molecule. Examples of this include the transformation of morphine to diacetylmorphine by acetylation at the 3 and 6 positions. The main goals of opioid structural modification are to increase the affinity for various species of opioid receptors, alter the activity of the drug from agonist to antagonist, change the lipid solubility, and alter the resistance to metabolic breakdown [5].

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## PHARMACOLOGY

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Opioids have been the mainstay of pain treatment for thousands of years. Opioids exert their effects by mimicking naturally occurring endogenous opioid peptides or endorphins [5]. Although many new opiates have been developed with pharmacological properties similar to morphine, morphine remains the standard against which new analgesics are measured [5].

### ENDOGENOUS OPIOID PEPTIDES

The endogenous opioid system is complex and subtle, with diverse functions. The system plays a sensory role, which is prominent in inhibiting response to painful stimuli; a modulatory role in gastrointestinal, endocrine, and autonomic functions; an emotional role evidenced by the powerful rewarding and addicting properties of opioids; and a cognitive role involving modulation of learning and memory [5].

There are three distinct families of classical opioid peptides: enkephalins, endorphins, and dynorphins. Each of these families is derived from a distinct precursor protein and has a characteristic anatomical distribution. The precursor proteins, preproenkephalin, prepro-opiomelanocortin (POMC), and preprodynorphin are encoded by three corresponding genes. The primary opioid peptide derived from POMC is beta-endorphin. The POMC precursor is also processed into the non-opioid peptides adrenocorticotrophic hormone (ACTH), melanocyte-stimulating hormone (alpha-MSH), and beta-lipotropin (beta-LPH), suggesting a common precursor for the stress hormone ACTH and the opioid peptide beta-endorphin. This association indicates a shared physiological linkage between the stress axis and opioid systems, which has been validated by the observation of stress-induced analgesia [5].

## OPIOID RECEPTORS

Opioids produce their effects through activity at three major receptor subtypes: mu, kappa, and delta. These G-protein-coupled receptors are linked to adenylate cyclase. The endogenous ligands for these receptors, beta-endorphin, enkephalin, and dynorphin, are expressed heterogeneously throughout the central and peripheral nervous systems, with a distribution pattern parallel with that of opioid receptors. Opioid receptors are also found in the central respiratory centers. Functional studies have revealed substantial parallels between mu and delta receptors and dramatic contrasts between mu/delta and kappa receptors [22].

Most opioid therapeutics, and all opioids with abuse potential, are selective for mu receptors, reflecting their similarity to morphine. However, drugs that are relatively selective at standard doses can interact with additional receptor subtypes at higher doses, resulting in divergent pharmacological profiles [5]. A large number of endogenous ligands activate a small number of opioid receptors, a pattern strikingly different from most other neurotransmitter systems, in which a single ligand interacts with a large number of receptors that have different structures and second messengers [5].

## ABSORPTION, DISTRIBUTION, METABOLISM, AND ELIMINATION

Typically, opioids are readily absorbed from the gastrointestinal tract. The more lipophilic opioids are easily absorbed through the nasal or buccal mucosa. The most lipophilic opioids can be absorbed transdermally [5]. Most opioids, including morphine, undergo variable but significant hepatic first-pass metabolism, limiting oral bioavailability relative to parenteral administration. Most opioids act quickly when given intravenously. Compared with more lipid-soluble opioids, such as codeine, heroin, and methadone, morphine crosses the blood-brain barrier at a considerably lower rate [5].

## CLINICAL EFFECTS

Morphine and most other opioid agonists share in common the following physiological effects [5]:

- Analgesia
- Changes in mood and reward behavior
- Disruption of neuroendocrine function
- Alteration of respiration
- Changes in gastrointestinal and cardiovascular function

## ANALGESIA

Morphine-like drugs produce analgesia, drowsiness, changes in mood, and mental clouding, all without loss of consciousness. Patients in pain report that the pain is less intense, less discomforting, or entirely gone when given therapeutic doses of these drugs. The pain relief is fairly selective, and other sensory modalities are not affected. Some patients experience euphoria. When morphine in the same dose is given to a pain-free individual, the experience may be unpleasant. Nausea and vomiting is common, and drowsiness, difficulty in mentation, apathy, and decreased physical activity may occur. The subjective analgesic and toxic effects, including respiratory depression, become more pronounced as the dose is increased. Morphine-class drugs seldom cause slurred speech, emotional lability, or significant motor incoordination [5].

## EFFECT ON MOOD AND REWARD

Although the mechanisms by which opioids induce euphoria, tranquility, and other alterations of mood (including rewarding properties) have not been entirely determined, the neural systems mediating opioid reinforcement are distinct from those involved in physical dependence and analgesia [23]. Behavioral and pharmacological data point to the probable role of dopaminergic pathways, with interactions between opioids and dopamine mediating the opioid-induced reinforcement [5].

## NEUROENDOCRINE SYSTEM

Morphine acts in the hypothalamus to inhibit the release of gonadotropin-releasing hormone and corticotropin-releasing hormone (CRH), which decrease circulating luteinizing hormone (LH), follicle-stimulating hormone (FSH), ACTH, and beta-endorphin. This in turn reduces the plasma concentrations of testosterone and cortisol [5].

## RESPIRATION

Morphine-like opioids depress respiration in part through a direct effect on the brainstem respiratory centers. Therapeutic doses of morphine depress all phases of respiratory activity and possibly induce irregular and periodic breathing. Clinically significant respiratory depression seldom occurs at standard therapeutic doses. The primary mechanism of respiratory depression involves a diminished responsiveness of the brainstem respiratory centers to carbon dioxide [5].

## GASTROINTESTINAL TRACT

Morphine-like drugs directly stimulate the chemoreceptor trigger zone for emesis in the area postrema of the medulla, resulting in the nausea and vomiting experienced by some patients [5]. Morphine also decreases gastric motility; diminishes biliary, pancreatic, and intestinal secretions; and delays digestion of food in the small intestine. In the colon, peristaltic waves are diminished or abolished and tone is increased to the point of spasm, delaying the passage of bowel contents [5].

## CARDIOVASCULAR SYSTEM

There are no opioid receptors on the heart, so morphine does not act directly on the heart muscle. However, opioid agonists indirectly affect cardiovascular processes through suppression of reflex vasoconstriction, which may result in bradycardia and hypotension [86]. In cases of injecting use, bacterial endocarditis can develop [86].

## OTHER EFFECTS

Opioid agonists may also affect reflexes, particularly swallow/cough reflexes and pupillary dilation. Morphine and related opioids depress the cough reflex by direct action on the cough center in the medulla [5]. Morphine and most mu and kappa agonists also constrict the pupils through excitation of the parasympathetic nerve stimulating the pupil [5].

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## SPECIFIC OPIATE DRUGS

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### FULL AGONISTS

#### Heroin

Heroin, or diacetylmorphine, is a highly potent, semisynthetic analgesic produced by the anhydrous acetylation of morphine. Heroin is generally believed to have no significant opioid receptor activity; however, heroin is rapidly metabolized to 6-monoacetylmorphine and then to morphine. While diacetylmorphine and 6-monoacetylmorphine readily cross the blood-brain barrier, morphine itself is much slower to do so; thus, heroin can be considered a prodrug that facilitates the brain entry of morphine [22]. The drug rapidly enters the brain after IV administration, where it binds to mu, kappa, and other stereospecific opiate-receptor binding sites in the locus coeruleus [4]. The onset of euphorogenic action is approximately 30 minutes after intranasal ingestion, 15 minutes after subcutaneous injection, and almost instantaneously after IV injection, with a duration of about 3 to 4 hours [4]. As with many other opiates, heroin reduces the anticipatory anxiety associated with emotional or physical pain and alters the perception of pain [4].

Heroin is rapidly deacetylated in the microsomes of the endoplasmic reticulum in the liver to 6-mono-acetyl morphine (6-MAM), which is further deacetylated to morphine. It is excreted in the urine over a 30- to 40-hour period as free morphine and morphine 3-glucuronide [4]. Other drugs, including tricyclic antidepressants (TCAs), can inhibit the metabolism of heroin. Genetic variation in the expression of the enzymes involved in opioid metabolism and the potential for drug interactions at these sites may contribute to variation in response to heroin administration both among various individuals and within one individual [22].

The sought-after effects of heroin include intense tranquility, euphoria, analgesia, and a clouding of the sensorium, with the state of ecstasy and contentment immediately following IV injection being the most desired. Many novice heroin users experience adverse effects, such as mild nausea and vomiting. However, tolerance to these effects is soon achieved [4].

The lifestyle of the heroin addict seriously decreases life expectancy. Age-adjusted mortality rates have been found to be least seven times greater than that of the general population, adjusting for age, with death usually attributable to violence or drug effects. Also, the desire to replicate the most intense rush may compel the heroin addict to escalate the dose, resulting in acute heroin overdoses [4].

### Codeine

Codeine is approximately 60% as effective orally versus parenterally as an analgesic and respiratory depressant. Several codeine analogs, such as levorphanol, oxycodone, and methadone, have a high ratio of oral-to-parenteral potency, with the greater oral bioavailability reflecting lower hepatic first-pass metabolism [5].

Approximately 10% of ingested codeine is O-demethylated to morphine. Free and conjugated morphine can be found in the urine after therapeutic doses of codeine. Codeine has an exceptionally low affinity for opioid receptors, and the analgesic effect of codeine is due to its conversion to morphine. However, the antitussive effects of

this drug may involve distinct receptors that bind codeine itself. The plasma half-life of codeine is 2 to 4 hours [5].

### Tramadol

Tramadol, sold as Ultram, is a synthetic codeine analog and a weak mu-opioid receptor agonist. Tramadol is unusual among opiates in that a portion of its analgesic effect is produced by norepinephrine and serotonin uptake inhibition [5]. Tramadol is as effective as morphine or meperidine in the treatment of mild-to-moderate pain. It is 68% bioavailable following a single oral dose and 100% available following intramuscular administration. The affinity of tramadol for the mu-opioid receptor is only 1/6000th that of morphine. However, the primary O-demethylated metabolite of tramadol is two to four times as potent as the parent drug and may partially explain the analgesic effect. Physical dependence with tramadol has been reported [5].


### Levorphanol

Levorphanol (brand name Levo-Dromoran) is the only commercially available opioid agonist of the morphinan series, and it possesses pharmacological effects very similar to those of morphine. Levorphanol is metabolized less rapidly than morphine and has a half-life of 12 to 16 hours [5].

### Meperidine

Meperidine is predominantly a mu-receptor agonist. This agent, available under the brand name Demerol, is no longer recommended for treatment of chronic pain due to concerns of metabolic toxicity. Meperidine should not be used for longer than 48 hours or in doses greater than 600 mg/day. The central nervous system effects are similar but not identical to that of morphine. In equianalgesic doses, meperidine produces comparable sedation, respiratory depression, and euphoria as morphine. Some patients may experience dysphoria. Meperidine can cause central nervous system excitation, characterized by tremors, muscle twitches, and seizures, primarily due to accumulation of the metabolite normeperidine [1]. Large doses repeated at short intervals by addicts who have developed a tolerance to the sedative effects can produce an excitatory syndrome characterized by

hallucinations, tremors, muscle twitches, dilated pupils, hyperactive reflexes, and convulsions [5]. Meperidine is primarily abused by health professionals [5].



The Substance Abuse and Mental Health Services Administration (SAMHSA) asserts that prescription opioid addiction in health professionals should be viewed as an occupational hazard of the practice of medicine. Health professionals with substance abuse disorders often require specialized, extended care.

([http://www.guidelines.gov/summary/summary.aspx?doc\\_id=5887](http://www.guidelines.gov/summary/summary.aspx?doc_id=5887). Last accessed February 11, 2009.)

**Level of Evidence:** Expert Opinion/Consensus Statement

### Diphenoxylate and Loperamide

Diphenoxylate (in combination with atropine as Lomotil or Lonox) and loperamide (Imodium) are meperidine congeners that are approved by the U.S. Food and Drug Administration (FDA) for the treatment of diarrhea. These drugs slow gastrointestinal motility by affecting the circular and longitudinal muscles of the intestine, presumably through interaction with opioid receptors in the intestine [5].

### Fentanyl and Congeners

Fentanyl is a synthetic opioid related to the phenylpiperidines. The actions of fentanyl and its congeners (sufentanil, remifentanil, and alfentanil) are similar to those of other mu-receptor agonists. Fentanyl is a popular drug in anesthesia practice because of its relatively short time to peak analgesic effect, rapid termination of effect after small bolus doses, and relative cardiovascular stability. Fentanyl is approximately 100 times more potent than morphine, and sufentanil is approximately 10 times more potent than fentanyl. These drugs are usually administered intravenously and are substantially more lipophilic than morphine. Time to peak analgesia is rapid, usually within 5 minutes. Respiratory depression potential is similar to other mu-receptor agonists with a more rapid onset. Fen-

tanyl and sufentanil treatment of chronic pain has become more widespread, and transdermal patches that provide sustained release for 48 hours or more are available [5].

Fentanyl is delivered via the transdermal route for up to 72 hours, with patches containing 2.5, 5, 7.5, or 10 mg of fentanyl. Abuse of both the injectable formulation of fentanyl (Sublimaze) and the transdermal patch is primarily, but not exclusively, a problem among health professionals due to availability and proximity. Fentanyl may be extracted from the patch and injected, or the patch contents may be chewed, ingested, or inhaled. Even a patch that has been used for 3 days contains sufficient fentanyl to be abused [1].

### Methadone

Methadone was first synthesized as an analgesic in Germany during World War II as a response to the difficulty in obtaining raw opium [24]. Methadone is a long-acting mu-receptor agonist with pharmacological properties quantitatively similar to those of morphine [5]. Methadone is well-absorbed from the gastrointestinal tract and can be detected in plasma within 30 minutes of oral ingestion. Peak concentrations occur in the brain within 1 or 2 hours of subcutaneous or intramuscular administration [5]. Oral bioavailability approaches 90% [24].

In contrast to heroin, the activity of methadone is due almost exclusively to the parent drug rather than its metabolites. The drug is characterized by a long, but highly variable, half-life. One of the primary elimination pathways of methadone is *N*-demethylation, with cytochrome P450 3A4 (CYP 3A4) the major enzyme involved. Inhibition of CYP 3A4 with drugs such as ketoconazole and erythromycin may enhance and prolong the effect of methadone. Its induction with drugs such as rifampin, carbamazepine, and phenytoin will have the opposite effect [22]. Liver disease can increase the half-life of methadone, but renal failure will not [24]. Additionally, CYP 2D6 may be involved in the metabolism of the active enantiomer of methadone; less than 7% of white persons and more than 25% of Ethiopian persons are ultrarapid

metabolizers at CYP 2D6. Individuals with this polymorphism may be more likely to experience methadone overdose [22; 67].

Following absorption, methadone is distributed to the brain, liver, kidneys, muscles, and lungs. Tissue binding predominates over binding to plasma proteins, and accumulation of the drug occurs in these tissues with repeated dosing. Plasma concentrations are maintained by this peripheral reservoir. Methadone reabsorption from the tissues may continue for weeks after administration has ceased. It has an elimination half-life of about 22 hours, but metabolism varies in each person [25].

Some of the characteristic properties of methadone are its analgesic activity, its efficacy by the oral route, its extended duration of action in suppressing withdrawal symptoms in physically dependent individuals, and its ability to demonstrate persistent effects with repeated administration [5]. One of the most important advantages of methadone is that it alleviates cravings for opiates, a primary reason for relapse, and blocks many of the pleasurable effects of heroin, which helps reinforce abstinence [24].

In methadone clinics, methadone is usually dispensed in prepared individual doses mixed with fruit juice to discourage IV use. Methadone is also prescribed for pain. Until recently, there had been little evidence that diversion of methadone from pain management was occurring on any substantial scale. The majority of diverted methadone is used by heroin addicts to self-medicate symptoms of opiate withdrawal. To date, there is no evidence that diversion of methadone from methadone clinics has resulted in significant numbers of new opiate addicts [1].

More frequent side effects associated with methadone use include sweating, decreased libido, weight gain, constipation, and irregular menstrual periods, all occurring primarily during the initial stabilization process. Uncommon side effects include facial flushing, pruritus, euphoria or dysphoria, insomnia, urinary retention, and bradycardia. Rarely observed side effects include biliary spasm, urticaria, syncope, overdose death, and torsades de pointes [24].

Tolerance to the opiate properties of methadone develops within 4 weeks. The minimal effective dose is regarded as 50 mg, but some patients require much greater doses [24]. Subcutaneous administration of 10 to 20 mg methadone to former opioid addicts unambiguously produces euphoria similar in duration and magnitude to that of morphine. Methadone's overall abuse potential is comparable to that of morphine [5].

### **Propoxyphene**

Propoxyphene (Darvon) is structurally related to methadone and binds primarily to mu-opioid receptors to produce analgesic and other central nervous system effects similar to those seen with morphine-like opioids. As an analgesic, propoxyphene is about 50% to 65% as potent as codeine when given orally. The average half-life of propoxyphene in plasma after a single dose is 6 to 12 hours. Very large doses produce a degree of respiratory depression in morphine-tolerant addicts, suggesting incomplete cross-tolerance between propoxyphene and morphine. Administration via the intramuscular or intravenous routes results in severe damage to veins and soft tissues. The widespread popularity of propoxyphene has been largely a result of exaggerated concern about the addictive liability of codeine [5]. Due to an increased risk for potentially serious or fatal heart rhythm abnormalities, the FDA asked the manufacturers to voluntarily withdraw propoxyphene from the market in 2010 [88].

### **Levo-Alpha Acetylmethadol (LAAM)**

Levo-alpha acetylmethadol (LAAM) was first developed by German chemists in 1948. As early as 1952, LAAM was identified as an agent that could prevent opiate withdrawal symptoms for more than 72 hours. In 1993, the FDA approved LAAM for the treatment of opiate dependence [26]. LAAM is a more potent derivative of methadone, and opioid replacement therapy with LAAM was designed to build on the strengths and improve on the drawbacks of methadone [24]. Heightened concerns regarding the risk of arrhythmia and subsequent underutilization led the manufacturer of LAAM to withdraw the drug from the U.S. market in 2004 [24].

LAAM is a synthetic mu-opioid receptor agonist that is rapidly absorbed through the gastrointestinal tract following oral administration, although oral bioavailability is somewhat lower than methadone [24]. LAAM blocks the euphoric effects of other opiates while controlling opiate craving by creating a pharmacologic cross-tolerance to other opioids. The clinical utility of LAAM is based primarily on the activity of two metabolites: nor-LAAM and dinor-LAAM. The combined activity of these compounds gives LAAM its long duration of action [26]. LAAM actually has very little opioid effect in its parent form, essentially acting as a prodrug, and is metabolized in the liver by the hepatic P450 isozyme CYP3A4 into four major metabolites [24].

The onset of action of LAAM, 90 minutes, is slower than methadone. However, the duration of action (48 to 72 hours) is significantly longer, enabling administration 3 times per week. Similar to methadone, LAAM suppresses the symptoms of withdrawal and produces cross-tolerance to illicit opioid use. The average daily dose is 75 to 115 mg, and adverse effects of LAAM are infrequent and comparable to methadone [24].

### Hydrocodone

Hydrocodone is a semi-synthetic codeine derivative first used clinically as an antitussive and analgesic in the 1920s. Following a 10-mg oral dose, maximum serum level is observed in 1.3 hours [27]. Hydrocodone exhibits a complex pattern of metabolism, including O-demethylation, N-demethylation, and 6-keto reduction to the corresponding 6-a- and 6-b-hydroxymetabolites. The 2D6 enzyme demethylates hydrocodone at the 3-carbon position into hydromorphone, which has much stronger mu binding than hydrocodone. Similar to codeine, it has been proposed that hydrocodone is a prodrug. Its analgesic properties are generally considered equipotent to codeine [28; 29].

### Oxycodone

Oxycodone is similar in structure to hydrocodone, with the addition of a hydroxyl group at the 14-carbon. Oxycodone, as a hydrochloride salt, is a pure agonist opioid that has been in clinical use since 1917. Unlike codeine and hydrocodone, oxycodone is a potent analgesic in its own right and not a prodrug, although 2D6 activity creates the active opioid analgesic metabolite oxymorphone (synthesized and marketed as the analgesic Numorphan). Oxycodone is suitable for oral administration due to high bioavailability (60%) but may also be given intramuscularly, intravenously, subcutaneously, or rectally. In terms of analgesic potency and lipophilicity, oxycodone is comparable to morphine, and both drugs possess similar abuse potential. With the exception of hallucinations, which occur more rarely with oxycodone than with morphine, the side effects of these drugs are highly similar [30].

Oxycodone is metabolized by demethylation to noroxycodone and oxymorphone followed by glucuronidation. A urine screen may reveal oxycodone alone, oxycodone and oxymorphone, or oxymorphone alone [31].

Since 1995, oxycodone has been marketed in the U.S. as OxyContin, a Schedule II controlled-release oral tablet formulation. Oxycodone is also available in immediate-release tablets in combination with aspirin or acetaminophen under various trade names, including Percodan and Percocet, which contain 2.5 mg to 10 mg of oxycodone. The oxycodone content of OxyContin ranges from 10 mg to 80 mg. When taken orally, OxyContin tablets release oxycodone over a 12-hour period. However, when the controlled-release mechanism is destroyed by crushing the tablet, the oxycodone can be snorted, ingested, or injected. It is this delivery of a large amount of the active drug in a relatively brief time period (compared to the intact tablet and the low-dose immediate-release form) that underlies addicts' interest in OxyContin [1].

## Hydromorphone

Hydromorphone is a semi-synthetic hydrogenated ketone of morphine and shares the pharmacologic properties typical of mu-opioid agonists. Hydromorphone is a more potent analgesic than morphine; on a milligram basis, hydromorphone is 5 times as potent orally and 8.5 times as potent intravenously. Hydromorphone can be administered by infusion, intramuscularly, orally, or rectally [32].

Following oral administration of conventional-release hydromorphone, the drug is rapidly absorbed and undergoes hepatic first-pass elimination of approximately 50%. The terminal elimination half-life after IV administration is 2.5 to 3 hours. The primary mode of elimination is by urinary excretion as hydromorphone-3-glucuronide, the primary metabolite. Some metabolites may have greater analgesic activity than hydromorphone itself but are unlikely to contribute to the pharmacological activity. Side effects are comparable to morphine [32].

## MIXED AGONISTS/ANTAGONISTS

Discovery of an opioid analgesic with the efficacy but not the side effects or abuse potential of mu-agonists has been the ultimate goal of analgesic research for the past 50 years [14]. Mixed agonist-antagonist compounds have been developed with the hope that they would have less addictive potential and create less respiratory depression than morphine and related drugs. However, achieving the same degree of analgesia produces a similar magnitude of side effects, and a “ceiling effect,” limiting the amount of analgesia attainable, is often seen with these drugs. Also, some mixed agonist-antagonist drugs, such as pentazocine and nalorphine, can produce side effects not often seen with pure agonists, including severe, irreversible psychotomimetic effects [5].

Drugs such as nalbuphine and butorphanol are competitive mu-receptor antagonists, with their kappa receptor agonist action mediating the analgesic effect. Pentazocine qualitatively resembles these drugs but is a weaker mu-receptor antagonist or partial agonist while retaining its kappa-agonist activity. Buprenorphine is a partial mu-receptor agonist [5].

## Pentazocine

Pentazocine was developed in an effort to synthesize an effective analgesic with little or no abuse potential. With agonistic actions and weak opioid antagonistic activity, the pattern of central nervous system effects is similar to that of morphine-like opioids, including analgesia, sedation, and respiratory depression. Dysphoric and psychotomimetic effects can be precipitated by higher doses (60 to 90 mg) [5].

In the 1970s and early 1980s, pentazocine (Talwin) was combined with the crushed, blue-colored antihistamine tablet tripeleminamine and used intravenously, known as “Ts and Blues.” Factors contributing to its widespread abuse included placement outside Schedule II and the erroneous belief that the drug was not abusable. Pentazocine was also widely abused by physicians because it could be prescribed in large quantities outside of the stringent Schedule II monitoring system. At one point, pentazocine abuse became so prevalent that the manufacturer contemplated removing the drug from the market. Pentazocine was ultimately reformulated by the inclusion of the opiate antagonist naloxone. Similar to buprenorphine formulations containing naltrexone, when this formulation is taken as directed, the user experiences only the pentazocine effect because of poor oral naloxone absorption. However, if the tablet is dissolved and injected, the naloxone blocks the opiate effects of the pentazocine and precipitates acute opiate withdrawal [1].

### **Nalbuphine**

Nalbuphine, available under the trade name Nubain, is an agonist-antagonist opioid related to naloxone and oxymorphone, with a spectrum of effects that qualitatively resembles that of pentazocine but with a lower potential to produce dysphoric side effects. Although doses of 10 mg or less produce few side effects, much higher doses (70 mg) can produce psychotomimetic side effects such as dysphoria, racing thoughts, and distorted body image. Prolonged administration of nalbuphine can produce physical dependence and withdrawal [5].

### **Butorphanol**

Butorphanol is a morphinan congener with a profile of actions similar to those of pentazocine. It is generally more suitable for the relief of acute pain than chronic pain. Major side effects include drowsiness, weakness, sweating, feelings of floating, and nausea. Although the incidence of psychotomimetic side effects is lower than that with equianalgesic doses of pentazocine, they are qualitatively similar. Physical dependence to butorphanol can develop from regular use [5].

### **Buprenorphine**

Buprenorphine was initially suggested in 1978 as an alternative oral opiate substitution therapy for opiate addicts. Buprenorphine is a semi-synthetic opiate derivative made from thebaine, one of the numerous naturally-occurring alkaloids in opium [33]. Buprenorphine, sold as Buprenex or Subutex, is a long-acting partial opioid agonist that is classified as a Schedule III narcotic, in contrast to methadone and LAAM, which are Schedule II [24].

Buprenorphine has a very low oral bioavailability due to substantial intestinal and hepatic metabolism. The sublingual formulation used to treat opiate dependence is well-absorbed and produces opiate agonistic effects comparable to subcutaneous administration. Maximum plasma level is achieved 70 to 90 minutes after sublingual administration, and absolute bioavailability is 35% to 50% [33].

Following absorption, buprenorphine initially accumulates in the liver, kidneys, muscular tissue, and fatty tissue. It is released from fatty tissue when the plasma level drops and is then available at the opioid receptor. The slow dissociation kinetics explain the prolonged period of effectiveness. Buprenorphine is metabolized through the hepatic cytochrome P450 pathway. Approximately 80% is eliminated through biliary excretion of the glucuronidated metabolites and 20% via the urinary route [33].

The minimum daily dose needed to suppress opiate use is about 4 mg. Larger doses of buprenorphine (32 mg) result less in an increase in therapeutic effect but more in an extension of the effect, which can last for up to 48 hours [33].

Buprenorphine use is contraindicated for patients with alcohol intoxication, delirium tremens, and treatment with monoamine oxidase (MAO) inhibitors. Cases of lethal buprenorphine intoxication almost always involve polyintoxication [33]. Upon discontinuation, a withdrawal syndrome develops, with a delayed emergence in 2 days to 2 weeks. Signs and symptoms of buprenorphine withdrawal are typical of a milder morphine-type withdrawal and last roughly 1 to 2 weeks [5]. The more benign withdrawal syndrome is due to its partial agonist property at the mu receptor and weak antagonist property at the kappa receptor [24].

## **OPIOID ANTAGONISTS**

Opioid antagonists have obvious therapeutic value in the treatment of opioid overdose. Relatively minor changes in the structure of an opioid can convert an agonist drug into one with antagonistic actions at one or more opioid receptor types. Opioid antagonists include nalorphine, levallorphan, naloxone, naltrexone, and nalmefene. Interestingly, naloxone also appears to block the analgesic effects of placebo medications and acupuncture. Naltrexone and naloxone have little or no potential for abuse [5].

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## NATURAL HISTORY OF OPIATE DEPENDENCE

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Although the time from initiation to daily use and serious physiological and psychological dependence is highly variable, the different stages of opiate dependence are clearly delineated [4]. These stages include initiation, continuation, withdrawal, and relapse. Each stage is characterized by specific neurotransmitter action, involvement of specific brain structures, and activation of specific neural circuits. An understanding of these different processes is crucial to develop an understanding of the therapeutic strategies [8].

### INITIATION

During the initiation phase, acute reinforcement of the initial drug effect is mediated by mu-opioid receptors and dopamine that inhabit the ventral tegmental area and nucleus accumbens. This results in conditioned responses and drug craving [8].

### CONTINUATION

The second phase of continued drug use is characterized by diverse neurotransmitter involvement, including dopamine in the nucleus accumbens, corticotrophin-releasing hormone in the amygdala, and glutamate in the frontal-cingulate circuit. As tolerance develops, the dose and route of administration often change, with progression to IV use a frequent outcome [4].

### DETOXIFICATION AND WITHDRAWAL

During detoxification and withdrawal from opiates and other central nervous system depressants, glutamate and norepinephrine in the locus coeruleus are primarily involved in causing the associated symptoms [8].

## RELAPSE FOLLOWING SUSTAINED ABSENCE

Brain regions implicated in relapse to opiate use include the orbitofrontal cortex, anterior cingulate gyrus, and amygdala. Norepinephrine and corticotrophin-releasing hormones are involved in stress-induced relapse. Gamma-aminobutyric acid (GABA) and glutamate mediate brain systems are involved in compulsive and habitual behavior and mediate cue-induced relapse [8].

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## PATHOPHYSIOLOGY

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### OPIATE TOLERANCE

Tolerance refers to a decrease in effectiveness of a drug with repeated administration. Tolerance to opioid effects is encountered in both the clinical use of opioids for pain relief and in recreational use of heroin [22]. Acute tolerance stems from transient administration of opioids; sustained administration leads to the development of classical or chronic tolerance. Short-term receptor desensitization may underlie the development of tolerance, probably involving phosphorylation of the mu and delta receptors by protein kinase C, protein kinase A, and beta-adrenergic receptor kinase (beta ARK). Long-term tolerance is believed to be associated with increases in adenylyl cyclase activity, a counter-regulation to the decrease in cyclic adenosine monophosphate levels [5].

The degree of tolerance can be influenced by changes in the environment in which drug use occurs. In the presence of cues previously associated with drug ingestion, tolerance is markedly enhanced, compared to the tolerance observed in a novel environment. Thus, administration of an opioid in an environment not previously associated with administration of the drug will be associated with lower tolerance and therefore a higher risk of overdose [22].

## OPIATE DEPENDENCE

Opiate dependence is best described as a central nervous system disorder characterized by neurobiological changes leading to compulsive drug-taking behaviors. As the result of chronic use, the cells producing endogenous opiates cease to function and degenerate, causing the user to become physically dependent on exogenous opiates [34].

According to the classical theory of addiction, opiate dependence results from the need to reduce distress, as withdrawal is a physical expression of distress. This is referred to as negatively reinforced behavior. This hypothesis has been challenged by the finding that the degree of physical dependence does not predict the intensity of subsequent craving, nor does detoxification and recovery from physical dependence prevent recidivism. Additionally, the motivational aspects of withdrawal are independent of the intensity and pattern of the physical symptoms of withdrawal [35].

Alternative hypotheses focus on the role of the mesocorticolimbic dopamine system, an anatomical pathway that originates from the ventral tegmental area in the midbrain and projects to several forebrain regions, including the nucleus accumbens and medial prefrontal cortex [35]. Dependence on most drugs of abuse is characterized by an altered physiological state inferred from the emergence of a withdrawal syndrome following cessation of drug administration. Alleviation of an increasingly severe, withdrawal-induced negative affective state may reinforce continued drug taking and directly contribute to the development of dependence [36].

### Molecular Basis

The diverse biological effects of opiates are manifested through specific opioid receptors distributed throughout the central and peripheral nervous system. Opioid receptors, upon the binding of opiate drugs (or endogenous opioid peptides), regulate a multitude of intracellular signaling pathways.

Involvement of opioid receptors in opiate dependence is unequivocal. This is reliably demonstrated by the rapid precipitation of withdrawal syndromes in opiate addicts by opioid receptor antagonists such as naxolone [37].

Repeated exposure to short-acting opioids can result in durable alterations in opioid receptor kinetics, transmembrane signaling, and postreceptor signal transduction [38]. Opiate dependence requires sustained activation of opiate receptors, and this chronic signaling process ultimately leads to changes in protein functions of gene transcription [37].

Opioid receptors are members of the G-protein receptor family, and each opiate receptor uses inhibitory G-proteins for signal transduction. Opioid receptors have the capacity to interact with five different forms of G proteins, regulating a diverse spectrum of effectors ranging from adenylyl cyclases and ion channels to mitogen-activated protein kinases. These isoform-specific and differential regulations of various classes of effectors are combined into a sophisticated signaling network that mediates opioid actions. The enormous diversity in opioid signaling stems from the array of effectors and signaling molecules that functionally interact with the G protein beta gamma complex [37].

Prolonged administration of opiates causes molecular and cellular adaptations that rapidly develop into tolerance and dependence. An upregulation of adenylyl cyclase responsiveness, referred to as adenylyl cyclases superactivation, is a classic sign of this tissue adaptation [37].

G-protein signals lead to changes in gene expression, and opioid-induced long-term functional alterations of the nervous system involve changes in gene expression. Many opioid-induced signals converge at the level of transcription factors, although little is known about the exact mechanisms of gene transcription in the development of opiate tolerance and dependence [37].

## Mechanism of Reinforcement

Drugs with an abuse liability have habit-forming actions that can be localized in a variety of brain regions. Drugs of abuse mimic or enhance the actions of endogenous chemical messengers in the brain [39]. The mesolimbic dopamine system is the likely substrate upon which opiates act to produce their reinforcing effects. Both the positive (rewarding) and negative (aversive) reinforcement of opiate mu- and kappa-receptor agonists are mediated by the mesolimbic dopamine system [35].

Opioids produce reinforcement by inhibition of the GABA neurons that normally inhibit dopaminergic neurons in the ventral tegmental area. This results in a surge of dopamine in the nucleus accumbens and other mesolimbic-mesocortical brain regions [9]. The neurochemical cascade begins with activation of mu- or kappa-opioid receptors differentially distributed on GABAergic cells in the ventral tegmental area and nucleus accumbens and dopamine terminals in the nucleus accumbens. This activation produces rewarding and aversive effects by increasing or decreasing dopamine release in the nucleus accumbens. Inhibition of medium spiny GABAergic neurons in the nucleus accumbens by dopamine and opiates can synergistically facilitate opiate reinforcement. Increases in glutamatergic afferents into the ventral tegmental area may facilitate opiate reinforcement by activating dopamine neurons. An increase in glutamate activity in the nucleus accumbens may decrease opiate action by activating nucleus accumbens GABAergic cells. Also, an increase in nucleus accumbens 5-HT by opiates modulates opiate reinforcement by activation of 5-HT1 and/or 5-HT3 receptors [35].

## EFFECTS OF OPIATE ABUSE AND DEPENDENCE

The misuse of opiates results in several acute and long-term effects. Signs and symptoms of acute opiate intoxication include drowsiness, decreased respiration, euphoria, and impaired judgment (*Table 1*).

## INFECTIOUS DISEASE

Infectious complications from opiate use generally stem from injection use, primarily of heroin, in which blood-borne pathogens are transmitted via contaminated needles. An estimated 60% to 90% of injection users have hepatitis C virus infection [40; 41]. Other common infectious diseases include human immunodeficiency virus (HIV) and hepatitis B; common bacterial infections include *Staphylococcus aureus*, cellulitis and abscesses around the injection site, pneumonia, and bacteremia [4]. Of HIV-positive persons in the U.S., more than one-third have injected opioids and more than 25% report sharing needles with other users [6].

SIGNS AND SYMPTOMS OF ACUTE OPIATE INTOXICATION	
Constricted pupils (or dilated pupils with meperidine)	
Euphoria	
Apathy	
Dysphoria	
Drowsiness	
Loss of consciousness	
Coma	
Psychomotor agitation or retardation	
Decreased respiration	
Decreased heart rate	
Pulmonary edema	
Impaired social judgment	
Slurred speech	
Impaired attention and memory	
Impaired occupational functioning	
Source: [47]	Table 1

## ENDOCRINE/METABOLIC EFFECTS

Opiate use affects multiple endocrine functions and is associated with hypogonadism, adrenal dysfunction, reduced bone mineral density, and growth hormone abnormalities [42].

### Hypothalamic-Pituitary-Gonadal (HPG) Axis

Opiate use has been implicated in gonadal dysfunction. Central hypogonadism can result from opiate receptor activation in the vicinity of the hypothalamus. Resultant diminished secretion of gonadotropin-releasing hormone can lead to decreases in gonadotropin and testosterone levels. This effect may decrease over time secondary to the development of tolerance [42].

### Metabolic Effects

Heroin use has been associated with abnormalities in glucose metabolism by multiple mechanisms. Fasting insulin levels can be substantially higher in heroin addicts than in control subjects, and insulin resistance stemming from opiate use may be coupled with beta cell dysfunction. Heroin addicts often have lower acute insulin response than control patients evaluated by oral glucose tests and response to a standard meal. This blunted glucose response suggests an association between opiate use and abnormal glucose metabolism [42]. The use of highly active anti-retroviral therapy (HAART) for the treatment of HIV infection is also associated with a number of metabolic problems, including increased prevalence of insulin resistance, dyslipidemia, and changes in fat distribution. Because opiate use can also result in metabolic abnormalities, the presentation of patients who are both HIV-positive and opiate dependent may be complicated.

Chronic heroin use may also complicate dyslipidemia, evidenced by elevated total cholesterol levels, hypertriglyceridemia, and decreased total cholesterol, high-density lipoprotein, and elevated triglyceride levels relative to controls [42].

### Hypothalamic-Pituitary-Adrenal (HPA) Axis

Opiate addicts may also have impaired adrenal function, documented by a high prevalence of adrenal insufficiency and abnormal response to the cosyntropin test. The action of heroin on neurotransmitters that regulate the secretion of corticotrophin-releasing factor, leading to disturbances in cortisol levels, has been hypothesized as the underlying pathophysiology. This is supported by the observation of lower plasma cortisol levels concurrent with depressed ACTH levels in heroin addicts [42].

In addition, chronic opiate use may contribute to low bone mineral density through reduction in lumbar bone mineral density. Growth hormone axis abnormalities are also seen in heroin addicts [42].

## NEUROCOGNITIVE EFFECTS

Cognitive impairment may contribute to drug abuse and dependence in at least two ways. The first involves increasing the likelihood of drug-seeking behavior through various cognitive deficits, such as failure of impulse control mechanisms. The second involves the interference with users' ability to assimilate and participate in rehabilitation programs that have an educative and cognitive emphasis [43].

The chronic use of illicit drugs is often associated with a generalized profile of neuropsychological deficit. However, there may be important differences in the patterns of interaction associated with different neurotransmitter systems, coupled with corresponding differences in the distributions of various receptor subtypes, that are associated with the effects of specific drugs of abuse [43].

Compared with marijuana and stimulants, there has been substantially less research into neuropsychological deficits in chronic opiate abusers. Early studies found relatively little impairment in tasks involving abstraction and reasoning, leading investigators to conclude that chronic opiate use was not associated with deficient frontal lobe functioning.

However, newer studies, utilizing more sensitive measures, have demonstrated that opiate abusers do have marked deficits in frontal lobe functioning relative to healthy control subjects. It should be noted that these deficits may include problems with altered attentional control, altered decision making, or problems with choices involving motivationally significant outcomes. Further research is needed to determine whether this pattern reflects increased impulsivity [43]. Determining causation in studies involving drug users is difficult due to comorbid psychiatric disorders and polysubstance abuse [43].

### **Cognitive-Motor Effects of Methadone Maintenance**

While under the influence of acute opiate ingestion, the ability to work safely or drive a car can be impaired. This does not appear to be the case with methadone patients who have adapted to the effects of opiates for months or even years, a reflection of the substantial tolerance to the central depressing effect when opiates are taken regularly on a long-term basis [44].

A review of the cognitive functioning of methadone patients found that [44]:

- On measures of concentration and attention, methadone patients tended to perform less well than controls.
- Methadone patients performed equally or slightly faster in speed of information processing and equally or slightly worse in motor reaction on measures of simple reactions and simple-choice reactions.
- Performance was inconsistent on complex-choice reactions under reactive stress.
- No evidence for inferior performance of methadone patients in vigilance tasks has been found.

- Methadone patients have performed worse than control groups in visual orientation.
- In tests combining tracking with a reaction task, slower reaction to peripheral signals have been observed in methadone patients together with equal accuracy and greater tracking deviation or smaller number of correct responses and equal tracking deviation.

Researchers concluded that among methadone-maintained patients without complicating comorbidity, visual structuring and reaction are not impaired [44]. Performance of attention, visual orientation, and eye-hand coordination are worsened. In general, performance of methadone patients and comparable healthy subjects overlap to a substantial degree. The study results may be better explained by sociodemographic factors than by the grouping factor; age, gender, and educational attainment showed a greater influence than methadone use. The authors concluded that being a methadone patient does not necessarily mean that impairment of cognitive-motor skills performance is inevitable [44].

The practical application of these findings suggests that methadone-maintained patients may be as capable as healthy persons in job performance. If the job demands encompass skills with no differences found between healthy subjects and methadone patients, if minimum prerequisites are not extraordinarily high, or if patients exhibit otherwise favorable features except of their opiate dependence, job performance is unlikely to be affected [44].

## OPIATE OVERDOSE

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Research suggests that the increase in the incidence of fatal overdose is not the result of an increase in the number of persons using opiates. Possible mechanisms of fatal overdose include loss of tolerance, synergistic interactions with other central nervous system depressants, or systemic factors [20]. Although the risk for overdose occurs with the use of all opiates, heroin overdose is the most commonly seen.

### RISK FACTORS

Heroin purity has only a moderate relationship to heroin-related fatalities, and despite the increasing incidence of heroin ingestion by smoking, almost all overdose deaths remain the result of injection. In fatal overdoses, instantaneous death is uncommon, indicating that there is time to intervene in the majority of cases. However, public responsiveness to overdoses is often poor, with the most common reason for delayed response being fear of police involvement [45]. The time following release from prison is a very high-risk period for both fatal and nonfatal overdose [45].

### Tolerance in Overdose

Variation has been found in the acquisition of tolerance to different opiate effects, including respiratory depression [20]. The role of tolerance in heroin overdose is suggested by the rigors of the heroin lifestyle, which often results in a reduction in use after a decade or more of use. Often, heroin addicts increase the use of other drugs, such as alcohol, to compensate for reduced heroin use. Both of these factors increase the risk for overdose.

### Polysubstance Use

Polysubstance use in cases of fatal heroin overdose is so frequent that polydrug toxicity is often a better description of the cause of death. The primary drugs associated with fatal and nonfatal overdose are alcohol, benzodiazepines, and TCAs. The risk of nonfatal heroin overdose is increased significantly by TCA use but not by selective serotonin reuptake inhibitor (SSRI) use [45].

Alcohol and benzodiazepines are relatively weak respiratory depressants but can act synergistically with opiate agonists to produce substantial respiratory depression. Stimulants act as functional or physiological opiate antagonists and may therefore minimize the respiratory depressant effects of opiates [22].

### SYMPTOMS

In the case of opiate overdose, symptoms include mental clouding, stupor or coma, miotic pupils, bradypnea, diminished response to painful stimuli, and mottled, cooled skin. Respiratory depression is the most feared acute adverse effect. Direct suppression of the brain stem respiratory center leads to bradypnea, shallow respirations, and a significant overall reduction of tidal volume. Death from opiate overdose is almost always caused by respiratory depression [4].

Sequelae of nonfatal overdose include [20]:

- Pulmonary conditions, most frequently edema
- Pneumonia
- Cardiac complications such as arrhythmia, acute cardiomyopathy, and hemoglobinemia
- Rhabdomyolysis (disintegration or dissolution of muscle cells leading to myoglobinuria)
- Neurological damage through prolonged hypoxia

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## OPIATE WITHDRAWAL

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A withdrawal syndrome can be precipitated in humans after even a single dose of morphine. Physical dependence to opiates is assessed by observing the emergence of a withdrawal syndrome following discontinuation of opiate administration or through the administration of a competitive opiate antagonist, such as naloxone [46]. Signs and symptoms of opiate withdrawal include [47]:

- Dilated pupils
- Rhinorrhea
- Epiphora/lacrimation
- Piloerection
- Nausea
- Vomiting
- Diarrhea
- Yawning
- Muscle cramps
- Restlessness
- Elevated vital signs

Although the neurophysiology underlying opiate withdrawal is incompletely understood, several neurotransmitter systems are believed to play a role, including dopaminergic, cholinergic, noradrenergic, and glutamatergic systems [46]. The extended amygdala is robustly implicated in affective signs of withdrawal from chronic exposure to opioids. Less is known about the cellular mechanisms underlying acute dependence [36]. The progressive escalation of withdrawal severity that occurs across repeated acute opioid exposure separated by prolonged intervals suggests the involvement of long-term cellular plasticity in acute dependence [36].

## ACUTE OPIATE WITHDRAWAL

Most research regarding acute withdrawal from an opiate has been conducted with heroin users. Withdrawal symptoms are the result of mu-agonist withdrawal in the case of heroin and begin approximately 8 hours after the last dose. The symptoms begin slowly, peak at 48 to 72 hours, and then gradually taper during the next 4 to 7 days. As noted, typical symptoms of withdrawal include agitation, anxiety, piloerection, tachycardia, mild hypertension, and pupillary mydriasis. Approximately 8 to 12 hours after the last dose, increases in vital signs, pulse, blood pressure, and respiratory vital rate are observed. At the peak, pronounced anxiety, tremors, shakes, smooth and skeletal muscle cramps, and joint and deep bone pain begin to manifest [4].

## PROTRACTED WITHDRAWAL

Withdrawal symptoms may persist long after elimination of the opioid agent. Such persistent behavioral change suggests plastic alternation within the nervous system, some of which may be mediated by the regulation of gene expression [46]. Chronic exposure to opioids may be associated with changes to the mu receptor, resulting in the propagation of signal transduction in the absence of an agonist. The withdrawal phase can be extended due to the cellular changes that occur after long-term opiate exposure [34].

## PERSISTENT NEUROADAPTATION AND RELAPSE VULNERABILITY

Opiate dependence is a chronic relapsing disorder characterized by compulsive drug seeking and use. More than 80% of addicts relapse to drug seeking and use after a period of abstinence during the protracted withdrawal phase, underscoring the long-standing nature of the compulsion and high rates of recidivism [48]. Two important brain alterations occur following dependence and withdrawal that are believed to underlie the heightened vulnerability to relapse: conditioned responses of norepinephrine A1/A2 neuron release in the extended amygdala and changes in the mesocorticolimbic dopamine system and its afferents that alter hedonic

nic processing. At the same time, motivation or learning for drug reward and drug-associated cues is increased [48].

Abstinence from chronic drug use unmasks neuroadaptation in brain function that contributes to an ill-defined feeling of dysphoria, anxiety, or malaise that can only be alleviated by renewed administration of the drug. Continued drug use is rewarding because it stimulates the natural reward circuitry and also because the action offsetting the anti-reward response (stress hypersensitivity and anxiety) produces an additional reinforcing effect that increases the sum of positive reinforcement. The protracted withdrawal period is often characterized by elevated anxiety involving alterations in the noradrenergic input to the bed nucleus of the stria terminalis or amygdala. Drug-associated stimuli activate noradrenergic A1/A2 neurons during protracted withdrawal, leading to elevated anxiety through the ensuing release of noradrenergic neurons in the extended amygdala. In turn, additional reinforcing properties are produced via the alleviation of anxiety when these noradrenergic neurons are inhibited, reflecting negative reinforcement [48].

Additionally, chronic drug exposure results in a generalized hedonic deficit for natural rewards and an incentive value for drugs. This deficit in the capacity for obtaining reinforcement from non-drug sources generates symptoms such as anhedonia and depression. The sensitized hedonic drug value is also believed to increase motivation for drug use. Furthermore, the changes that occur in hedonic processing mechanisms following chronic opiate exposure may involve multiple systems that recover at different rates. Changes in the afferents to the ventral tegmental area or in plasticity within the ventral tegmental area itself could play a vital role in altered hedonic processing during protracted withdrawal [48].

Taken together, these findings suggest that elevated drug seeking during protracted withdrawal may involve two processes: prolonged and elevated anxiety leading to a negative reinforcement mechanism for opiates and increased incentive motivation for drug reward through a sensitization mechanism [48].

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## LIABILITY OF ABUSE/ DEPENDENCE OF LEGITIMATELY PRESCRIBED OPIATE DRUGS

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There is broad consensus that patients with acute and chronic pain have often received inadequate pain control out of a fear of creating dependence. This is typified by the results of a survey in which 35% of Canadian family physicians reported they would never prescribe opioids for moderate-to-severe chronic pain and 37% identified dependence as a major barrier to prescribing opioids [82]. These statistics reflect an attitude among physicians that leads to undertreatment of pain and unnecessary suffering among patients experiencing pain [82]. In response to this, the Joint Commission and other organizations have enacted accreditation standards that consider pain to be the fifth vital sign, assessed whenever other vital signs are measured [1].

However, with the growing concern about the undertreatment of pain and the underuse of opioids in pain treatment, there is also a renewed concern about prescription opiate dependence and overdose deaths [1]. The disparate concerns regarding undertreatment of pain and facilitation of dependence is underscored by the fact that, until recently, pain management and addiction specialists rarely communicated. Pain management physicians rightly concern themselves with alleviation of pain and have traditionally underestimated dependence among their patients, with such patients often simply dismissed from further care. Addiction specialists, on the other hand, seldom encounter pain patients whose quality of life is vastly improved by opioids, but instead see failed patients from pain treatment programs [1].

Until the 1990s, Schedule II opiate analgesics were primarily used in operating rooms and in-patient settings, as they were administered intravenously or intramuscularly. More recently, non-parenteral Schedule II opioids have been approved by the FDA for use in the treatment of moderate-to-severe pain. Many of these newer agents are high-dose, extended-release formulations of pre-existing opiates, including OxyContin (a controlled-release oral formulation of oxycodone), MS Contin (a formulation of morphine sulfate), and Palladone XL (a formulation of hydromorphone hydrochloride), all of which have fulfilled a genuine clinical need by providing an elevated, constant plasma level for extended periods without the fluctuations seen with the short-acting versions. These long-acting formulations may both reduce euphoric effects of the drug and reduce pain more effectively by treating pain before it becomes established (pre-emptive effect) rather than after, when higher doses may be required. However, these formulations can be abused by crushing the tablet or capsule and ingesting the powder intranasally, sublingually, or orally or dissolving the powder in water and injecting the substance. These approaches to ingestion alter the pharmacokinetics by disabling the slow-release mechanism and make a very high dose of the substance available, which substantially increases the reinforcing effects compared with oral consumption of the drug in its unaltered form [14].

Abuse liability is related to the ease of extraction and modification to produce the desired psychological effect. Medication tends to be more readily abusable if it has a rapid onset and short duration of action, is highly potent, and is smokable or easily ingested. Examples of opiates with high abuse liability include hydromorphone (Dilaudid) tablets, which can be easily dissolved in water and injected, and OxyContin tablets, which can be crushed to disable the controlled-release properties and then snorted or dissolved in solution and injected. A specific black box warning on the labeling of a medication can alert potential substance abusers of the abuse liability. Also, brand name drugs, which carry a higher street value, are more likely to be abused and diverted than generic equivalents [1].

In a study of trends in medical use and abuse of opioid analgesics, a corresponding increase in the rate of abuse was not found [84]. Thus, the increased medical use of opiate analgesics for the treatment of pain has not appeared to contribute to an increase in opiate analgesic abuse. The exception to this is the abuse of hydrocodone and oxycodone products, which has increased disproportionately to their availability since 2000 [1]. Results of epidemiological studies indicate a high prevalence of lifetime abuse of other substances and of substance-related disorders in patients with OxyContin dependence, suggesting that substance abuse predated the use of OxyContin [83].

## DEVELOPMENT OF DEPENDENCE

The dependence of a patient to a drug initially prescribed for a medical condition is referred to as iatrogenic dependence. Opioid prescriptions fall into two major subgroups: treatment of acute pain with short-term opioids and treatment of chronic pain with long-term opioids. In contrast to the rare association of dependence with short-term use, long-term administration of opioids is estimated to result in opiate abuse or dependence in 2.8% to 18.9% of patients, which parallels the rate of abuse or dependence among opioid users in the general population [15].

There is no adequately validated instrument to differentiate pain patients who are at risk of dependence from those who are not. Research suggests that patients, even alcoholics, with no history of opioid dependence are not at heightened risk of becoming addicted with short-term opioid exposure. However, those with a positive history of dependence would benefit from active recovery efforts while receiving such medications [1].

One way to gauge the adequacy of pain control is to consider whether the use of added opiates has resulted in improvements in the functional restoration, physical capacity, psychological well-being, family and other social interactions, and healthcare resource use, which are weighed against unwanted effects such as daytime sedation, mental confusion, constipation, and other side effects.

Despite the rise in the prescribing and abuse of opioid analgesics, definitive data on the rate of dependence among patients administered opioids for acute pain does not yet exist. There is, however, agreement on how to minimize the risk of iatrogenic dependence. These steps include screening for dependence risk potential based on a family history of substance abuse and the exploration of different delivery systems that adequately treat pain but minimize abuse potential [19]. Although a pattern of aberrant behavior may be grounds for caution, a history of opioid abuse does not necessarily preclude a patient from successful treatment with an opiate [1].

The final word on the dilemma of balancing the desire for patient pain relief with the desire to minimize the chance of iatrogenic abuse or dependence comes from the authoritative pharmacology textbook *The Pharmacological Basis Of Therapeutics*, which states, “neither the presence of tolerance and dependence nor the fear that they may develop should ever interfere with the appropriate use of opioids for pain relief” [5].

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## MANAGEMENT OF OPIATE ABUSE AND DEPENDENCE

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In 1914, the Harrison Act was passed, which had the effect of criminalizing addiction and led to significant apprehension among physicians in treating narcotic addicts. Treatment for opiate dependence was basically non-existent until 1935, when U.S. Public Health Services opened a hospital in Lexington, Kentucky, devoted to the treatment of opiate dependence. However, treatment was entirely detoxification-based at that time. In 1963, the New York Academy of Sciences recommended that clinics be established to dispense narcotics to opioid-dependent patients. During this time, research identified methadone as a possibly efficacious agent because of its long half-life, which allowed once-daily dosing. In 1972, the FDA created stringent regulations governing methadone, reducing the flexibility of practitioners caring for

opioid-dependent patients. The Office of National Drug Control Policy subsequently made changes in the 1995 Federal Regulations of Methadone Treatment to encourage the development of a less restrictive approach and to give physicians more latitude in prescribing methadone [24].

Today, management of opiate dependence entails different methods to achieve different goals, depending on the health situation and treatment history of the patient. These treatment approaches include [8]:

- **Crisis intervention:** Directed at immediate survival by reversing the potentially lethal effects of overdose with an opiate antagonist.
- **Harm reduction:** Intended to reduce morbidity and mortality associated with use of dirty needles and overdose.
- **Detoxification/withdrawal:** Aims to remove the opiate of abuse from the patient’s body, either through gradual taper and substitution of a long-acting opiate or through ultra-rapid opiate detoxification.
- **Maintenance treatment or opiate (agonist) replacement therapy:** Aimed at reduction/elimination of illicit opioid use and lifestyle stabilization. Maintenance follows detoxification/withdrawal, whereby the patient is tapered from short-acting opiates and introduced to long-acting opiate agonist, such as methadone or buprenorphine. Patients remain on agonist therapy short-term, long-term, or indefinitely depending on individual needs.
- **Abstinence-oriented therapy:** Treatment directed at cure. The patient is tapered off of short-acting opiates during the detoxification/withdrawal process and may be placed on an opiate antagonist with the goal of minimizing relapse.

All treatment approaches share the common goal of improving health outcomes and reducing drug-related criminality and public nuisance [8].

## CRISIS INTERVENTION

In response to acute overdose, the short-acting opioid antagonist naloxone is considered the gold standard. Naloxone is effective in reversing respiratory depression and coma in overdose patients. There is no evidence that subcutaneous or intramuscular use is inferior to intravenous naloxone. This has prompted discussion of making naloxone available to the general public for administration outside of the healthcare setting to treat acute opiate overdose [8].

## HARM REDUCTION

Harm reduction measures are primarily employed to minimize the morbidity and mortality from opiate abuse and to reduce public nuisance [45]. As a part of this effort, measures to prevent and minimize the frequency and severity of overdoses have been identified. Enrollment in opioid substitution therapy, with agents such as methadone and buprenorphine, substantially reduces the risk of overdose as well as the risk for infection and other sequelae of illicit opiate use [45].

### Education

Reducing the risk for harm involves education on polydrug use and needle-exchange programs [45]. The authors of one review noted that there was positive evidence, though limited, to support education regarding noninjecting routes of administration, brief interventions, and supervised injecting facilities [49].

To improve response to overdoses, opiate abusers and their friends and families should be taught simple cardiopulmonary resuscitation skills to keep comatose users alive until emergency medical personnel arrive. Associates of users should be encouraged to call an ambulance when overdose occurs. The provision of naloxone to opiate users should be tested and evaluated; naloxone could be distributed through existing outlets, such as needle and syringe exchanges, pharmacies, urgent care facilities, or treatment agencies. Heroin users should also be encouraged to switch to noninjecting routes of administration to reduce related morbidity and mortality [45].

## Needle-Exchange Programs

Needle-exchange programs have been shown to be effective in reducing drug-related health problems, reducing injection frequency, and increasing entry and retention in drug treatment [8]. According to one review, there is sufficient evidence of efficacy, effectiveness, and financial benefit to recommend needle-exchange and outreach programs [49]. It is important to note that information regarding infection prevention strategies be provided to all participants in needle-exchange programs, as increased incidences of HIV and other bloodborne pathogens have been noted in this population [50].

## Injection Rooms

Medically supervised injecting rooms are officially designated areas where injecting opiate users, often persons who use heroin, can inject without fear of arrest and with knowledge that medical assistance is available if overdose occurs. Such facilities have existed in Switzerland since 1986, in Germany since 1994, and in the Netherlands since 1996. The goal of user rooms is to promote health and reduce risk behaviors and public nuisance, with a specific focus on overdose reduction and hygiene. Several descriptive studies have shown significant effects on harm reduction and reduction of public nuisance [8].

## Heroin Maintenance

Heroin maintenance is the implementation of heroin prescriptions under medical supervision. This option may improve health and reduce heroin overdoses, illicit opioid use, and crime. However, formidable barriers to heroin maintenance exist in the U.S. [45].

## DETOXIFICATION AND WITHDRAWAL

The process of tapering opioid-dependent patients from agonist therapy is often referred to as detoxification [24]. Detoxification alone should not be considered a treatment and should only be promoted in the context of a well-planned relapse-prevention program [8].

Discontinuation of opiate use must be implemented slowly and cautiously to avoid a marked abstinence syndrome. Withdrawal symptoms may not begin for days after abrupt discontinuation of methadone or buprenorphine given their longer half-lives. Protracted abstinence, or post-acute withdrawal, may last for several months and is characterized by asthenia, depression, and hypotension. Post-acute withdrawal is more likely to occur with methadone than other opiates [24].

The three primary treatment modalities used for detoxification are opioid agonists, non-opioid medications, and rapid and ultra-rapid opioid detoxification [24]. The most frequently employed method of opiate withdrawal is a slow, supervised detoxification during which an opiate agonist, usually methadone, is substituted for the abused opiate [34]. Methadone is the most frequently used opiate agonist due to the convenience of its once-a-day dosing [24]. Methadone is highly bound to plasma proteins and accumulates more readily than heroin in all body tissues. Methadone also has a longer half-life, approximately 22 hours, which makes withdrawal more difficult than from heroin. Substitution therapy with methadone has a high initial dropout rate (30% to 90%) and an early relapse rate. Alternative pharmacological detoxification choices include clonidine (with or without methadone), midazolam, trazodone, or buprenorphine [34].

Many opiate withdrawal symptoms, such as restlessness, rhinorrhea, lacrimation, diaphoresis, myosis, piloerection, and cardiovascular changes, are mediated through increased sympathetic activation, the result of increased neuron activity in the locus ceruleus. Non-opioid agents (such as clonidine), which inhibit hyperactivation of noradrenergic pathways stemming from the locus ceruleus nucleus, have been used to manage acute withdrawal [34].

However, some withdrawal symptoms, including anxiety and myalgias, are resistant to clonidine; benzodiazepines and nonsteroidal anti-inflammatory agents may be necessary to treat these symptoms. To mitigate withdrawal symptoms and assist in detoxification, alpha<sub>2</sub>-agonists, opioid agonist-antagonists, benzodiazepines, and antidepressants have been used [34].

Following detoxification, patients may feel exhausted and weak. Other complications, such as slight variations in hemodynamic status and gastrointestinal tract symptoms, follow quickly and may take several days to resolve. Muscle cramps and low back pain can be treated with nonsteroidal anti-inflammatory drugs. However, the newer cyclooxygenase-2 (COX-2) inhibitors may be advantageous because they produce fewer gastrointestinal side effects [34]. Insomnia is a frequent aspect of acute and protracted withdrawal, as opiates disrupt the normal sleep-wake cycle and many addicts require narcotics to sleep. Although long-term disruption of the normal sleep-wake cycle cannot be corrected rapidly, melatonin (3 mg), benzodiazepines, or antihistamines can be used with beneficial effects. Hypnosis and relaxation techniques are nonpharmacological methods that may also be used [34]. Psychosocial treatments offered in addition to pharmacological detoxification treatments positively impact treatment retention and completion, results at follow-up, and compliance [51].

Ultrarapid opiate detoxification (UROD) has been developed as a means of avoiding the physical symptoms of withdrawal from opiates through the use of general anesthesia.

### Ultra-Rapid Opioid Detoxification

UROD consists of naltrexone-assisted detoxification under heavy sedation or full anesthesia. Chemical sedation has been used since the early 1940s in the management of drug withdrawal. The major breakthrough in the management of opiate withdrawal occurred with the addition of an opiate antagonist during chemical sedation [52]. UROD was introduced in 1990 primarily by private practitioners in a for-profit setting [53].

Traditional withdrawal management utilizes the substitution of the short-acting opioid with a long-acting opioid and subsequent tapering or use of non-opioids. This may involve substantial discomfort to patients, who often terminate the detoxification process and return to opioid use. Some may not even attempt to quit due to fears of the discomfort of the withdrawal process. Thus, attempts have been made to induce and shorten opiate withdrawal through the use of UROD [53].

UROD is also referred to as rapid, ultra-rapid, or anesthesia-assisted detoxification. One reason for the proliferation of terms is that the anesthesia-assisted procedure was commercially used and was submitted as a registered trademark or patent. Therefore, other researchers had to devise novel names for the process. Suggested classification is [53]:

- Ultra-rapid opiate detoxification (UROD): General anesthesia; duration <6 hours
- Rapid opiate detoxification (ROD): Deep sedation; duration 6 to 72 hours
- Compressed opiate detoxification (COD) and naltrexone-compressed opiate detoxification (NCOD): Duration 3 to 6 days; preceded by a period of abstinence from opioids under sedation prior to introduction of naltrexone

The common underlying themes in all UROD techniques are a desire to condense the detoxification process into a shorter period to blunt the awareness of physical discomfort and to shorten the time lag between a patient's last dose of opioid and transfer to naltrexone maintenance [53]. This is accomplished by precipitating withdrawal following the administration of opioid antagonists under deep sedation or anesthesia.

A highly specific subgroup of patients may benefit more from UROD. This includes patients unable to abstain with methadone substitution despite adequate motivation, patients unable to stop methadone, and patients who are socially and occupationally active and cannot go through a

lengthy detoxification. Patient preference is also an important variable [53].

Absolute contraindications include pregnancy; a history or clinical suspicion of cardiac disease; chronic renal impairment; liver disease; current dependence on benzodiazepines, alcohol, or stimulants; and history of psychotic illness [53]. Relative contraindications include a history of treatment for depression and unstable social circumstances. A comprehensive plan to stabilize such patients should be undertaken before the procedure [53]. Patients with chronic pain syndromes requiring opioid medication are not good candidates unless their pain can be controlled by alternative methods [34].

UROD is best performed in an intensive care unit with full resuscitative equipment and monitoring available [34]. Initiation of opiate withdrawal is precipitated by IV injection of high-dose antagonist, usually naloxone. Antagonists are chosen that have high binding coefficients relative to agonists (naltrexone binds at the mu receptor 34 times more than morphine) [34]. Parameters that indicate adequacy of withdrawal include a 20% decrease of ventilation below the maximum minute ventilation, an EKG detection of decreased QQ variability, and EEG normalization [34].

Detoxification and withdrawal are rarely complete following UROD, and residual withdrawal symptoms can include drug craving, sympathetic hyperactivity, muscle pain, bone pain, nausea, vomiting, diarrhea, and insomnia. UROD does little to prevent protracted abstinence syndrome, which can last 3 to 10 weeks. Naltrexone may reduce opiate craving during the post-UROD period, with 50 mg per day recommended for relapse prevention [34]. However, patients undergoing long-term naltrexone therapy can become sensitized to opiate drugs, heightening the risk of fatal overdose if opiate use is resumed. Patients with a history of pre-existing liver dysfunction should undergo naltrexone maintenance therapy only under careful supervision. Clonidine may diminish sympathetic hyperactivity and should be continued through the protracted abstinence syndrome [34].

The withdrawal syndrome observed in many of the published studies on UROD was protracted, as reflected in the duration of inpatient stay, which varied from 24 hours to 8 days, with a mean duration of 3 to 4 days. Therefore, alternatives to UROD are considered to be more cost-effective [53]. Krabbe et al. compared abstinence rates and withdrawal effects of UROD with standard methadone tapering in a prospective 3-month trial [54]. They found significantly higher abstinence rates and fewer withdrawal symptoms in UROD patients versus methadone patients at 1 and 2 months, with no differences at 3 months.

A major shortcoming of UROD is the lack of evidence that an opiate antagonist can accelerate the restoration of neurobiological homeostasis following opiate withdrawal [53]. Although significant drawbacks and questionable long-term efficacy exist with UROD, popular demand has proven difficult to restrain, in part due to the marketing of the procedure as a “painless cure” for opiate dependence. Marketing and the media have also blurred the fact that the original purpose of the procedure was to induce patients as rapidly as possible onto naltrexone and not to magically and permanently “terminate” years of opiate dependence [52].

There are a number of drawbacks to UROD relative to other detoxification methods. Serious adverse events related to the anesthetic procedure have been reported. A randomized, controlled trial directly comparing naltrexone-assisted detoxification with and without full anesthesia clearly stated that heavy sedation or full anesthesia should not be used because it does not confer any advantages in withdrawal symptom severity or increased rates of initiation or maintenance and it increases the potential for life-threatening adverse events [8]. A trial comparing naltrexone-induced, anesthesia-assisted detoxification with buprenorphine- or clonidine-assisted detoxification found no difference in withdrawal severity and rates of completion. However, potentially life-threatening adverse events associated with the UROD anesthesia were observed. The authors concluded that the data do not support use of anesthesia for detoxification [55].

Heavy sedation compared to light sedation does not confer additional benefits in terms of less severe withdrawal or increased rates of initiation and retention on naltrexone maintenance treatment. The risk for adverse events, the high monetary cost, and use of scarce intensive care resources suggest that this form of treatment should not be pursued [56]. Additionally, UROD has not undergone the processes of therapeutic protocols, which are recognized as essential in scientific medicine, and no animal studies have been conducted with the procedure [52].

### **AGONIST REPLACEMENT OR ABSTINENCE THERAPY**

Two principle treatment modalities are offered for opiate dependent patients: agonist maintenance or detoxification followed by outpatient or residential drug-free treatment. Both can be effective, with no clear indication for each, although agonist maintenance leads to greater treatment retention [57]. A reasonable approach would be an initial outpatient or residential treatment referral for patients relatively new to treatment, with agonist maintenance appropriate for patients with history of treatment failures, greater disease severity, or a history of drug overdoses. Naltrexone is best reserved for patients with strong legal incentives to abstain, family involvement to monitor treatment, or concurrent enrollment and involvement in a psychosocial intervention [58].

At present, there are no direct interventions that are capable of reversing the effects of drugs of dependence on learning and motivation systems [19]. Instead, the management of opiate dependence often consists of pharmacotherapy with methadone and buprenorphine, which do not eliminate physical dependence on opioids. These medications instead reduce the use of illicit opiates and produce very strong positive health outcomes as measured by decreased mortality, improved mental and physical health, and reduced risk of disease transmission [19]. Considering the high rate of relapse after detoxification, maintenance therapy with methadone or buprenorphine is currently considered to be the first-line treatment for opiate-dependent patients [8].

Any treatment for opioid dependence must take into consideration the chronic relapsing nature of opioid dependence, characterized by a variable course of relapse and remission in many patients. Treatments should emphasize patient motivation, psychoeducation, continuity of care, integration of pharmacotherapy and psychosocial support, and improved liaison between the treatment staff and the judicial system. Pharmacotherapy must be offered in a comprehensive healthcare context that also addresses the psychosocial aspects of dependence [8]. Opioid-dependent patients frequently suffer from physical and psychiatric disorders, and targeted interventions of psychiatric comorbidity are essential in improving treatment outcome for these patients [8]. Polysubstance abuse is the rule rather than the exception in opiate dependence, and concurrent use of other substances should be carefully monitored and treated when necessary [8]. Incarceration should never automatically result in discontinuation of an existing treatment; imprisonment offers a window of opportunity to initiate or restart treatment with a necessary continuation after release [8].

### **Agonist Replacement Therapy**

The goal of opioid replacement therapy is to reduce illicit drug use and associated health risks, with secondary goals of reducing unsafe sexual practices, improving vocational and psychosocial functioning, and enhancing quality of life [24]. The theoretical basis of opioid replacement stems from the finding that chronic opiate use results in an endogenous opioid deficiency as a result of the down-regulation of opioid production. This creates overwhelming cravings and necessitates interventions that shift the dependent patient's attention and drive from obsessive preoccupation with the next use of opiates to more adaptive areas of focus, such as work, relationships, and non-drug leisure activities [24].

The neurobiological changes resulting from prolonged opioid exposure provide a rationale for specific pharmacotherapies, such as long-acting opioid agonists, that are aimed at stabilizing these complex systems [38]. Opioid agonist maintenance treatment stabilizes brain neurochemistry by replacing short-acting opioids, which can create rapid changes in opioid levels in the serum and brain, with a long-acting opioid that has relative steady-state pharmacokinetics. Opioid agonist maintenance treatment is designed to have minimal euphoric effect, block the euphoria associated with administration of exogenous opioids (competitive antagonism), eliminate the risk of infectious disease and health consequences associated with injection drug use, and prevent opioid withdrawal [38].


Successful maintenance treatment entails stabilization of opiate dependence through opioid receptor occupation. Positron emission tomography studies have revealed that only 25% to 35% of brain opioid receptors are occupied during steady-state methadone maintenance, suggesting that unoccupied opioid receptors disrupted during cycles of opioid abuse could normalize during methadone maintenance [24]. Additionally, opiate replacement therapy blocks much of the euphoria from illicit heroin use. Long-term opioid agonist treatment also has a positive impact on public health, through significantly reducing overdose deaths, criminal activity, and the spread of infectious disease [24].

More than 200,000 patients in the U.S. are currently enrolled in opioid replacement therapy in more than 1000 opioid treatment programs [24]. However, this represents only an estimated 14% of all opioid-dependent patients. Although some have criticized the practice of methadone and buprenorphine therapy on the grounds that one opioid is merely being substituted for another, the clinical benefits strongly support this treatment modality [24].

## Methadone

The first demonstrated efficacy of methadone treatment for opioid dependence was published in 1965. Methadone is now the most inexpensive and empirically-validated agent available for use in opiate replacement therapy. Studies have shown one-year treatment retention rates of 80%, with significant reductions in illicit opioid use [24]. Individual and group counseling are the main ancillary therapies and consist primarily of cognitive-behavioral and supportive-expressive approaches. There is some evidence that augmentation of methadone with intensive psychosocial therapy significantly improves outcomes [24]. Efforts to provide methadone in an office-based setting have been successful, although federal regulation has limited the flexibility of providers [38].

Treatment is initiated with a dose of 25 to 30 mg and is gradually titrated in 5- to 10-mg increments per day to a desired range of 60 to 120 mg. Low-dose treatment is associated with less positive outcomes than doses of 80 mg per day or greater [24].



According to SAMHSA, there is strong evidence to support the use of daily methadone doses in the range of 80 mg or more for most patients, but considerable variability exists in patient responses. Some do well on dosages below 80 to 120 mg per day, and others require significantly higher dosages. Clinicians should exercise additional caution with higher dosages, guarding against diversion of take-home methadone to individuals who are opioid intolerant because higher dosages can be lethal for such individuals.

([http://www.guidelines.gov/summary/summary.aspx?doc\\_id=8349](http://www.guidelines.gov/summary/summary.aspx?doc_id=8349). Last accessed February 11, 2009.)

**Level of Evidence:** Expert Opinion/Consensus Statement

As noted, methadone maintenance treatment offers substantial benefits over no treatment, including reduced risk of death and disease, reduced heroin use, reduced criminal involvement,

and improved well-being. However, the benefits are less with poor-quality programs. The quality of the staff-patient interaction, attitudes of staff, good management of clinics, and good record-keeping characterize higher-quality programs [59].

Methadone is cost-effective. To contrast, the estimated 6-month costs are about \$21,000 for an untreated drug abuser, \$20,000 for an incarcerated drug abuser, and \$1750 for a patient enrolled in a methadone maintenance program [24].

Frequently, there may be a belief that opiate users should be able to stop using all drugs. Although some successfully stop, dependence is a chronic problem for most patients, associated with frequent relapses, serious health risks, and psychosocial impairment [59]. Unfortunately, a serious stigma surrounds methadone treatment, which is experienced most acutely by patients but also by professionals. This may pose a barrier to treatment support [59].

A review of the efficacy literature concluded that high doses of methadone (>50 mg daily) are more effective than low doses (<50 mg daily) in reducing illicit opiate use. Additionally, high doses of methadone are more effective than low doses of buprenorphine (<8 mg daily). High dosages of methadone are comparable to high dosages of buprenorphine ( $\geq 8$  mg daily) on measures of treatment retention and reduction of illicit opiate use [8].

## Buprenorphine

Buprenorphine offers several advantages over methadone, including milder withdrawal symptoms following abrupt cessation, lower risk of overdose, and longer duration of action, allowing alternate-day dosing [24]. Identifying subpopulations of opiate addicts who differentially respond to buprenorphine versus methadone has not been clearly established. However, patients with less chronic and less severe heroin dependence benefit more fully from buprenorphine than from a pure opioid agonist like methadone [24].

Studies support buprenorphine as a viable alternative for opioid maintenance therapy. However, its mixed agonist/antagonist action entails special considerations. Buprenorphine may precipitate opioid withdrawal, and patients being switched from short-acting opioids must abstain from illicit opioid use for at least 24 hours before initiating buprenorphine therapy [24]. Another drawback is associated with the sublingual route of administration. This administration presents some difficulties because the tablet is relatively large and slow to dissolve under the tongue and swallowing diminishes its effectiveness. Also, the transition to buprenorphine from long-acting opioids is difficult [19].



SAMHSA recommends that care in the prescribing of buprenorphine for patients who abuse alcohol or sedative/hypnotic drugs (especially benzodiazepines) must be exercised because of the documented potential for fatal interactions.

([http://www.guidelines.gov/summary/summary.aspx?doc\\_id=5887](http://www.guidelines.gov/summary/summary.aspx?doc_id=5887). Last accessed February 11, 2009.)

**Level of Evidence:** Expert Opinion/Consensus Statement

Higher doses of buprenorphine (12 mg or greater) are more effective than lower doses in reducing illicit opioid use, with comparable efficacy to methadone on major treatment-outcome measures. The primary advantage of buprenorphine over methadone is its superior safety profile [19].

### ***Slow-Release Oral Morphine***

Slow-release formulations of morphine that are effective with once-daily dosing are a viable alternative in the treatment of opioid dependence. These formulations considerably delay time to peak concentration after oral administration, resulting in delayed onset of action and making the reinforcing effects very weak when it is administered orally. Several trials suggest that slow-release morphine has approximately equal efficacy with methadone [19].

### ***Diacetylmorphine (Heroin)***

The pharmacokinetic properties of heroin make it less than ideal for use as a maintenance drug, and the main rationale for heroin maintenance has been the treatment of patients who simply do not respond to any other treatment modality. Although preliminary results seem to be positive, suggesting that heroin treatment may have a place with a subpopulation of patients, further studies using standardized protocols are needed. Significantly, studies so far clearly indicate that heroin maintenance, with or without methadone, can be implemented safely. The relatively high cost of heroin maintenance compared with standard methadone or buprenorphine treatment is a drawback of this approach. However, at least one study suggests that heroin combined with methadone may be more cost-effective than methadone alone [19].

The results of medically prescribed heroin administration to chronic, treatment-refractory, heroin-dependent patients have been detailed in two reports. One report from Switzerland concluded that supervised medical prescription of heroin was associated with favorable treatment retention, reduced illicit drug use, reduced criminality, and improved health outcomes and social functioning. These findings were also reported in a controlled trial from Spain and Germany [8].

### ***Agonist Replacement and Psychosocial Therapy***

The addition of any psychosocial support to agonist replacement therapy significantly reduces illicit use during treatment; treatment retention and results at follow-up are also improved [51]. There are two general types of psychosocial therapy used for treating addictive disorders. The first includes therapies developed for treating depression and anxiety that were later adapted for treating persons with addictive disorders, examples of which include cognitive behavioral therapy, supportive expressive therapy, and interpersonal therapy. The second type includes therapies developed specifically for persons with addictive disorders, such as the closely-related motivational interviewing and motivational enhancement therapy [60].

Drug counseling, another approach specific to addictive disorders, emphasizes abstinence, involvement in 12-step programs, and assistance with social, family, and legal problems. Drug counseling is not considered psychotherapy because it focuses on behaviors and external events rather than the intrapsychic processes [60].

Most studies of psychotherapy with opiate-dependent patients have been conducted in methadone programs and are actually pharmacotherapy/psychotherapy studies. In addition to pharmacological intervention, methadone programs typically use behavioral contingencies that are based on cessation of illicit drug use and other improvements [60].

A review of the literature on psychosocial therapy outcomes with opiate-dependent patients receiving methadone has found evidence of an interaction between measures of psychiatric symptoms, therapy assignment, and outcomes [60]. Patients with minimal psychiatric symptoms did equally well with drug counseling alone or with drug counseling plus supportive expressive therapy or cognitive-behavioral therapy. Patients with moderate-level symptoms did somewhat better if they received additional psychotherapy, and patients with more severe psychiatric symptoms had substantially better outcomes with additional psychotherapy than with drug counseling alone. Improvements were observed in employment, legal, psychiatric, and drug use indices. Patients with opiate dependence and antisocial personality disorder did not benefit from additional psychosocial therapy beyond drug use reduction, but patients with opiate dependence, antisocial personality, and depression exhibited improvement in multiple areas [60].

Therapist variables played an important role in outcome, with better results associated with therapists who formed a positive, helping relationship with the patient. There is also some evidence that the best patient outcomes come from methadone programs with a higher level of services that include counseling, medical, and psychiatric services [60].

### **Abstinence-Oriented Therapies**

The primary goal of abstinence-oriented interventions is cure, which is defined as long-term, stable abstinence from all opioids. Abstinence is achieved in two phases: detoxification and relapse prevention. Outcomes in abstinence-oriented programs are generally poor [8].

The primary goal of pharmacotherapy during detoxification is to alleviate opiate withdrawal severity and associated distress and medical complications and to enhance patient motivation to continue treatment. Withdrawal can also be reduced by psychosocial measures, such as contingency management or counseling, and as discussed, the addition of psychosocial therapy to pharmacological treatment increases efficacy. Buprenorphine and clonidine are both used to manage withdrawal symptoms, but buprenorphine's advantages, compared with clonidine, are related to its favorable side effect profile and positive effects on well-being and psychosocial variables [8].

### **Opioid Antagonist Therapy**

Relapse-prevention programs have traditionally involved long-term residential placement of 9 months or more, often using the therapeutic community format. More recently, pharmacotherapeutic agents, such as naltrexone, have been added to reduce relapse risk. A drawback with opiate antagonist therapy is the high dropout rate during detoxification, which results in highly selective patient samples in most of the naltrexone maintenance studies. Naltrexone maintenance or relapse-prevention treatment should be reserved only for those patients who are highly motivated for long-term total abstinence and who are otherwise psychosocially stable. Relapse prevention with naltrexone may also be suitable for pregnant women who are unable to stabilize on methadone or buprenorphine. Patients should be warned that reduced tolerance following naltrexone treatment may increase the risk of overdose [8].

The primary problem with naltrexone treatment is low compliance, with retention in treatment ranging from 6% to 45% [19]. Strategies to improve treatment compliance include combining naltrexone maintenance with contingency management, involving the provision of vouchers redeemable for goods and services contingent on naltrexone intake and drug-free urines [9]. At present, reviewers conclude “there is no sufficient evidence of efficacy of naltrexone to justify its use in the maintenance treatment of opioid dependence” [61].

### **Psychosocial Monotherapy**

There is no data to support psychosocial interventions as a sole intervention for opiate dependence [51]. Psychosocial treatments alone are not adequately proven treatment modalities nor are they superior to any other type of treatment for opiate dependence [62].

### **12-Step/Self-Help Programs**

Twelve-step programs for opiate abuse and dependence include Narcotics Anonymous (NA) and Methadone Anonymous (MA) and are modeled after Alcoholics Anonymous (AA), an abstinence-based support and self-improvement program that is based on the 12-step model of recovery. AA is widely considered the most successful treatment for alcoholism and has helped hundreds of thousands of alcoholics achieve sobriety [63]. The 12-step model emphasizes acceptance of dependence as a chronic progressive disease that can be arrested through abstinence but not cured. Additional elements include spiritual growth, personal responsibility, and helping other addicted persons. By inducing a shift in the consciousness of the addict, 12-step programs offer a holistic solution and are a resource for emotional support [63]. Although research on efficacy and patient outcomes in NA and MA is very limited, many prominent researchers emphasize the important role ongoing involvement in 12-step programs plays in recovery from substance abuse [64].

The understanding of drug dependence as a chronic and relapsing disorder has helped professionals gain a better comprehension of the vital role played by 12-step programs. Every patient attempting to recover from a substance use disorder will encounter a time when he or she faces urges to use without the resources or assistance of healthcare professionals. Twelve-step programs are not considered treatment, nor are they intended as substitutes for treatment. Instead, they are organizations that provide ongoing and indefinite support in the achievement and maintenance of abstinence and in personal growth and character development [64].

Part of the effectiveness of NA and MA is related to their ability to provide a competing and alternative reinforcer to drug use. Involvement in 12-step programs can enhance the quality of social support and the social network of the member, a potentially highly reinforcing aspect the person stands to forfeit if they resume drug using. Other reinforcing elements of 12-step involvement include recognition for increasingly durable periods of abstinence and frequent awareness of the consequences of drug and alcohol use through attendance of meetings [65]. Research shows that establishing a pattern of 12-step program attendance early in treatment predicts the level of ongoing involvement. Emphasis and facilitation of early engagement in a 12-step program involvement are key [66].

**Narcotics Anonymous (NA).** Relative to the more established AA, there are few studies published on NA. However, some research has revealed important information about how NA functions to help both new and long-term members abstain from opiates and other drugs. Being active as an NA sponsor over a 1-year period was found to be strongly associated with substantial improvements in sustained abstinence rates for the sponsors. This suggests that providing direction and support to other newer addicts is a way to enhance the likelihood of one's own abstinence [69].

Improvement in psychological functioning as a result of NA involvement has been observed by Christo and Sutton [68]. Among the 200 NA members in their study, those who had been off drugs and involved with NA for longer periods tended to have lower trait anxiety and higher self-esteem scores, with those abstinent for more than 3 years exhibiting levels of anxiety and self-esteem similar to those of a comparison group of 60 students from a vocational training college [68].

**Methadone Anonymous (MA).** MA was begun in 1991 when a staff member of a methadone maintenance treatment clinic in Baltimore attended an NA meeting and observed a woman receiving an “Anniversary Chip” in recognition of abstinence from heroin, only to be told to return the chip when she shared that methadone maintenance helped make it possible. This staff person went on to develop a 12-step program for methadone patients [70].

MA is based on the belief that “methadone is a therapeutic tool of recovery that may or may not be discontinued in time, dependent upon the needs of the individual,” and that continued abstinence from drugs of abuse, including alcohol, is the foremost goal of recovery [71]. Most MA meetings are hosted by methadone clinics, and there are at least 600 MA chapters worldwide [71].

There are very few published studies involving MA. One study found that, similar to other 12-step programs, MA members undergo a spiritually-mediated transformation in their recovery process, with members describing methadone as the core of the group experience and an aid to spiritual transformation [72]. Length of time in MA has been found to be associated with reductions in the use of other substances as well, including alcohol, cocaine, and marijuana. Clients in methadone maintenance programs have rated components of MA to be significantly more helpful to recovery than methadone treatment components, suggesting that MA participation has benefits not available in professionally-driven methadone therapy programs [73].

## ACUPUNCTURE

Auricular acupuncture is the most common acupuncture approach for substance abuse, including opiate abuse and dependence, in the U.S. and the United Kingdom. This technique consists of bilateral insertion of acupuncture needles in the outer ears [74]. There is controversy surrounding the presumed mechanism of action of acupuncture. Western scientists attempt to explain its action on the body’s electromagnetic system, with the acupuncture needle creating a difference in electrical potential that stimulates extracellular ion flow. Chinese practitioners, who have been using acupuncture for several thousand years to treat a wide range of maladies, attribute its effects to unblocking or removing an excess of “qi”, or life energy, along key channels referred to as meridians [75].

Results from well-designed studies indicate that auricular acupuncture treatment is not sufficient in efficacy as a stand-alone treatment for opiate dependence. The placebo response rate is substantial, and the body of evidence does not demonstrate the type of qualitative and quantitative rigor needed to validate acupuncture efficacy in the treatment of opiate-addicted patients. Common adverse events from acupuncture include needle pain, fatigue, and bleeding; fainting and syncope are uncommon. Feelings of relaxation are reported by as many as 86% of patients [74]. There is some evidence that differences in efficacy may be influenced by racial physiological differences among persons of European and Asian descent [74].

## INTERVENTIONS FOR NON-ENGLISH PROFICIENT PATIENTS

For those who are not proficient in English, it is important that information regarding the risks associated with the use of opiates and available resources be provided in their native language, if possible. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient’s lack of proficiency in the English language, an interpreter is required. Interpreters can be a valuable resource to help bridge the communication and cultural gap between patients and practitioners. Interpreters

are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers, who ultimately enhance the clinical encounter. In any case in which information regarding treatment options and medication/treatment measures are being provided, the use of an interpreter should be considered. Print materials are also available in many languages, and these should be offered whenever necessary.

## MANAGEMENT OF COMORBID PSYCHOPATHOLOGY

Psychiatric comorbidity often accompanies opiate dependence and plays an important role in treatment outcome. Major depression prevalence among opiate-dependent patients is estimated to be 20% to 30% lifetime and 10% to 20% at enrollment in treatment. Depression is also associated with the use of prescription opiates for chronic pain and worse treatment outcomes [58]. The prevalence of depression is lower in out-of-treatment patients than in those seeking treatment and is associated with increased retention in methadone treatment. Thus, depression has a mixed effect on prognosis. It appears to be a motivating factor in treatment-seeking while at the same time interfering with treatment effectiveness [58]. In addition, opioid-dependent patients with Axis I psychiatric comorbidity often require significantly higher methadone doses [24].

A main issue in managing comorbid conditions is the differentiation of independent versus substance-induced disorders, as therapeutic plans differ for the two conditions. Substance abuse can result in changes in mood, appetite, sleep patterns, beliefs, and perceptual experiences, all of which may present as psychiatric disorders but resolve with stabilization of drug use. Treatment should not focus solely on the non-substance-use psychiatric diagnosis, as symptom reduction will not translate into reduced drug use. Active substance use can also alter the presentation of personality and diagnosis of a personality disorder [76].

## ASSESSMENT

It is important to assess dependent opiate users for other psychiatric and substance use disorders, especially alcohol and cocaine dependence because they are frequent comorbidities in opiate-dependent patients and can aggravate depressive symptoms. Bipolar illness is rare but has substantial treatment implications. Anxiety disorders frequently co-occur with depression, and traumatic experiences and post-traumatic stress disorder are common and should be thoroughly evaluated and treated [58]. Independent disorders are psychiatric conditions occurring during periods of sustained abstinence or having an onset before the substance-use disorder. A positive family history can aid in identifying an independent psychiatric disorder.



After a possible co-occurring disorder is identified during the screening of an opioid-dependent patient, an experienced, licensed mental health clinician (e.g., psychiatrist, psychologist, clinical social worker) should perform additional evaluation to make or confirm a diagnosis.

([http://www.guidelines.gov/summary/summary.aspx?doc\\_id=8356](http://www.guidelines.gov/summary/summary.aspx?doc_id=8356). Last accessed February 11, 2009.)

**Level of Evidence:** Expert Opinion/Consensus Statement

## TREATMENT APPROACH

Treatment should initially focus on stabilization of the patient's substance-abuse disorder, with an initial goal of 2 to 4 weeks abstinence before addressing comorbidities. Patients who persistently display symptoms of a psychiatric disorder during abstinence should be considered as having an independent disorder and should receive prompt psychiatric treatment [76].

Although depressive symptoms often improve following treatment admission, significant symptoms will persist in some patients [58]. Antidepressant medications can be effective in patients dually diagnosed with opiate dependence and depression when used at adequate doses for at least 6 weeks [77]. Factors emphasizing prompt antidepressant

treatment include greater severity of depression, suicide risk, and co-occurring anxiety disorders [58].

SSRIs are generally safe and well-tolerated, but clinical trials with these agents in methadone patients have been negative [58]. Therefore, SSRIs may be considered first-line treatment based on their safety profile, but if the patient does not respond, then TCAs or newer generation agents should be considered. More stimulating antidepressants, such as venlafaxine and bupropion, may be suitable in patients with prominent low energy or past or current symptoms consistent with attention deficit hyperactivity disorder (ADHD) [58]. The utility of nonpharmacologic treatments should be emphasized. Psychosocial therapies are as effective as pharmacotherapy in the treatment of mild-to-moderate depressive and anxiety symptoms. Treatment of personality disorders is nonpharmacologic [76]. If depression persists, psychosocial modalities, such as cognitive therapy, supportive therapy, or contingency management, have some evidence to support their efficacy in opiate-dependent patients [58].

In the treatment of insomnia and anxiety, trazodone and nefazodone are helpful agents, although nefazodone should be used with caution because of reports of liver toxicity. Mirtazapine, a sedating antidepressant, is a logical alternative. A baseline electrocardiogram (ECG) is recommended prior to a TCA trial in opiate users [58]. Benzodiazepines for anxiety should be avoided due to the liability of abuse and the potential of drug-seeking behavior, which is detrimental to treatment. Effective alternatives to benzodiazepines include antidepressants and anticonvulsant mood stabilizers. Sedating atypical antipsychotics may also be useful but should be used with caution due to potential side effects [58].

Medical comorbidities that may impact mental status and treatment response include [58]:

- Hypothyroidism
- HIV infection
- Hepatitis C and B
- Chronic lung disease
- Hypertension
- Diabetes
- Cardiovascular disease

### TREATING POLYSUBSTANCE ABUSE/DEPENDENCE

As noted, polysubstance use is the norm rather than the exception among opioid-dependent patients. The optimal approach to treating multiple substance abuse depends on the substances being used, the severity of the abuse, the treatment setting, familiarity of the clinician with treatment of the substance problem, and available resources for treatment. Optimal patient outcomes occur with pharmacologic and psychosocial combination therapy [76].

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### OPIATE USE AND PREGNANT WOMEN

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A portion of pregnant women with substance dependence continue using addictive substances despite awareness of the potential harm to the fetus [78]. Infants can sustain adverse effects from maternal opiate use, although it is difficult to separate factors due to opiate use from those due to the abuse of other drugs, poor prenatal care, poor nutrition, or other complications [46]. In utero exposure to opiates is associated with withdrawal symptoms of variable onset and severity in as many as 55% to 94% of exposed infants [79]. Opioid withdrawal is a physiologic rebound from the chronic drug effects on brain function. In pregnant women, rapid opioid withdrawal may precipitate preterm labor; in neonates, it may be fatal [78].

Reports of adverse effects of opiate use on fetuses and neonates include [78]:

- Fetal growth restriction
- Intrauterine withdrawal with increased fetal activity
- Depressed breathing movement
- Preterm delivery
- Preterm rupture of the membranes
- Meconium-stained amniotic fluid
- Perinatal death

Neonatal abstinence syndrome (NAS) may result in disruption of the mother-infant relationship, sleep-wake abnormalities, feeding difficulties, weight loss, and seizures [80]. Compared to supportive care only, opiate treatment of NAS reduces the time to regain birth weight, reduces the duration of supportive care, and increases the length of hospital stay. There is no evidence of effect on treatment failure [81]. Treatment with opiates has been shown to be superior to phenobarbital and diazepam in infants with NAS [81].

In treating pregnant women with substance dependence, psychological and pharmacologic treatments are often combined. Psychosocial treatments include contingency treatment, community reinforcement, behavioral marital therapy, cognitive-behavioral skills training, motivational enhancement therapy, and 12-step approaches [78].

## HEROIN

Heroin rapidly crosses the placental blood barrier. Roughly one-third of infants born to IV heroin users exhibit signs of neonatal withdrawal, with a small minority showing neonatal seizure activity [4]. Methadone maintenance has been found to be an effective harm-reduction strategy and can reduce acute neonatal withdrawal problems, including seizures [4].

## METHADONE

Pregnant women who are opioid dependent should be maintained on the lowest effective dose of methadone; detoxification, if attempted, should be done in the second trimester [78]. Outcomes are poor for patients who leave treatment. Fetal exposure can result in lower birth weight, smaller head circumference, jaundice, and thrombocytosis, although the cause of these conditions is difficult to distinguish between methadone and other concurrently-used substances. Methadone in the newborn infant will produce physical dependence and subsequent withdrawal symptoms that may not emerge until 48 hours after birth, regardless of maternal dose. Methadone-exposed infants function within a normal range of cognition at 1- and 2-year evaluations [78]. Methadone levels in breast milk appear to be small [87].



Methadone is currently the standard of care in the United States for the treatment of opioid dependence in pregnant women. Pregnant women who present for treatment of opioid addiction should be referred to specialized services in methadone maintenance treatment programs.

([http://www.guidelines.gov/summary/summary.aspx?doc\\_id=5887](http://www.guidelines.gov/summary/summary.aspx?doc_id=5887). Last accessed February 11, 2009.)

**Level of Evidence:** Expert Opinion/Consensus Statement

## BUPRENORPHINE

Buprenorphine has been administered successfully to opioid-dependent pregnant women as a maintenance replacement opioid. Placental transfer may be less than methadone, reducing fetal exposure and subsequent dependence and withdrawal. Buprenorphine has a low incidence of labor and delivery complications and of neonatal abstinence syndrome [78]. However, buprenorphine enters breast milk, and treatment with buprenorphine is strongly advised against during the nursing period [33].

## OXYCODONE

Oxycodone is metabolized to noroxycodone, oxymorphone, and their glucuronides and primarily excreted through urine. Oxycodone has been detected in breast milk, and although not found to be a teratogenic in experimental animals, it is not recommended for use in pregnancy. Management of infants born to mothers abusing oxycodone is of particular concern because the drug and its metabolites are difficult to detect by the enzyme immunoassay methods typically used for urine and meconium opiate screens [79].

## NALTREXONE

The literature is limited and equivocal regarding naltrexone and pregnancy. The substantial dropout rates due to the reward-blocking and dysphorigenic effects of this drug have resulted in limited reports on pre- and perinatal complications. One Australian study showed no obstetric complications and healthy-appearing infants, leading the authors to conclude naltrexone is a safe alternative in select pregnant patients [78]. However, other authors have found that naloxone can cause premature labor and fetal death, and it is considered to be pregnancy category C [4].

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## PROGNOSIS OF TREATMENT FOR OPIATE DEPENDENCE

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The relapse rate among patients receiving treatment for opiate dependence and other substance abuse is high, comparable to that of other patients with chronic relapsing conditions, including hypertension and asthma. Many cases of relapse are attributable to treatment noncompliance and lack of lifestyle modification [47].

Duration of agonist replacement therapy is usually recommended as a minimum of 1 year, and some patients will receive agonist replacement therapy indefinitely. Longer durations of treatment are associated with higher rates of abstinence from illicit opioids [19].

Much remains unknown about patient outcomes following termination of long-term opioid replacement therapy. Some patients aim to achieve total abstinence from all opiates, but little is known about patient characteristics and strategies used among those who remain abstinent. It is likely that at least some of the patients who remain abstinent from all opiates do so with the help of a 12-step support program, such as NA [19].

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## CONCLUSION

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Dependence on opioids is associated with serious morbidity and mortality, and advances in the understanding of the dependence have led to the development of effective treatments. More recently, the abuse of prescription opiates has become considerably more widespread, fueled in part by the availability of such drugs over the Internet. This has resulted in opiate abuse and dependence in populations seldom afflicted in the past. Thus, medical, mental health, and other healthcare professionals in a variety of settings may encounter patients with an opiate use disorder. The knowledge gained from the contents of this course can greatly assist the healthcare professional in identifying, treating, and providing an appropriate referral to patients with opiate use disorders.

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## GLOSSARY

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**Acetylation:** the process of introducing an acetyl group into a compound.

**Adenylate cyclase:** an enzyme that converts ATP to cAMP.

**Anhydrous:** having no water.

**Axis I mental disorders:** clinical syndromes, including major mental disorders such as depression, schizophrenia, and obsessive-compulsive disorder.

**Bioavailability:** the amount of active drug that reaches systemic circulation after ingestion.

**Congener:** a compound of the same kind or category.

**Cosyntropin test:** a test to determine how well the adrenal glands respond to the hormone ACTH. Involves the measurement of cortisol in the blood before and after injection of cosyntropin.

**Effectors:** a molecule that binds to and changes the activity of a protein.

**Enantiomer:** either of a pair of isomers that are mirror images of each other.

**Endogenous opioid:** an opioid that occurs naturally in the body, such as endorphin.

**Equianalgesic:** having the same analgesic effect.

**First-pass metabolism:** reduction of drug concentration prior to systemic circulation, often due to hepatic metabolism.

**Free morphine:** unmetabolized morphine.

**Full agonist:** chemicals or drugs that bind to and activate a receptor and display full efficacy (response) at that receptor.

**Glucuronidation:** a detoxification pathway in the liver whereby glucuronic acid is conjugated with toxins.

**Hedonic:** having a positive or pleasurable effect.

**Ketone:** water-soluble compound produced when fatty acids are metabolized in the liver and kidney.

**Kinase:** an enzyme that largely acts to transmit signals and control the complex activities of cells.

**Ligand:** a signal-triggering molecule.

**Lipophilic:** fat-soluble.

**Metabolite:** a substance involved in metabolism, either as a by-product or as a necessary component.

**Parent drug:** the drug initially consumed or administered prior to metabolism.

**Peptide:** a short chain of amino acids.

**Phosphorylation:** the addition of a phosphate group to an organic molecule.

**Plastic alternation:** pliable or alterable exchange.

**Polymorphism:** genetic variation within a population.

**Prodrug:** a pharmacologically inactive compound that converts to an active form within the body.

**Pseudoaddiction:** preoccupation with and pursuit of opiate medication driven by a desire for pain relief and not for the drug's mood-altering effects. Results from poorly treated pain.

**Sensorium:** an individual's perception and entire sensory environment.

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