# *Opioid Use Disorder*

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- Complete the questions at the end of the course.
- Return your completed Answer Sheet/Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. Your postmark or facsimile date will be used as your completion date.
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***Faculty***

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***Faculty Disclosure***

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

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

***Audience***

This course is designed for dental professionals who may be involved in identifying or treating opioid use disorder.

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### *Course Objective*

Practice guidance for opioid use disorder in primary care has not kept pace with rapid, profound changes in this area, leaving healthcare professionals with outdated and incomplete information to guide the clinical management of opioid use disorder and related morbidity. The purpose of this course is to close this gap to allow dental professionals to provide the best, evidence-based care to patients with opioid use disorder.

### *Learning Objectives*

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

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

## INTRODUCTION

The purpose of this course is to provide the reader with a current, evidence-based overview of opioid use disorder and its treatment. Topics covered in this review include the history and demographics of illicit and prescription opioid abuse; risk factors, background characteristics, and comorbid conditions of opioid abusers; the pharmacology of opioid drugs; the biologic and behavioral characteristics of opioid dependence; and management of opioid 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 opioids and the impact of opioids on the fetus.

## DEFINITIONS

The definitions and terminology used to describe opioids, addiction, and pain vary in meaning to different stakeholders, and while periodically revised, previous iterations circulate. Some terminology perpetuates misinformation or myths. A few widely used updated definitions include [1; 2; 3; 4; 5; 6]:

- **Misuse, nonmedical use**: Any use of a drug prescribed to someone else or of one's own prescription departing from the authorized directions.
- **Abuse**: This term from older DSMs has been largely replaced by misuse. Definition varies widely depending on the context, but generally means a maladaptive pattern of use with the primary intent of achieving euphoria or getting high. The Drug Enforcement Agency (DEA) defines abuse as the use of a schedule II through V drug in a manner or amount inconsistent with the medical or social pattern of a culture. 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."
- **Addiction**: Defined by the American Society of Addiction Medicine (ASAM) as "a primary chronic, neurobiologic 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. Addiction has been referred to as psychologic dependence, but this terminology is incorrect as persons with addiction have become psychologically dependent on the substance, but not all persons with psychologic dependence develop addiction.
- **Dependence**: Introduced by the APA to replace the term "addiction," opioid dependence described both psychologic dependence (a symptom of addiction) and physical dependence (a process of neurobiologic adaptation that can manifest as tolerance and withdrawal symptoms reflecting uninterrupted exposure to the opioid independent of addiction). This terminology is largely abandoned as imprecise and obsolete.

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5-TR) defines opioid use disorder as a problematic pattern of opioid use, leading to clinically significant impairment or distress. The diagnosis of OUD is made by meeting two or more criteria in a one-year period [2; 7]:

- Opioids taken in larger amounts or over a longer period than was intended
- A persistent desire or unsuccessful efforts to cut down or control use
- Excessive time spent to obtain, use, or recover from using the opioid
- Craving, an intense urge to use
- Opioid use interferes with obligations
- Continued use despite life disruption
- Reduction or elimination of important activities due to use

- Recurrent use in physically hazardous situations
- Continued use despite physical or psychologic problems
- Tolerance
  - Need for increased doses of the opioid for the desired effect
  - A markedly diminished effect with continued use of the same amount
- Withdrawal

Note: The criteria for tolerance and withdrawal are not considered to be met for those taking opioids solely under appropriate medical supervision.

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 [8]. Despite replacement of "opioid dependence" with opioid use disorder in the DSM-5-TR, use of this term persists, along with conflation of tolerance with opioid addiction and exposure to medically indicated opioid analgesics with opioid dependence with opioid addiction.

Pseudoaddiction describes drug-seeking behaviors iatrogenically produced in pain patients by inadequate pain treatment. This is manifested as preoccupation with and pursuit of opioid 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; 3; 4; 5].

## BACKGROUND

The first reference to opium is found in the 3rd century B.C.E. The use of opium was well-understood by Arab physicians, and Arab traders introduced the drug to Asia, where it was utilized primarily for the control of dysentery [9].

The isolation of morphine from opium was achieved in 1806 and was named for Morpheus, the Greek god of dreams [9]. 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 [9].

In addition to the highly beneficial therapeutic effects, the toxic side effects and addictive potential of opioids 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 opioids 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 [9].

Nonmedical use of prescription opioids was reported in literature as early as 1880. A report in 1928 documented that injection of opioids contributed to the development of nonmedical use and misuses of prescription opioids. Before 1930, the prevalence of nonmedical opioid injecting in the United States 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 [10].

## EPIDEMIOLOGY OF OPIOID USE DISORDER

As of 2021, the estimated worldwide prevalence of past-year opioid use was 60 million people [11]. In 2021, an estimated 9.2 million people in the United States had misused prescription opioids in the past year, and of those people, 8.7 million reported the nonmedical use of prescription opioids while nearly 1.1 million reported past-year use of heroin [12]. With only 4.23% of the world's population, the United States annually consumes more than 80% of all opioid supplies, including [13; 14]:

- 99% of all hydrocodone
- 68% of all oxycodone
- 52% of all methadone
- 40% of all hydromorphone
- 19% of all fentanyl

The nonmedical use of opioids is a virtually universal phenomenon, but Asia and the Americas account for the majority of users [11]. Subregions with a relatively high prevalence of past-year opioid use include North America (3.3%), and Near, Middle East, and South-West Asia (3.19%) [11]. In the majority of Europe, Africa, and Asia, heroin is the most prevalent illegally consumed opioid. In the Americas and Oceania (Australia and New Zealand), illegally diverted or misused prescription opioids (e.g., codeine, hydrocodone, morphine, hydromorphone, oxycodone, meperidine) are the primary opioids of abuse. However, some African and European nations have reported a surge in prescription opioid abuse in the last decade, and there is growing evidence of the nonmedical use of opioids in India [11]. Traditional opium-cultivating countries and their neighbors contain the majority of raw opium users.

The Drug Abuse Warning Network (DAWN) was established in 1972 by the DEA to track and publish data collected from participating states on emergency department (ED) visits resulting from substance misuse or abuse, adverse reactions, drug-related suicide attempts, and substance abuse treatment [15]. By its final year in 2011, DAWN had collected data from metropolitan areas in 37 states, with complete coverage in 13 states. Although their total figures did not capture all 50 states, the population rates were representative and able to be extrapolated to the United States as a whole [15].

Data from the DAWN network indicates that opioid abuse is a growing problem in the United States. In 2011, the overall admission rate for misuse or abuse of opioid analgesics (excluding adverse reactions) was 134.8 per 100,000, an increase of 153% compared with 2004. In the 13 states involved in the DAWN network, the top four opioid analgesics involved in drug-related ED visits for 2011 were various formulations of oxycodone (175,229), hydrocodone (97,183), methadone (75,693), and morphine (38,416). Between 2004 and 2011, ED admissions increased 74% for methadone, 220% for oxycodone, 96% for hydrocodone, and 144% for morphine. Heroin-related ED episodes increased from 213,118 in 2009 to 258,482 in 2011 [16]. There was no meaningful change in ED admission rates involving opioid analgesics between 2009 and 2011 [15]. However, more than 81,000 drug overdose deaths occurred in the United States in the 12 months ending in May 2020, the highest number of overdose deaths ever recorded in a 12-month period, and the rise was mainly attributed to synthetic opioids [17]. From 2013 to 2019, the age-adjusted rate of deaths involving synthetic opioids other than methadone increased 1,040% [18].

Although prescription opioid abuse decreased by approximately 12% between 2010 and 2011, heroin use increased. There were 119,000 total users in 2003, but 281,000 by 2011 and 948,000 by 2016 [19]. In addition, first-time past-year use increased significantly between 2006 (90,000) and 2016 (170,000), with the greatest increases among young adults 18 to 25 years of age [19]. In 2016, an estimated 11.8 million people in the United States 12 years of age or older reported past-year use of heroin and 3.6 million reported past-month use [12].

According to the National Survey on Drug Use and Health, there were 26,000 new heroin users older than 12 years of age in 2021 [12]. Most new users were female. In 2021, an estimated 829,000 persons received treatment for heroin abuse [12]. 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 [12].

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 declined slightly from 2017 to 2020 [20]. In 2023, the level of annual use was 0.4% or less in each grade [20]. Lifetime heroin use (at least one use in an individual's lifetime) declined significantly in 2023, bringing prevalence to 2.4%, which is the second-lowest recorded by NIDA [20]. Past 12-month use also significantly declined in 2023, to 1% [20]. The survey also monitors the use of diverted opioids and shows past year oxycodone use rates significantly declined in grades 10 and 12 and was 0.8% lower in all grades [20].

Nonmedical use of prescription opioids has caused increasing concern among law enforcement officials and regulatory, pain relief advocacy, and drug abuse organizations [21]. Between 1992 and 2003, the U.S. population increased 14%, while persons abusing opioid analgesics increased 94% and first-time nonmedical opioid analgesic users 12 to 17 years of age increased 542% [21]. The prevalence of past-year nonmedical oxycodone use increased from 8.9% in 2019 to 12.8% in 2021 [12]. During 2021 in the United States, an estimated 71.7 million (12.2%) individuals misused prescription pain relievers; 1.8 million (20.9%) initiated misuse of prescription pain relievers; and almost 1.9 million (0.7%) had a substance use disorder involving prescription pain relievers [12]. ED visits involving treatment from prescription opioids were estimated to be 239,000 in 2021 [12].

Among high school seniors, use of hydrocodone/acetaminophen (Vicodin) was less than 1% across grades 10, 11, and 12 in 2023. Levels of use significantly declined to record lows in 2023 for 12th- and 10th-grade students. The low levels in 2023 are the result of a marked declined from peaks before 2010 of 3% in 8th grade, 8% in 10th grade, and 11% in 12th grade [20]. More than 40 million prescriptions were written for acetaminophen/hydrocodone in 2020, making it the twelfth most prescribed drug in the United States [22]. At least 35.5 million Americans have ever used a hydrocodone product illicitly [12]. In 2014, the DEA reclassified hydrocodone-containing products from Schedule III to Schedule II of the Controlled Substances Act. Following the rescheduling, prescriptions dropped from 120 million in 2014 to 5.5 million in 2018 [23; 24].

Some studies estimate that as many as 20% of individuals in the United States have used a prescription opioid for nonmedical purposes at least once during their lifetime [25; 26]. In 2019, 9.1 million young adults had used an prescription pain reliever for nonmedical purposes in the past year. This number dropped to 8.2 million in 2021 [12]. The greatest misuse was among individuals 26 to 49 years of age, and the incidence was similar between men and women [12]. Among persons 12 years of age or older, treatment admissions for prescribed opioid abuse have more than doubled between 2000 and 2010. In 2019, 731,000 people received past-year substance use treatment for prescription pain relievers. This number increased slightly to 746,000 in 2021 [12].

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 2019; the largest increase occurred with pain relievers. In 1990, there were 628,000 initiates compared with 1.8 million in 2021 [12]. As of 2021, it is conservatively estimated that 5 million individuals have a substance use disorder related to prescription pain medication [12]. The number of primary treatment admissions for pain medication use disorder was 746,000 in 2021 [12].

In 2021, 1.8 million individuals reported using prescription pain relievers nonmedically for the first time within the last year—nearly 4,930 per day [12]. Approximately 87.1 million individuals 12 years of age or older were past-year users of prescription pain relievers in 2019 [12].

## DEMOGRAPHICS OF ILLICIT OPIOID USERS

Male-to-female ratios for lifetime heroin-only users and lifetime heroin and oxycodone users show that use is higher for men than for women [12]. In 2021, 65.3% of admissions to substance use treatment services (for all substances) were male and 34.6% were female [27]. Male opioid users are more likely to also use other illicit drugs; female opioid users are more likely to also abuse other prescription drugs [28]. There is a high incidence of mood/anxiety disorders among opioid users, and this incidence is significantly greater among women than men.

In 2021, the percentages of past-year nonmedical use of pain relievers among the predominant racial and ethnic groups were [12]:

- White: 3.0%
- Hispanic or Latino: 3.1%
- Native Hawaiian or Pacific Islander: Not reported
- American Indian/Alaska Native: 4.4%
- Black or African American: 3.5%
- Asian: 2.2%

As of 2021, individuals 18 to 25 years of age have the highest percentage of past year (3.1%) and past month (0.9%) illicit pain medication use [12].

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 [29]. The two populations for whom prescription opioid 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 neurobiologic changes and behavioral consequences that differ from adults [29].

## GEOGRAPHIC PATTERNS OF MISUSE

Nonmedical use of opioid analgesics has been observed in both rural and urban areas. Among people 18 years of age and older, the highest percentage of past-year illicit pain medication users live in small metro (3.5%) areas followed by completely rural (3.2%), less urbanized (3.2%), urbanized nonmetro (3.2%), and large metro (3.1%) areas [12]. Research data also suggest a problem with injecting among rural opioid users, a problem more typically associated with urban drug users [10]. The West (3.4%) and the South (3.3%) areas have the highest percentage of past-year users, followed by and the Northeast (3.2%) and Midwest (3.0%) [12].

## RISK FACTORS FOR OPIOID USE DISORDER

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 [8]. Of course, not all persons who use drugs regarded as having a high liability of misuse 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 [30].

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 opioids may become conditioned to the activities of daily living. As a result, environmental stimuli become powerfully associated with opioid use, which can trigger cravings for the drug [29]. The visibility of pharmaceutical marketing and advertising of medications may also play a role by changing the attitudes

toward ingestion of these agents [29]. 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 [29].

Individuals who use nonmedical prescription opioids before 13 years of age are more likely to become addicts than those who initiate use at 21 years of age or older. The odds of becoming an addict are reduced 5% each year after 13 years of age [31]. Additionally, it is a commonly held view among adolescents (27%) that prescription drugs are "much safer" than street drugs [32]. This belief is undoubtedly shared with much of the adult population and has led to the extraordinary rise in recreational prescription drug users.

Marked increases in prescriptions written for opioids in the United States and Internet access to prescription drugs may explain a portion of the increase in opioid use disorder. 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 [29]. 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 misuse [29].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Institute for Clinical Systems Improvement recommends considering screening patients for substance use disorders when there is an unclear etiology of pain.

(https://www.icsi.org/wp-content/uploads/2019/10/Pain-Interactive-7th-V2-Ed-8.17.pdf. Last accessed March 21, 2024.)

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

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. This is now clearly known to be the result of increases in illicitly manufactured formulations. Similar excessive increases in emergency department mentions relative to prescriptions have been observed with oxycodone but not morphine or hydrocodone [29].

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

Long-term use of prescription opioids for chronic pain results in abuse or dependence in 2.8% to 18.9% of patients [29]. Predictors of dependence on opioid medications among pain patients include substance abuse-related diagnoses, positive toxicology for opioids, and other medical diagnoses, including diagnosis of comorbid psychiatric conditions [33]. Other patients at risk include those with idiopathic pain (no clear etiology) or high levels of psychologic distress or disability [7]. Alcoholism and other drug dependence are often viewed as contraindications for opioid medications in chronic noncancer pain.

## EPIDEMIOLOGY OF OVERDOSE

Overdose is a major cause of premature death among opioid drug users. Nonfatal 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 this population [34]. As noted, the Centers for Disease Control and Prevention (CDC) reported the highest overdose rate in the year ending May 2020, primarily driven by rapid increases in overdose deaths involving synthetic opioids excluding methadone [17; 35]. From 1999 to 2021, an estimated 280,000 people in the United States died from an overdose involving prescription opioids [35]. Of all drug overdose deaths in 2021 (106,699), deaths involving opioids (80,411) accounted for 75.4% [36].

### Synthetic Opioid Overdose

The number of overdose deaths involving synthetic opioids in 2021 was almost 23 times the number of such deaths in 2013. Death rates from synthetic opioids increased more than 22% from 2020 to 2021 and accounted for almost 88% of all opioid-related deaths in 2021 [35; 36]. Age-adjusted rates of overdose deaths from synthetic opioids increased significantly from 2001 through 2021, with different rates of change over time [36]. Rates of drug overdose deaths involving synthetic opioids increased from 17.8 per 100,000 population in 2020 to 21.8 per 100,000 population in 2021 [37]. Increases in overdose deaths from synthetic opioids are being driven by increases in fentanyl-involved overdose deaths from nonpharmaceutical fentanyl [36]. From 2018 to 2019, a total of 20 states experienced relative increases in death rates from synthetic opioids, with the highest rate in 2019 in Delaware (38.4). The largest relative rate increase occurred in Colorado (95.5%), and the largest absolute rate increase occurred in the District of Columbia (7.6). No state experienced a significant decrease [38].

The opioid overdose rate among women has increased faster than it has in men. From 1999 to 2015, overdose fatality increased 471% in women, compared with 218% for men. There has been an alarming increase in the rates of synthetic opioid-related deaths, which increased 850% in women between 1999 and 2015 [39]. In aggregate, women tend to possess background characteristics and opioid analgesic use patterns that may contribute to overdose vulnerability. Women are more likely to experience chronic pain, receive prescriptions for opioid analgesics, receive higher doses of opioids, and use opioids for longer periods than men. Substance use disorders involving opioid analgesics are thought to develop more rapidly in women, and women may be more likely to obtain opioid prescriptions from multiple prescribers than men [40].

#### *Fentanyl Contamination of Other Drugs*

Fentanyl and fentanyl analogs are being increasingly mixed into counterfeit opioids, heroin, and other drugs. This contamination of other drugs is a growing concern as it can lead to an increase in overdose deaths in unsuspecting opioid users as well as among individuals who are opioid naïve [36]. A 10-state study (Kentucky, Maine, Massachusetts, New Hampshire, New Mexico, Ohio, Oklahoma, Rhode Island, West Virginia, and Wisconsin) found that nearly 57% of people who died from a drug overdose tested positive for fentanyl and fentanyl analogs as well as cocaine, methamphetamine, or heroin. Ohio reported the largest numbers and most substantial increases in deaths with any fentanyl analog detected [41]. Among the overdose deaths with fentanyl analogs detected, the analogs were determined by either medical examiners or coroners to have contributed to the death in more than 95% of cases [41]. The most potent fentanyl analog that has been detected in the United States is carfentanil, and it is responsible for the largest number of deaths involving fentanyl analogs. Among 11,045 opioid overdose deaths in 10 states from July 2016 to June 2017, more than 20% tested positive for any fentanyl analog and more than 11% tested positive for carfentanil [42].

### Heroin Overdose

Overdose death rates involving heroin decreased by nearly 32% from 2020 to 2021 in the United States. However, in 2021 more than 9,000 people died from a heroin overdose, a rate of nearly three deaths for every 100,000 Americans. The number of heroin-involved overdose deaths in 2021 was three times the number in 2010, and more than 11% of all opioid deaths involved heroin [36].

### Risk Factors for Heroin/Opioid 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 [34]. (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 opioid concentrations. However, this does not explain the strong association of fatal overdose with age [34].

Risk factors for prescription opioid overdose are similar to those for heroin overdose, but also include obtaining overlapping prescriptions from multiple providers/pharmacies, taking high daily doses of prescription pain relievers, self-medication, polypharmacy, living in a rural area, and mental illness [43]. Most people who abuse prescription opioids get them free from a friend or relative. However, those at highest risk of overdose (i.e., those who use the drugs nonmedically 200 or more days per year) obtain them differently. More than 42% of those at highest risk of overdose obtain opioids using their own prescriptions; 33.9% obtain them from friends or relatives for free; 7.3% purchase the drugs from friends or relatives; and 7.9% purchase them from a drug dealer [12]. Individuals at highest risk of overdose are four times more likely than the average user to buy the drugs from a dealer or other stranger [44].

**Risk Factors for Methadone Overdose**

Historically, methadone was used primarily as pharmacotherapy for heroin addiction. During the 1990s, however, methadone gained increased acceptance for use as an analgesic, and methadone began to be prescribed to outpatients with moderate-to-severe noncancer pain. Prescribing rates soared over the next decade; comparison of methadone sales quantity between 1997 and 2007 shows an increase of 1,293% [45; 46]. This rising use of methadone occurred simultaneously with concerns over the abuse potential of other opioids and the search for a relatively inexpensive long-acting opioid analgesic alternative [47].

Since the mid-2000s, methadone has become disproportionately represented in cases of opioid analgesic fatality. Based on data showing that 70% of fatalities among those prescribed methadone occurred in the first seven days of treatment, the FDA changed the methadone labeling in 2006 to lengthen dosing intervals from every 3 to 4 hours to every 8 to 12 hours; the initial recommended dose of 2.5–10 mg was unchanged [48]. In 2008, use of the highest oral dose (40 mg) preparations was prohibited from use in pain treatment and restricted to addiction therapy [49].

In addition to the general risk factors for opioid overdose, specific factors that contribute to methadone fatality include [49]:

- Payer policies that encourage or mandate methadone as first-line therapy
- Methadone prescribing in opioid-naïve patients
- Lack of prescriber knowledge of methadone pharmacology

## CLASSIFICATION

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 latex sap of the opium poppy *Papaver somniferum*. Drugs derived from opium, including the natural products morphine, codeine, and thebaine, may be referred to as opiates [9]. However, for the purposes of simplification, all compounds will be referred to as opioids throughout this course.

The narcotic analgesics can be categorized into three groups. The first group includes the natural opium derivatives (heroin, morphine, and codeine) and the semisynthetic derivatives from this group, including hydromorphone, oxymorphone, hydrocodone, oxycodone, dihydrocodeine, and buprenorphine. The two other groups are synthetic chemicals: the phenylpiperidines, including meperidine and fentanyl, and the pseudo-piperidines, including methadone and propoxyphene [50].

## OPIOID SYNTHESIS

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 sap 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 [9].

Heroin, or diacetylmorphine, is synthesized by collecting and converting powdered opium to heroin hydrochloride in clandestine laboratories [8]. 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 United States. The purity of Colombian and Mexican heroin powder averages 40% to 60% [8]. From the point of entry in the United States 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 [8].

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 [9].

## PHARMACOLOGY

Opioids have been the mainstay of pain treatment for thousands of years, exerting their effects by mimicking naturally occurring endogenous opioid peptides or endorphins [9]. Although many new opioids have been developed with pharmacologic properties similar to morphine, morphine remains the standard against which new analgesics are measured [9].

### 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 [9].

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 adrenocorticotropic 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 physiologic linkage between the stress axis and opioid systems, which has been validated by the observation of stress-induced analgesia [9].

### 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 [51].

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 pharmacologic profiles [9]. 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 [9].

### 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 [9]. 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 [9].

## CLINICAL EFFECTS

Morphine and most other opioid agonists share in common the following physiologic effects [9]:

- 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 [9].

### 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 [52]. Behavioral and pharmacologic data point to the probable role of dopaminergic pathways, with interactions between opioids and dopamine mediating the opioid-induced reinforcement [9].

### 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 [9].

### 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 [9].

### 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 [9]. 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 [9].

### 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 [53]. In cases of injecting use, bacterial endocarditis can develop [53].

### 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 [9]. Morphine and most mu and kappa agonists also constrict the pupils through excitation of the parasympathetic nerve stimulating the pupil [9].

## SPECIFIC OPIOID DRUGS

### 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 (6-MAM) 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 [51]. The drug rapidly enters the brain after IV administration, where it binds to mu, kappa, and other stereospecific opioid-receptor binding sites in the locus coeruleus [8]. The onset of euphorigenic action is approximately 30 minutes after intranasal ingestion, 15 minutes after subcutaneous injection, and almost instantaneously after IV injection, with a duration of about three to four hours [8]. As with many other opioids, heroin reduces the anticipatory anxiety associated with emotional or physical pain and alters the perception of pain [8].

Heroin is rapidly deacetylated in the microsomes of the endoplasmic reticulum in the liver to 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 [8].

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 [51].

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 [8].

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 [8].

**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 [9].

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 two to four hours [9].

Codeine and promethazine syrup is the active component of the recreational drug "purple drank;" other common names include "syrup" and "lean" [54]. The combination of the purple antitussive, soft drinks, and in some cases candy has been mentioned in hip-hop music since the late 1990s and has been particularly popular in the South [54]. All opioid/soft drink concoctions may colloquially be referred to as "sizzurp."

**Tramadol**

Tramadol is a synthetic codeine analog and a weak mu-opioid receptor agonist. Tramadol is unusual among opioids in that a portion of its analgesic effect is produced by norepinephrine and serotonin uptake inhibition [9]. 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 1/6,000th 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 [9].

**Levorphanol**

Levorphanol (brand name Levo-Dromoran) is the only commercially available opioid agonist of the morphinan series, and it possesses pharmacologic effects very similar to those of morphine. Levorphanol is metabolized less rapidly than morphine and has a half-life of 12 to 16 hours [9; 55].

**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 [55].

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 [9]. Meperidine is primarily abused by healthcare professionals [9].

**Diphenoxylate and Loperamide**

Diphenoxylate (in combination with atropine as Lomotil) and loperamide (Imodium) are meperidine congeners that are approved by the U.S. Food and Drug Administration (FDA) for the treatment of diarrhea [55]. These drugs slow gastrointestinal motility by affecting the circular and longitudinal muscles of the intestine, presumably through interaction with opioid receptors in the intestine [9].

**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 five minutes. Respiratory depression potential is similar to other mu-receptor agonists with a more rapid onset. Fentanyl and sufentanil treatment of chronic pain has become more widespread, and transdermal patches that provide sustained release for 48 hours or more are available [9]. 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 healthcare 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 three 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 [56]. Methadone is a long-acting mu-receptor agonist with pharmacologic properties quantitatively similar to those of morphine [9]. 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 one or two hours of subcutaneous or intramuscular administration [9]. Oral bioavailability approaches 100% [55; 56].

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 [55]. 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 [51; 55]. Liver disease can increase the half-life of methadone, but renal failure will not [56]. 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 [51; 57].

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 [58].

One of the most significant advantages of methadone is that it alleviates cravings for opioids (a primary reason for relapse) and blocks many of the pleasurable effects of heroin, which helps reinforce abstinence [56]. 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 [9]. Accidental overdose fatalities can occur when pain patients re-administer methadone when the analgesia wears off and pain returns, potentially elevating plasma concentrations to life-threatening levels. These same pharmacologic properties also imperil those who use it illicitly. Opioid abusers often co-administer benzodiazepines, which greatly elevates lethality risk with methadone. Concurrent use of alcohol poses the same risk [47].

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 opioid withdrawal. To date, there is no evidence that diversion of methadone from methadone clinics has resulted in significant numbers of new opioid addicts [59].

More frequent adverse 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 [55]. Rarely observed side effects include biliary spasm, urticaria, syncope, overdose death, and torsades de pointes [56]. These effects are more common at higher doses and when methadone is combined with certain other drugs [60]. Risk of QTc prolongation and arrhythmia led to a 2006 black box warning [55].

Tolerance to the opioid properties of methadone develops within four weeks. The minimal effective dose is regarded as 40 mg, but some patients require much greater doses [55; 56]. Subcutaneous administration of 10-20 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 [9].

**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 [61]. 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 [62].

**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 Opana). Oxycodone is suitable for oral administration due to high bioavailability (60%) but may also be taken intramuscularly, intravenously, subcutaneously, or rectally; however, oxycodone is only commercially available in oral preparations [55]. 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 [63].

Oxycodone is metabolized by demethylation to noroxycodone and oxymorphone followed by glucuronidation [55]. A urine screen may reveal oxycodone alone, oxycodone and oxymorphone, or oxymorphone alone [64].

Since 1995, oxycodone has been marketed in the United States 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 2.5–10 mg of oxycodone [55]. 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].

In 2014, the FDA approved an extended-release version of oxycodone that is formulated to include naloxone in order to deter misuse [65]. If crushed and snorted or crushed, dissolved, and injected, the naloxone will block the euphoric effects of oxycodone, potentially deterring this type of abuse. This combination drug is intended for patients for whom alternative treatment options for chronic pain are ineffective or not tolerated [65]. The drug is no longer available in the United States [55].

**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 [66].

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 pharmacologic activity. Side effects are comparable to morphine [66].

In 2023, the FDA issued a drug safety communication to update the prescribing information for immediate-release (IR) and extended-release (ER)/long-acting (LA) opioid analgesics. The safety communication includes updates to boxed warnings, indications and usage, dosage and administration, warnings and precautions, and the medication guide [67]. Revised labels must state that [67]:

- The risk of overdose increases as the dosage increases for all opioid pain medicines.
- IR opioids should not be used for an extended period of time unless a patient's pain remains severe enough to require them and alternative treatment options continue to be inadequate.

- Many acute pain conditions treated in the outpatient setting require no more than a few days of an opioid pain medicine.
- It is recommended to reserve ER/LA opioid pain medicines for severe and persistent pain that requires an extended treatment period with a daily opioid pain medicine and for which alternative treatment options are inadequate.
- A warning about opioid-induced hyperalgesia (OIH), including information on differentiating OIH symptoms from those of opioid tolerance and withdrawal.

## 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 60 years [25]. 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, mixed agonist-antagonist drugs (e.g., pentazocine) can produce side effects not often seen with pure agonists, including severe, irreversible psychotomimetic effects [9].

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 [9].

### 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) [9].

In the 1970s and early 1980s, pentazocine (Talwin) was combined with the crushed, blue-colored antihistamine tablet tripelennamine 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 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 opioid 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 opioid effects of the pentazocine and precipitates acute opioid withdrawal [1].

### Nalbuphine

Nalbuphine 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 [9].

### 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 [9; 55].

**Buprenorphine**

Buprenorphine was initially suggested in 1978 as an alternative oral opioid substitution therapy for opioid addicts. Buprenorphine and methadone are the two most widely used and effective pharmacotherapies for opioid use disorder, and both have regulatory approval in the United States for this indication [68]. Buprenorphine is a semi-synthetic opioid derivative made from thebaine, one of the naturally occurring alkaloids in opium [69]. Buprenorphine, sold as Buprenex, Subutex, Belbuca, or Sublocade, 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 [55; 56; 70].

Buprenorphine has a very low oral bioavailability due to substantial intestinal and hepatic metabolism. The sublingual formulation used to treat opioid dependence is well-absorbed and produces opioid 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% [69]. 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 explains the prolonged period of effectiveness. Buprenorphine is metabolized through the hepatic cytochrome P450 pathway. Approximately 80% is eliminated through binary excretion of the glucuronidated metabolites and 20% via the urinary route [69].

The minimum daily dose needed to suppress opioid 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 [69].

In 2014, the FDA approved a buccal film containing both buprenorphine and naloxone [71]. This combination therapy is applied once daily to suppress signs and symptoms of opioid withdrawal [55]. In 2016, the FDA approved the first buprenorphine implant (Probuphine) for opioid dependence [72]. The implant provides a constant, low-level dose of buprenorphine for six months. It is designed for use in patients who are already stable on a low dose of other forms of buprenorphine, as part of a complete treatment program. Because Probuphine must be inserted and removed surgically, healthcare providers are required to complete training and certification through the Probuphine Risk Evaluation and Mitigation Strategy (REMS) program [72]. In 2017, the FDA approved a once-monthly subcutaneous injection (Sublocade) for opioid use disorder [73]. Sublocade is intended for use in adult patients with moderate-to-severe opioid use disorder who have been on a stable dose of buprenorphine treatment for a minimum of seven days. The drug must be administered in a healthcare setting to avoid inadvertent IV administration that could result in death [73]. In 2023, the FDA approved buprenorphine extended-release (Brixadi) for subcutaneous injection [74]. Brixadi is approved in both weekly and monthly subcutaneous injectable formulations at varying doses, including lower doses that may be appropriate for those who do not tolerate higher doses of extended-release buprenorphine that are currently available. The weekly doses are 8, 16, 24, and 32 mg; the monthly doses are 64, 96, and 128 mg [74]. Buprenorphine use is contraindicated for patients with alcohol intoxication, delirium tremens, and treatment with monoamine oxidase inhibitors. Cases of lethal buprenorphine intoxication almost always involve polyintoxication [69]. Buprenorphine contains a black box warning regarding the potential for serious, life-threatening, or fatal respiratory depression, especially during initiation or dose escalation [55]. Upon discontinuation, a withdrawal syndrome develops, with a delayed emergence in two days to two weeks. Signs and symptoms of buprenorphine withdrawal are typical of a milder morphine-type withdrawal and last roughly one to two weeks [9]. The more benign withdrawal syndrome is due to its partial agonist property at the mu receptor and weak antagonist property at the kappa receptor [56]. Section 1262 of the Consolidated Appropriations Act of 2023 removes the federal requirement for practitioners to apply for a

special waiver prior to prescribing buprenorphine for the treatment of OUD. It also removes other federal requirements association with the waiver, such as patient limits. Separately, section 1263 of the Act requires new or renewing DEA registrants to meet one of three requirements (i.e., training, certification, or education). This section became effective June 27, 2023. Additional information is available on the SAMHSA website at https://www.samhsa.gov/medications-substance-use-disorders/waiver-elimination-mat-act [75; 76].

### 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 naloxone, naltrexone, and nalmefene. Nalmefene is not approved in the United States [55]. Interestingly, naloxone also appears to block the analgesic effects of placebo medications and acupuncture. Naltrexone and naloxone have little or no potential for abuse [9].

## NATURAL HISTORY OF OPIOID DEPENDENCE

Although the time from initiation to daily use and serious physiologic and psychologic dependence is highly variable, the different stages of opioid dependence are clearly delineated [8]. 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 [77].

### 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 [77].

### 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 [8].

### DETOXIFICATION AND WITHDRAWAL

During detoxification and withdrawal from opioids and other central nervous system depressants, glutamate and norepinephrine in the locus coeruleus are primarily involved in causing the associated symptoms [77].

### RELAPSE FOLLOWING SUSTAINED ABSENCE

Brain regions implicated in relapse to opioid 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 that are involved in compulsive and habitual behavior and mediate cue-induced relapse [77].

## PATHOPHYSIOLOGY

### OPIOID 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 [51]. Tolerance (as well as withdrawal and physiologic dependence) are expected responses to opioids and other controlled substances when given in sufficient doses over time and are not, by themselves, indicative of addiction [78; 79]. 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 [9].

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 [51].

## OPIOID DEPENDENCE

Opioid dependence is best described as a central nervous system disorder characterized by neurobiologic changes leading to compulsive drug-taking behaviors. As the result of chronic use, the cells producing endogenous opioids cease to function and degenerate, causing the user to become physically dependent on exogenous opioids [80].

According to the classical theory of addiction, opioid 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 [81].

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 [81]. Dependence on most drugs of abuse is characterized by an altered physiologic 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 [82].

### Molecular Basis

The diverse biologic effects of opioids are manifested through specific opioid receptors distributed throughout the central and peripheral nervous system. Opioid receptors, upon the binding of opioid drugs (or endogenous opioid peptides), regulate a multitude of intracellular signaling pathways. Involvement of opioid receptors in opioid dependence is unequivocal. This is reliably demonstrated by the rapid precipitation of withdrawal syndromes in opioid addicts by opioid receptor antagonists such as naloxone [83].

Repeated exposure to short-acting opioids can result in durable alterations in opioid receptor kinetics, transmembrane signaling, and postreceptor signal transduction [84]. Opioid dependence requires sustained activation of opioid receptors, and this chronic signaling process ultimately leads to changes in protein functions of gene transcription [83].

Opioid receptors are members of the G-protein receptor family, and each opioid 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 [83].

Prolonged administration of opioids 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 [83].

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 opioid tolerance and dependence [83].

### 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 [85]. The mesolimbic dopamine system is the likely substrate upon which opioids act to produce their reinforcing effects. Both the positive (rewarding) and negative (aversive) reinforcement of opioid mu- and kappa-receptor agonists are mediated by the mesolimbic dopamine system [81].

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 [86]. 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 opioids can synergistically facilitate opioid reinforcement. Increases in glutamatergic afferents into the ventral tegmental area may facilitate opioid reinforcement by activating dopamine neurons. An increase in glutamate activity in the nucleus accumbens may decrease opioid action by activating nucleus accumbens GABAergic cells. Also, an increase in nucleus accumbens 5-HT by opioids modulates opioid reinforcement by activation of 5-HT1 and/or 5-HT3 receptors [81].

| SIGNS AND SYMPTOMS OF ACUTE OPIOID 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: [87]* *Table 1* |

## EFFECTS OF OPIOID USE DISORDER

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

### INFECTIOUS DISEASE

Infectious complications from opioid use generally stem from injection use, primarily of heroin, in which bloodborne pathogens are transmitted via contaminated needles. An estimated 60% to 90% of injection users have hepatitis C virus infection [88; 89]. Other common infectious diseases include human immunodeficiency virus (HIV) and hepatitis B [8]. Common bacterial infections include Staphylococcus aureus, cellulitis and abscesses around the injection site, pneumonia, bacteremia, and endocarditis. Of HIV-positive persons in the United States, more than 33% have injected opioids and more than 25% report sharing needles with other users [10]. Injection drug users represented 10.6% of new HIV infections in 2021 and 13.6% of those living with HIV in 2021 [90].

## ENDOCRINE/METABOLIC EFFECTS

Opioid use affects multiple endocrine functions and is associated with hypogonadism, adrenal dysfunction, reduced bone mineral density, and growth hormone abnormalities [91].

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

Opioid use has been implicated in gonadal dysfunction [92]. Central hypogonadism can result from opioid 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 [91].

### 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 opioid use may be coupled with beta cell dysfunction [93]. 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 opioid use and abnormal glucose metabolism [91]. 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 opioid use can also result in metabolic abnormalities, the presentation of patients who are both HIV-positive and opioid dependent may be complicated.

Chronic heroin use may also complicate dyslipidemia, evidenced by elevated total cholesterol levels, hypertriglyceridemia, decreased total cholesterol and high-density lipoprotein, and elevated triglyceride levels relative to controls [91].

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

Opioid addicts may also have impaired adrenal function, documented by a high prevalence of adrenal insufficiency and abnormal response to the cosyntropin test [92]. 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 [91].

In addition, chronic opioid 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 [91].

## NEUROCOGNITIVE EFFECTS

Cognitive impairment resulting from chronic drug use may contribute to abuse and dependence in at least two ways. The first involves increasing the likelihood of drug-seeking behavior through various induced 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 [94; 95].

The chronic use of illicit drugs is often associated with a generalized profile of neuropsychologic deficit. However, it is thought that important differences in the patterns of interaction associated with various neurotransmitter systems, coupled with corresponding differences in the distributions of receptor subtypes, are responsible for the distinct neurocognitive effects of specific drugs of abuse [94].

Compared with marijuana and stimulants, there has been substantially less research into neuropsychologic deficits in chronic opioid abusers. Early studies found relatively little impairment in tasks involving abstraction and reasoning, leading investigators to conclude that chronic opioid use was not associated with deficient frontal lobe functioning. However, newer studies, utilizing more sensitive measures, have demonstrated that opioid abusers do possess

marked deficits in frontal lobe functioning relative to healthy control subjects. These deficits may include problems with altered attentional control, altered decision making, or problems with choices involving motivationally significant outcomes [94]. Additional research is needed to establish whether this pattern reflects increased impulsivity. It should be noted that determining causation in studies involving drug users is difficult due to comorbid psychiatric disorders and polysubstance abuse [94].

### Cognitive-Motor Effects of Methadone Maintenance

While under the influence of acute opioid 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 opioids for months or even years, a reflection of the substantial tolerance to the central depressing effect when opioids are taken regularly on a long-term basis [96].

A review of the cognitive functioning of methadone patients found that [96]:

- 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 [96]. 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 [96]. Authors of more recent studies have reported similar findings [97; 98].

The practical application of these findings suggests that methadone-maintained patients may be as capable as healthy persons in job performance. If 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 favorable features exclusive of their methadone dependence, job performance is unlikely to be affected [96].

## OPIOID OVERDOSE

As discussed, there were approximately 81,230 drug-overdose deaths in the United States in the 12-month period ending in May 2020 [17]. In 2021, 106,699 drug-overdose deaths occurred in the United States, representing a 14% increase from 2020 [37]. Between 1999 and 2021, the age-adjusted death rate from drug overdose rose significantly (from 6.1 per 100,000 in 1999 to 32.4 in 2021) [37]. Overdose death rates from synthetic opioids other than methadone (e.g., fentanyl/fentanyl analogs, tramadol) increased from 0.3 per 100,000 in 1999 to 4.0 in 2021. The heroin overdose death rate increased from 0.7 per 100,000 in 1999 to 2.8 per 100,000 in 2021, a decrease from 4.1 in 2020 [37].

Overdose death rates involving natural and semi-synthetic opioids (e.g., oxycodone, hydrocodone) increased from 1.2 per 100,000 in 2001 to 3.5 per 100,000 in 2010, then did not change significantly from 2010 through 2021, where the rate remained at 4.0 in 2020 and 2021 [37]. Overdose deaths involving methadone increased from 0.5 per 100,000 in 2001 to 1.8 in 2006, declined to 0.9 in 2018, and was then stable through 2021 [37]. Most methadone fatalities occur when the drug is prescribed for pain rather than for addiction treatment [60].

## 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 [99]. The time following release from prison has also been identified as a very-high-risk period for both fatal and nonfatal overdose [99].

Methadone overdose decedents are more likely than other pharmaceutical opioid abusers to not have had a prescription for the overdose drug. Although they are also significantly more likely to be male, the gap between men and women is closing [100; 101]. Since 1999, the percentage increase in overdose deaths among women increased 400%, compared with 265% in men [100].

### Tolerance in Overdose

Variation has been found in the acquisition of tolerance to different opioid effects, including respiratory depression [34]. 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 [16].

Alcohol and benzodiazepines are relatively weak respiratory depressants but can act synergistically with opioid agonists to produce substantial respiratory depression. Stimulants act as functional or physiologic opioid antagonists and may therefore minimize the respiratory depressant effects of opioids [51].

## SYMPTOMS

In the case of opioid 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 opioid overdose is almost always caused by respiratory depression [8; 102].

Sequelae of nonfatal overdose include [34]:

- 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)
- Neurologic damage through prolonged hypoxia

## OPIOID WITHDRAWAL

A withdrawal syndrome can be precipitated in humans after even a single dose of morphine. Physical dependence to opioids is assessed by observing the emergence of a withdrawal syndrome following discontinuation of opioid administration or through the administration of a competitive opioid antagonist, such as naloxone [103]. Signs and symptoms of opioid withdrawal include [87; 104]:

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

Although the neurophysiology underlying opioid withdrawal is incompletely understood, several neurotransmitter systems are believed to play a role, including dopaminergic, cholinergic, noradrenergic, and glutamatergic systems [103]. 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 [82]. 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 [82]. The involvement of central mechanisms of the endothelin system in opioid withdrawal is also being investigated [105; 106].

There are a number of useful opioid withdrawal scales that can assist the clinician's evaluation of patients by identifying and quantitating the severity of opioid withdrawal symptoms. These include the Objective Opioid Withdrawal Scale (OOWS), the Subjective Opioid Withdrawal Scale (SOWS), and the Clinical Opioid Withdrawal Scale (COWS). The OOWS is useful for measuring and documenting measurable symptoms of opioid withdrawal. The SOWS records the patient's rating of withdrawal on a 16-item scale. The COWS includes 11 items and contains signs and symptoms (both objective and subjective) of withdrawal [107].

In 2014, the FDA cleared the Bridge Neurostimulation System (an electroauricular device) for use in acupuncture. In 2017, the FDA approved a new indication for the device for use in helping to reduce the symptoms of opioid withdrawal [108]. The NSS-2 Bridge is placed behind the patient's ear and emits electrical pulses to stimulate branches of certain cranial nerves. It can be used for up to five days during the acute phase of withdrawal. In one study, within 30 minutes of using the device, all patients showed a reduction in COWS score of nearly 31% [108].

In 2018, the FDA approved lofexidine for the management of opioid withdrawal symptoms [109]. This agent may be incorporated into the treatment of adults with opioid withdrawal symptoms for up to 14 days.

### ACUTE OPIOID WITHDRAWAL

Most research regarding acute withdrawal from an opioid has been conducted with heroin users. Withdrawal symptoms are the result of mu-agonist withdrawal in the case of heroin and begin approximately eight hours after the last dose. The symptoms begin slowly, peak at 48 to 72 hours, and then gradually taper during the next four to seven days [104]. 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 [8].

### 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 [103]. 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 opioid exposure [80].

### PERSISTENT NEUROADAPTATION AND RELAPSE VULNERABILITY

Opioid 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 [110]. 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 processing. At the same time, motivation or learning for drug reward and drug-associated cues is increased [110].

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 [110; 111].

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 [111]. 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 opioid 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 [110; 111].

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 opioids and increased incentive motivation for drug reward through a sensitization mechanism [110; 111].

## LIABILITY OF MISUSE OF LEGITIMATELY PRESCRIBED OPIOID DRUGS

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 [112]. Prescriber knowledge deficit has been identified as a key obstacle to appropriate opioid prescribing and, along with gaps in policy, treatment, attitudes, and research, contributes to widespread inadequate treatment of

pain [113]. A 2013 survey measured primary care physician understanding of opioids and addiction. Of the 200 participants, [114]:

- 35% admitted knowing little about opioid addiction.
- 66% and 57% viewed low levels of education and income, respectively, as causal or highly contributory to opioid addiction.
- 30% believed opioid addiction "is more of a psychologic problem," akin to poor lifestyle choices rather than a chronic illness or disease.
- 92% associated prescription analgesics with opioid addiction, but only 69% associated heroin with opioid addiction.
- 43% regarded opioid dependence and addiction as synonymous.

These statistics reflect knowledge and attitude gaps among physicians that lead to undertreatment of pain and unnecessary suffering among patients experiencing pain [112]. 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 opioid 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]. Additionally, there is a shortage of pain specialist physicians in the United States that is expected to worsen. This has resulted in most of the medical care for patients with chronic pain being delivered by primary care physicians, despite, as stated, significant and widespread knowledge deficits among these practitioners in the medical skills necessary for providing optimal pain management, managing drug abuse and addiction, and utilizing risk evaluation and mitigation strategies when prescribing opioids [115].

It is important to note that prescription opioid abuse has been tempered by improvements in opioid prescribing, community intervention, and improved awareness. Following a peak in opioid prescribing in 2011, numbers have consistently fallen. However, opioid use disorder rates and overdose fatalities continue to rise. This reinforces the need for appropriate opioid prescribing practices, patient assessment and referral, and optimal opioid use disorder treatment in patients with suspected addiction.

Abuse liability is related to the ease of extraction and modification to produce the desired psychologic 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 opioids 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 studies of trends in medical use and abuse of opioid analgesics, a corresponding increase in the rate of abuse with prescription rates has been apparent [116; 117; 118]. Thus, the increased medical use of opioid analgesics for the treatment of pain has contributed to an increase in opioid analgesic abuse and overdose fatalities. The abuse of hydrocodone and oxycodone products, which increased disproportionately to their availability between 2000 and 2011, is an extreme example of this trend [1].

Results of epidemiologic 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 [119].

Legitimate pain clinics offer large amounts of drugs with a high potential for abuse, often with little evaluation and follow-up [117]. In some states (e.g., Florida, Texas), increasingly liberal prescribing practices were linked to rising overdose death rates. Since 2011, misuse of prescription opioids has decreased; however, abuse of synthetic opioids (including illicitly manufactured fentanyl) has increased precipitously.

## 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 opioid abuse or dependence in 2.8% to 18.9% of patients, which typically parallels the rate of abuse or dependence among opioid users in the general population [29].

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 opioids has resulted in improvements in the functional restoration, physical capacity, psychologic well-being, family/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 [30]. Additionally, the CDC's 2022 guidelines for prescribing opioids includes recommendations for managing both acute and chronic pain, including assessing risk and addressing potential harms of opioid use [120]. 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 opioid [1]. Screening for psychologic disorders is also advisable, including psychosomatic causes of pain.

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" [9].

## MANAGEMENT OF OPIOID USE DISORDER

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 opioid dependence was basically non-existent until 1935, when U.S. Public Health Services opened a hospital in Lexington, Kentucky, devoted to the treatment of opioid 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 [56].

Today, management of opioid dependence entails different methods to achieve different goals, depending on the health situation and treatment history of the patient. These treatment approaches include [77]:

- Crisis intervention: Directed at immediate survival by reversing the potentially lethal effects of overdose with an opioid antagonist.
- Harm reduction: Intended to reduce morbidity and mortality associated with use of dirty needles and overdose.
- Detoxification/withdrawal: Aims to remove the opioid of abuse from the patient's body, either through gradual taper and substitution of a long-acting opioid or through ultra-rapid opioid detoxification.
- Maintenance treatment or opioid (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 opioids and introduced to a long-acting opioid 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 opioids during the detoxification/withdrawal process and may be placed on an opioid 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 [77].

### CRISIS INTERVENTION

In response to acute overdose, the short-acting opioid antagonist naloxone is considered the criterion 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 prompted discussion of making naloxone available to the general public for administration outside the healthcare setting to treat acute opioid overdose, and in April 2014, the FDA approved naloxone as an autoinjector dosage form for home use by family members or caregivers [121]. The autoinjector delivers 0.4 mg naloxone intramuscularly or subcutaneously. The autoinjector comes with visual and voice instruction, including directs to seek emergency medical care after use [121]. In November 2015, the FDA approved intranasal naloxone after a fast-track designation and priority review. Intranasal naloxone is indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or CNS depression. It is available in a ready-to-use 8-mg, 4-mg, or 2-mg single-dose sprayer

[122; 123; 124; 125]. In 2023, the FDA approved the first over-the-counter naloxone nasal spray [126]. It is available as a 3-, 4-, or 8-mg single dose, administered in one nostril [55].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the World Health Organization, people likely to witness an opioid overdose should have access to naloxone and be instructed in its administration to enable them to use it for the emergency management of suspected opioid overdose.

(https://www.who.int/publications/i/item/9789241548816. Last accessed March 21, 2024.)

**Strength of Recommendation/Level of Evidence:** Strong/very low

## HARM REDUCTION

Harm reduction measures are primarily employed to minimize the morbidity and mortality from opioid abuse and to reduce public nuisance [99]. 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 opioid use [99].

### Education

Reducing the risk for harm involves education on polydrug use and needle-exchange programs [99]. 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 [127]. Given that a harm-reduction approach can address risk behaviors that may occur alongside drug use, the authors of one paper suggest that risk-reduction education be based on harm reduction philosophy as a whole rather than on the specific harms of drug use and harm reduction strategies (e.g., needle-exchange programs) [128]. The authors defined six principles—humanism, pragmatism, individualism, autonomy, incrementalism, and accountability without termination—and generalized them for use in healthcare settings with patients beyond those who use illicit substances. Each principle was defined and providers were given descriptions of how to deliver interventions informed by the principles as well as examples of how to apply each principle in the healthcare setting [128].

To improve response to overdoses, opioid 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 opioid 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 [99].

### Needle-Exchange Programs

Needle-exchange programs, also referred to as syringe services programs, have been shown to be effective in reducing drug-related health problems, reducing injection frequency, and increasing entry and retention in drug treatment [77]. According to one review, there is sufficient evidence of efficacy, effectiveness, and financial benefit to recommend needle-exchange and outreach programs [127]. 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 [129]. The Consolidated Appropriations Act of 2016 gives states and local communities, under limited circumstances, the opportunity to use federal funds to support certain components of needle-exchange programs. Although federal funds cannot be used to purchase sterile needles or syringes for illegal drug injection, these funds can be used to support a comprehensive set of services as part of a needle-exchange program [130].

### Injection Rooms

Medically supervised injecting rooms, or overdose prevention centers (OPCs), are officially designated areas where injecting opioid 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 OPCs is to promote health and reduce risk behaviors and public nuisance, with a specific focus on overdose reduction and hygiene [131]. Several descriptive studies have shown significant effects on harm reduction and reduction of public nuisance [77].

### Heroin Maintenance

Heroin maintenance, also referred to as heroin-assisted treatment, 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 United States [99].

One systematic review compared heroin maintenance to methadone or other substitution treatments of opioid dependence for efficacy and acceptability; retaining patients in treatment; reducing the use of illicit substances; and improving health and social functioning [132]. Eight studies involving 2,007 patients met the inclusion criteria. Five studies compared supervised injected heroin plus flexible dosages of methadone to oral methadone alone. Results suggest an added value of heroin prescribed alongside flexible doses of methadone for long-term, treatment-refractory, opioid users to reduce use of illicit substances and sustain treatment [132].

## DETOXIFICATION AND WITHDRAWAL

The process of tapering opioid-dependent patients from agonist therapy is often referred to as detoxification, or more accurately, medically supervised withdrawal [56; 133; 134]. Its purpose is to eliminate physical dependence on opioid medications. It can be considered the medically supported transition to a medication-free state or to antagonist therapy. A careful and thorough review of the risks and benefits of detoxification should be provided and informed consent obtained from patients prior to choosing this option [102; 133]. Studies have shown that most patients with opioid use disorder who undergo medically supervised withdrawal will start using opioids again and will not continue in recommended care [135; 136; 137; 138; 139]. Detoxification alone should not be considered a treatment and should only be promoted in the context of a well-planned relapse-prevention program [77; 133; 134]. Discontinuation of opioid 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 opioids [56].

The three primary treatment modalities used for detoxification are opioid agonists, non-opioid medications, and rapid and ultra-rapid opioid detoxification [56]. The most frequently employed method of opioid withdrawal is a slow, supervised detoxification during which an opioid agonist, usually methadone, is substituted for the abused opioid [80]. Methadone is the most frequently used opioid agonist due to the convenience of its once-a-day dosing [56]. 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 pharmacologic detoxification choices include clonidine (with or without methadone), midazolam, trazodone, or buprenorphine [80]. Naltrexone is used following medically supervised withdrawal to help prevent relapse to opioid misuse [134].

Many opioid 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 coeruleus. Non-opioid agents (such as clonidine), which inhibit hyperactivation of noradrenergic pathways stemming from the locus coeruleus nucleus, have been used to manage acute withdrawal [80; 107]. The first non-opioid treatment approved for the management of opioid withdarawl symptoms is lofexidine [109]. In studies, patients treated with lofexidine reported less severe withdrawal symptoms and were more likely to complete treatment.

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, alpha2-agonists, opioid agonist-antagonists, benzodiazepines, and antidepressants have been used [80].

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 [80]. Insomnia is a frequent aspect of acute and protracted withdrawal, as opioids 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 nonpharmacologic methods that may also be used [80]. Psychosocial treatments offered in addition to pharmacologic detoxification treatments positively impact treatment retention and completion, results at follow-up, and compliance [140; 141].

**Ultra-Rapid Opioid Detoxification**

Ultra-rapid opioid detoxification (UROD) has been developed as a means of avoiding the physical symptoms of withdrawal from opioids through the use of general anesthesia. 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 opioid withdrawal occurred with the addition of an opioid antagonist during chemical sedation [142]. UROD was introduced in 1990 primarily by private practitioners in a for-profit setting [143].

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 opioid withdrawal through the use of UROD [143].

UROD is also referred to as 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 [143]:

- Ultra-rapid opioid detoxification (UROD): General anesthesia; duration <6 hours
- Rapid opioid detoxification (ROD): Deep sedation; duration 6 to 72 hours
- Compressed opioid detoxification (COD) and naltrexone-compressed opioid detoxification (NCOD): Duration three to six 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 [143]. 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 [143].

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 [143]. 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 [143]. Patients with chronic pain syndromes requiring opioid medication are not good candidates unless their pain can be controlled by alternative methods [80].

UROD is best performed in an intensive care unit with full resuscitative equipment and monitoring available [80]. Initiation of opioid withdrawal is precipitated by IV injection of a 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) [80]. Parameters that indicate adequacy of withdrawal include a 20% decrease of ventilation below the maximum minute ventilation, an electrocardiogram (ECG) detection of decreased QQ variability, and electroencephalogram (EEG) normalization [80].

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 opioid craving during the post-UROD period, with 50 mg per day recommended for relapse prevention [80]. However, patients undergoing long-term naltrexone therapy can become sensitized to opioid drugs, heightening the risk of fatal overdose if opioid 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 [80].

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 eight days, with a mean duration of three to four days. Therefore, alternatives to UROD are considered to be more cost-effective [143]. Krabbe et al. compared abstinence rates and withdrawal effects of UROD with standard methadone tapering in a prospective three-month trial [144]. They found significantly higher abstinence rates and fewer withdrawal symptoms in UROD patients versus methadone patients at one and two months, with no differences at three months.

A major shortcoming of UROD is the lack of evidence that an opioid antagonist can accelerate the restoration of neurobiologic homeostasis following opioid withdrawal [143]. 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 opioid 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 opioid dependence [142]. There are a number of drawbacks to UROD relative to other detoxification methods. For example, one study found that, when used alone, naloxone has a high relapse rate in the long term [145]. The study included 64 opioid-dependent men 18 years of age and older (mean age: 31.1 years) at the time of UROD. One month after UROD, 48 patients (75%) reported relapse and 16 patients (25%) reported abstinence. There was no significant difference between the two groups regarding marital status, level of education, and family history of opioid dependence. Four patients from the nonrelapsed group reported on episode of opiate use [145]. Another study was conducted to assess UROD efficacy with naltrexone and estimate the relapse rate in a two-year follow-up period [146]. A total of 424 opioid-addicted self-reporting patients were enrolled in the study and entered the UROD program; 400 patients completed the program. Of the total patients, 303 (75.75%) were successful and 97 (24.25%) relapsed. No patients in the relapse group continued naltrexone maintenance at six-month follow-up. The relapse rate was 14% at the first month visit and 24% at the six-month visit and thereafter. All relapsed patients had discontinued use of naltrexone before relapse occurred [146]. A Canadian review of the evidence for UROD found no significant differences between UROD and control groups in commencement or duration of withdrawal treatment [147].

Serious adverse events related to the anesthetic procedure also 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 [77]. 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 [148]. 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 [149; 150]. 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 [142].

## AGONIST REPLACEMENT OR ABSTINENCE THERAPY

Two principle treatment modalities are offered for opioid-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 [151]. A reasonable approach is 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 [152].

At present, there are no direct interventions that are capable of reversing the effects of drugs of dependence on learning and motivation systems [30]. Instead, the management of opioid 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 opioids and produce very strong positive health outcomes as measured by decreased mortality, improved mental and physical health, and reduced risk of disease transmission [30]. Considering the high rate of relapse after detoxification, maintenance therapy with methadone or buprenorphine is currently considered to be the first-line treatment for opioid-dependent patients [77; 107]. Both agents are superior to withdrawal management alone and both significantly reduce illicit opioid use [107].

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 [77; 107]. 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 [77; 107]. Polysubstance abuse is the rule rather than the exception in opioid dependence, and concurrent use of other substances should be carefully monitored and treated when necessary [77]. Concurrent use of other drugs or active engagement in other addictive behaviors should lead to consideration of other treatment plan components for the patient. The presence of co-occurring substance use disorders should provoke a re-evaluation of the level of care in which the patient is treated [107]. 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 [77; 107].

**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 [56]. The theoretical basis of opioid replacement stems from the finding that chronic opioid 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 opioids to more adaptive areas of focus, such as work, relationships, and non-drug leisure activities [56].

The neurobiologic 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 [84]. 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 [84].

Successful maintenance treatment entails stabilization of opioid 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 [56]. Additionally, opioid 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 [56].

As of 2020, 1,090,357 patients in the United States were enrolled in opioid replacement therapy in 1,754 opioid treatment programs [111]. However, this represents less than 20% 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 [56]. When compared to active street heroin users, these benefits include a four-times lower HIV seroprevalence rates, 70% fewer crime-days per year, and a one-year mortality rate of 1% (versus 8%) [60].

### *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 opioid replacement therapy. Studies have shown one-year treatment retention rates of 80%, with significant reductions in illicit opioid use [56]. 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 [56]. Efforts to provide methadone in an office-based setting have been successful, although federal regulation has limited the flexibility of providers [84; 107].

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 or under-funded programs. The quality of the staff-patient interaction, attitudes of staff, good management of clinics, and good record-keeping characterize higher-quality programs [153].


When considering initiation of methadone, the American Pain Society recommends that clinicians perform an individualized medical and behavioral risk evaluation to assess risks and benefits of methadone, given methadone's specific pharmacologic properties and adverse effect profile.

(https://www.jpain.org/article/S1526-5900(14)00522-7/fulltext. Last accessed March 21, 2024.)

**Strength of Recommendation/Level of Evidence:** Strong/low

Methadone maintenance is also cost-effective [56]. A 1997 study of Veterans' Affairs patients showed that the estimated six-month costs are about $21,000 for an untreated drug abuser, $20,000 for an incarcerated drug abuser, and $1,750 for a patient enrolled in a methadone maintenance program [154]. A study using data from one healthcare plan reached a similar conclusion regarding cost-effectiveness (albeit with differing cost estimates) [155]. The annual costs (in 2004 dollars) were $18,694 for patients receiving no methadone with 0 or 1 outpatient addiction treatment visits; $14,157 for patients receiving no methadone with 2 or more visits; and $7,163 for patients receiving methadone.

There is an unrealistic expectation that opioid users should be able to stop using all drugs. Although some do successfully stop, dependence is a chronic problem for most patients, associated with frequent relapses, serious health risks, and psychosocial impairment [153]. 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 [153].

Treatment is initiated with a dose of 25–30 mg and is gradually titrated in 5- to 10-mg increments per day to a desired range of 60–120 mg. Low-dose treatment is associated with less positive outcomes than doses of 60–120 mg/day or greater [55; 60]. One published review of efficacy literature concluded that high doses of methadone (>50 mg daily) are more effective than low doses (<50 mg daily) in reducing

illicit opioid use. This may be due to the increased availability of highly pure heroin [60]. 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 (>8 mg daily) on measures of treatment retention and reduction of illicit opioid use [77]. Methadone is contraindicated for the following patients [55; 107]:

- Those with known hypersensitivity to methadone hydrochloride
- Those experiencing respiratory depression
- Those with acute bronchial asthma or hypercapnia
- Those with known or suspected paralytic ileus

### *Buprenorphine*

Buprenorphine offers several advantages over methadone, including lower cost, milder withdrawal symptoms following abrupt cessation, lower risk of overdose, and longer duration of action, allowing alternate-day dosing [56; 156]. Identifying subpopulations of opioid 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 [56].

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 [56; 107]. 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 [30]. The ASAM warns that diversion and misuse are possible with buprenorphine, as is physical dependence. Respiratory depression may occur if buprenorphine is used with CNS depressants including alcohol, other opioids, and illicit drugs. Neonatal withdrawal has also been reported after use of buprenorphine during pregnancy. Buprenorphine is not recommended for patients with severe hepatic impairment [55; 107].

Higher doses of buprenorphine (12 mg or greater) are more effective than lower doses in reducing illicit opioid use, with some studies reporting similar efficacy to methadone on major treatment-outcome measures. One systematic review was conducted to evaluate buprenorphine maintenance compared to placebo and methadone maintenance in the management of opioid dependence [157]. Outcomes considered were treatment retention, suppression of illicit drug use, and reduction in criminal activity and mortality. A total of 31 trials involving 5,430 participants with moderate- to high-quality evidence were included in the review. According to the data reviewed, buprenorphine retained participants better than placebo at low doses (2–6 mg), at medium doses (7–15 mg), and at high doses (≥16 mg). Only high-dose (≥16 mg) buprenorphine was more effective than placebo at suppressing illicit opioid use (as measured by urinanalysis). Buprenorphine in flexible doses (i.e., adjusted to participant need) was less effective than methadone in retaining participants, and for those retained in treatment, no difference was observed in suppression of illicit opioid use. In low fixed-dose studies, methadone (≤40 mg) was more likely to retain participants than low-dose (2–6 mg) buprenorphine. However, there was no difference between medium-dose (7–15 mg) buprenorphine and medium-dose (40–85 mg) methadone in retention or in suppression of illicit opioid use. Similarly, there was no difference between high-dose (≥16 mg) buprenorphine and high-dose (≥85 mg) methadone in retention or suppression of self-reported heroin use [157]. In a study of 34,000 Massachusetts Medicaid beneficiaries, the incidence of relapse was greater with buprenorphine than with methadone [156]. The primary advantage of buprenorphine over methadone is its superior safety profile [30].

### *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 have suggested that slow-release morphine has approximately equal efficacy with methadone; however, there is no definitive evidence of this effect [30; 158; 159]. Slow-release oral morphine may be a viable alternative for patients who are intolerant to methadone [160].

### *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, before 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 [30].

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 [77]. Research projects were also performed in the Netherlands, Canada, and England, and others are planned in Belgium and Denmark. Based on the positive outcomes thus far, heroin maintenance has become routine treatment for otherwise untreatable heroin addicts in Switzerland, the Netherlands, Germany, and England and is being recommended in Canada [161; 162].

### Agonist Replacement and Psychosocial Therapy

The addition of any psychosocial support modality to agonist replacement therapy significantly reduces illicit use during treatment, and treatment retention and results at follow-up are also improved [140; 141]. 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 [163].

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 [163].

Most studies of psychotherapy with opioid-dependent patients have been conducted in methadone programs and are actually pharmacotherapy/psychotherapy studies. In addition to pharmacologic intervention, methadone programs typically use behavioral contingencies that are based on cessation of illicit drug use and other improvements [163].

A review of the literature on psychosocial therapy outcomes with opioid-dependent patients receiving methadone has found evidence of an interaction between measures of psychiatric symptoms, therapy assignment, and outcomes [163]. 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 opioid dependence and antisocial personality disorder did not benefit from additional psychosocial therapy beyond drug use reduction, but patients with opioid dependence, antisocial personality, and depression exhibited improvement in multiple areas [163].

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 [163].

### 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 [77].

The primary goal of pharmacotherapy during detoxification is to alleviate opioid withdrawal severity and associated distress/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 pharmacologic 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 [77].

#### *Opioid Antagonist Therapy*

Relapse-prevention programs have traditionally involved long-term residential placement of nine 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 opioid 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 able to give informed consent, are fully withdrawn from opioids, and have no specific contraindications for this treatment [107]. 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 [77].

The primary problem with naltrexone treatment is low compliance, with retention in treatment ranging from 6% to 45% [30; 107]. 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 [86]. The authors of one investigation evaluated prescribing patterns for opioid use disorder medications among a commercially insured population in the United States from 2010 to 2014.

The evaluation revealed consistently low treatment completion rates for two forms (e.g., injectable, oral) of naltrexone. At 30 days post-initiation, 52% of individuals treated with injectable naltrexone had discontinued treatment, and 70% of individuals treated with oral naltrexone had discontinued treatment. The proportion of patients treated with either form of naltrexone grew over time, but the discontinuation rates were significantly higher compared with individuals treated with sublingual or oral-mucosal buprenorphine/naloxone [164]. Although the focus of this investigation was not on the reasons for treatment discontinuation, it did highlight the poor treatment compliance with naltrexone. The extended-release injectable naltrexone formulation may help overcome the compliance issues associated with the oral formulation [107].

Naltrexone is contraindicated in patients with hypersensitivity reactions to the agent, in patients with current physical and physiologic dependence on opioids, and in patients in acute opioid withdrawal [107]. At present, reviewers conclude "there is no sufficient evidence of efficacy of naltrexone to justify its use in the maintenance treatment of opioid dependence" [165].

### *Psychosocial Monotherapy*

There is no data to support psychosocial interventions as a sole intervention for opioid dependence [140; 141]. Psychosocial treatments alone are not adequately proven treatment modalities, nor are they superior to any other type of treatment for opioid dependence [166]. However, psychosocial treatments offered in addition to pharmacologic detoxification treatments are effective in terms of treatment completion, opioid use, and participant abstinence at follow-up [141].


For patients with opioid use disorder for whom opioid use disorder pharmacotherapy is contraindicated, unacceptable, or unavailable, the Department of Veterans Affairs Work Group has found there is insufficient evidence to recommend for or against any specific psychosocial interventions.

(https://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPG.pdf. Last accessed March 21, 2024.)

**Strength of Recommendation**: Neither for not against

### 12-Step/Self-Help Programs

Twelve-step programs for opioid use disorder 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 [167]. 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 [167]. 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 [168].

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 [168].

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 [169]. 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 [170].

### *Narcotics Anonymous*

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 opioids and other drugs. Being active as an NA sponsor over a one-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 [171]. In addition to being a sponsor, having a sponsor also is associated with positive outcomes. One analysis explored the predictors and outcomes of having a 12-step sponsor among individuals receiving treatment for stimulant use disorders [172]. Four types of 12-step groups were evaluated: NA, AA, Cocaine Anonymous, and Crystal Meth Anonymous. Factors evaluated were the extent to which participants obtained sponsors, the extent to which other predictors (e.g., beliefs, expectations) were associated with having a sponsor, and the effect of sponsorship at the end of treatment. Participants in the 12-step facilitation intervention had higher sponsorship rates at the end of treatment and at three-month follow-up, and end-of-treatment sponsorship predicted a higher likelihood of abstinence and no drug-related problems at follow-up [172].

Improvement in psychologic functioning as a result of NA involvement has been observed by Christo and Sutton [173]. 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 three years exhibiting levels of anxiety and self-esteem similar to those of a comparison group of 60 students from a vocational training college [173].

### *Methadone Anonymous*

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 [174].

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 [175]. Most MA meetings are hosted by methadone clinics, and there are more than 1,000 MA clinics worldwide [176].

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 [177]. 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 [174].

## ACUPUNCTURE

Auricular acupuncture is the most common acupuncture approach for substance abuse, including opioid abuse and dependence, in the United States and the United Kingdom. This technique consists of bilateral insertion of acupuncture needles in the outer ears [178]. 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 [179].

Results from well-designed studies indicate that auricular acupuncture treatment is not sufficient in efficacy as a stand-alone treatment for opioid 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 opioid-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 [178]. There is some evidence that differences in efficacy may be influenced by racial physiologic differences among persons of European and Asian descent [178].

A 2016 review of 199 studies found that contradictory results, intergroup differences, and acupuncture placebo effects made it difficult to evaluate the effectiveness of acupuncture for drug addiction treatment [180]. The authors of another review looked at clinical trials of 100-Hz electroacupuncture for detoxification treatment. They found a potential for the treatment to allay opioid-associated depression and anxiety but no effect for opioid craving [181].

## 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 opioids 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 opioid dependence and plays an important role in treatment outcome. Multiple national population surveys have found that roughly 50% of those who experience mental illness during their lives will also experience a substance use disorder and vice versa [182; 183]. More than 60% of adolescents in community-based substance abuse treatment programs also meet diagnostic criteria for another mental illness [184]. An estimated 43% of individuals in treatment for nonmedical use of prescription opioids have a diagnosis or symptoms of a mental health disorder, particularly depression and anxiety [185].

Major depression prevalence among opioid-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 opioids for chronic pain and worse treatment outcomes. Approximately 50% of patients with chronic pain have a comorbid psychiatric condition, and 35% of patients with chronic back and neck pain have a comorbid depression or anxiety disorder [33; 152; 186; 187]. 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 [33; 152; 186; 187]. In addition, opioid-dependent patients with Axis I psychiatric comorbidity often require significantly higher methadone doses [56].

Psychiatric comorbidity is especially pronounced with serious mental illness, which is defined by the Substance Abuse and Mental Health Services Administration as individuals 18 years of age or older having, at any time during the past year, a diagnosable mental, behavior, or emotional disorder that causes serious functional impairment that substantially interferes with or limits one or more major life activities [188]. Approximately one in four individuals with a serious mental illness (e.g., major depression, schizophrenia, bipolar disorder) have a comorbid substance use disorder [189].

A main issue in managing comorbid conditions is the differentiation of independent versus substance-induced disorders, as therapeutic plans differ for the two conditions [186]. 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 [190].

### ASSESSMENT

It is important to assess dependent opioid users for other psychiatric and substance use disorders, especially alcohol and cocaine dependence because they are frequent comorbidities in opioid-dependent patients and can aggravate depressive symptoms [107; 189]. 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 [152; 189]. 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.

Comprehensive assessment tools can reduce the chance of a missed or incorrect diagnosis. Patients with psychiatric comorbidities often exhibit symptoms that are more persistent, severe, and resistant to treatment compared to patients who have either disorder alone [191; 192; 193; 194]. Assessment is critical to identify concomitant medical and psychiatric conditions that may need immediate attention and require transfer to a higher level of care [107]. The ASAM recommends that clinicians also assess social and environmental factors to identify facilitators and barriers to treatment, specifically to pharmacotherapy [107].

## TREATMENT APPROACH

Treatment should initially focus on stabilization of the patient's substance use disorder, with an initial goal of two to four 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 [190].

Although depressive symptoms often improve following treatment admission, significant symptoms will persist in some patients [152]. Antidepressant medications can be effective in patients dually diagnosed with opioid dependence and depression when used at adequate doses for at least six weeks [195]. Factors emphasizing prompt antidepressant treatment include greater severity of depression, suicide risk, and co-occurring anxiety disorders [152].

SSRIs are generally safe and well-tolerated, but clinical trials with these agents in methadone patients have been negative [152]. 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. SSRIs in combination with cognitive-behavioral therapy have been found to be highly effective for treating clients with comorbid depression [183]. 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) [152]. 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 [190]. If depression persists, psychosocial modalities, such as cognitive therapy, supportive therapy, or contingency management, have some evidence to support their efficacy in opioid-dependent patients [152; 183].

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 ECG is recommended prior to a TCA trial in opioid users [152]. 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 [152].

Medical comorbidities that may impact mental status and treatment response include [152]:

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

The presence of comorbid conditions increases severity and complicates recovery. Patients with comorbid disorders demonstrate poorer treatment adherence and higher rates of treatment dropout [193; 196]. A natural outgrowth of increased severity has been greater interest in and use of integrated treatment, compared with separate treatment of combined conditions [183]. Integrated treatment refers to a treatment focus on two or more conditions and the use of multiple treatments (e.g., combination of psychotherapy and pharmacotherapy). It is an approach supported by research that demonstrates the superiority of an integrated approach [197; 198; 199; 200; 201].

### 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 [190].

## OPIOID USE DURING PREGNANCY

A portion of pregnant women with substance dependence continue using addictive substances despite awareness of the potential harm to the fetus [202]. Infants can sustain adverse effects from maternal opioid use, although it is difficult to separate factors due to opioid use from those due to the abuse of other drugs, poor prenatal care, poor nutrition, or other complications [103; 203]. Reports of adverse effects of opioid use on fetuses and neonates include [202]:

- 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 opioid withdrawal syndrome (NOWS)

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 [202]. NOWS occurs when an infant becomes dependent on opioids or other drugs used by the mother during pregnancy [204]. It is an expected and treatable condition seen in 30% to 80% of infants born to women taking opioid agonist therapies [203]. According to hospital data from the National Inpatient Sample (covering 97% of the U.S. population), from 2004 to 2014, the incidence of NOWS among infants insured by Medicaid increased by five-fold (from 1.3 in 1,000 to 5.8 in 1,000 births). This is equivalent to diagnosing one newborn with NOWS every 25 minutes [204]. The increase in the incidence of NOWS has led to an increase in admission rates to neonatal intensive care units, from 7 per 1,000 to 27 per 1,000 cases, resulting in a an almost seven-fold increase in hospital costs ($462 million in 2014). Hospital charges tripled to $2.5 billion from 2012 to 2016 [204]. NOWS may result in disruption of the mother-infant relationship, sleep-wake abnormalities, feeding difficulties, weight loss, and seizures [204; 205]. Withdrawal symptoms in neonates can include tremors, diarrhea, fever, irritability, jitteriness, sweating, fever, vomiting, and generalized convulsions [204; 206; 207].

Although the optimal treatment for NOWS has not been established, The American Academy of Pediatrics recommends nonpharmacologic treatment as the first-line approach and continuing through hospital discharge [208]. The goal of nonpharmacologic treatment is to assist the self-organization of the neonate while maintaining the mother-infant dyad [208]. Because pharmacologic therapy can prolong hospitalization and expose the infant to additional agents that are often not necessary, it should be considered after supportive measures fail to ameliorate the infant's withdrawal. Pharmacotherapy is used for infants with more severe expression of NOWS to allow them to feed, sleep, gain weight, and interact with caregivers [206].

Opioids are considered the first choice if pharmacotherapy is necessary [206]. Opioid treatment of NOWS 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 [207]. Treatment with long-acting opioids has been shown to be superior to phenobarbital and diazepam in infants with NOWS [207]. Phenobarbital is generally considered a second-line agent and is effective for the treatment of withdrawal and polydrug exposure. Clonidine is also a safe second-line option for

treatment of NOWS symptoms that are refractory to opioid therapy [206; 209]. Buprenorphine and methadone have both been shown to be safe and effective treatments for opioid use disorder during pregnancy [210]. A meta-analysis showed that methadone was associated with higher treatment retention and buprenorphine resulted in a 10% lower incidence of NOWS, decreased neonatal treatment time of 8.46 days, and less morphine (3.6 mg) needed [211]. Infants whose mothers receive these medications may still experience NOWS; however, it is less severe than in the absence of treatment [211].

In treating pregnant women with substance dependence, psychologic 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 [202].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The World Health Organization recommends that healthcare providers should, at the earliest opportunity, advise pregnant women dependent on opioids to cease their use and offer, or refer to, detoxification services under medical supervision where necessary and applicable. Detoxification can be undertaken at any stage in pregnancy, but at no stage should antagonists (e.g., naloxone, naltrexone) be used to accelerate the detoxification process.

(https://www.who.int/publications/i/item/9789241548731. Last accessed March 21, 2024.)

**Strength of Recommendation/Level of Evidence:** Strong/very low

## HEROIN

Heroin rapidly crosses the placental blood barrier. Between 55% and 94% of infants born to IV heroin users exhibit signs of neonatal withdrawal, with a small minority showing neonatal seizure activity [212]. Methadone maintenance has been found to be an effective harm-reduction strategy and can reduce acute neonatal withdrawal problems, including seizures [213].

## 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 [202]. Inadequate maternal methadone dosage may result in mild-to-moderate opioid withdrawal signs and symptoms that may cause fetal stress and maternal drug cravings, which contributes to relapse and treatment discontinuation [203]. 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 one- and two-year evaluations [202]. Methadone levels in breast milk appear to be small [214].

## 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 [202]. Multiple small case series have examined maternal buprenorphine concentrations in breast milk and all concur that the amounts are small and unlikely to have short-term negative effects on the developing infant [215]. Advantages of buprenorphine over methadone include fewer drug interactions, the ability to be treated as an outpatient, and evidence of less need for dosage adjustments throughout pregnancy. Additionally, several trials demonstrate evidence of less severe NOWS in affected neonates [203; 216].

### 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 [55]. 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 opioid screens [217].

### NALTREXONE

The literature is limited and equivocal regarding naltrexone and pregnancy. Results of a national provider survey reveal that the accessibility of naltrexone and related care for pregnant women with opioid use disorder varies across the United States, with barriers (e.g., providers' discomfort and inexperience prescribing naltrexone) and educational gaps (e.g., lack of national guidelines) identified [218]. The substantial drop-out rates due to the reward-blocking and dysphoric 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 [202]. However, other authors have found that naltrexone can cause premature labor and fetal death, and it is considered to be pregnancy category C [8; 55]. The manufacturer recommends that nursing mothers either discontinue the drug or discontinue nursing [55].

## PROGNOSIS OF TREATMENT FOR OPIOID USE DISORDER

The relapse rate among patients receiving treatment for opioid dependence and other substance abuse is high (25% to 97%), comparable to that of other patients with chronic relapsing conditions, including hypertension and asthma [219]. Many cases of relapse are attributable to treatment noncompliance and lack of lifestyle modification [87].

Duration of agonist replacement therapy is usually recommended as a minimum of one year, and some patients will receive agonist replacement therapy indefinitely. Longer durations of treatment are associated with higher rates of abstinence from illicit opioids [30].

Much remains unknown about patient outcomes following termination of long-term opioid replacement therapy. Some patients aim to achieve total abstinence from all opioids, 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 opioids do so with the help of a 12-step support program, such as NA [30].

## CONCLUSION

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 opioids has become considerably more widespread, fueled in part by the availability of such drugs over the Internet. This has resulted in opioid 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 opioid 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 opioid use disorders.

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