# Illicit opioid intoxication: Diagnosis and treatment

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REVIEW

# Illicit Opioid Intoxication: Diagnosis and Treatment

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**Abstract:** Opioid intoxications and overdose are associated with high rates of morbidity and mortality. Opioid overdose may occur in the setting of intravenous or intranasal heroin use, illicit use of diverted opioid medications, intentional or accidental misuse of prescription pain medications, or iatrogenic overdose. In this review, we focused on the epidemiology of illict opioid use in the United States and on the mechanism of action of opioid drugs. We also described the signs and symptoms, and diagnoses of intoxication and overdose. Lastly, we updated the reader about the most recent recommendations for treatment and prevention of opioid intoxications and overdose.

**Keywords:** illicit opioids, intoxication, treatment

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## Introduction

Illicit drugs are a major cause of morbidity and mortality world wide. Illicit drug intoxications may constitute life threatening medical emergencies. Therefore, early detection and rapid intervention may be life saving in many cases. Opioids are approved by the Food and Drug Administration (FDA) for treatment of pain. Heroin is an illicit synthetic opioid which has been associated with a drug addiction epidemic in the United States (US) since the 1960s. Illicit use of prescribed opioids is an emerging epidemic in the US. Illicit use of heroin and prescribed opioids can be a major risk for overdose. Opioid intoxication and overdose are life threatening emergencies that need immediate medical attention. They are a common reason for increased morbidity and mortality in this population.

In this review, we present epidemiologic facts, mechanism of action, metabolism and pharmacokinetic profile, signs and symptoms, diagnosis and treatment of illicit opioid intoxications. We review the most recent recommendations for treatment and prevention of opioid intoxications and overdose.

## Epidemiology

The Drug Abuse Warning Network (DAWN) reported that the number of emergency department (ED) visits related to non medical use of prescribed opioid significantly increased (111%) between 2004 and 2008.[1] The highest numbers of visits were recorded for oxycodone, hydrocodone and methadone.[2] It was estimated that 1.6 million ED visits were for the misuse and abuse of all drugs in 2004 and 2 million in 2008. Among these, illicit drugs such as cocaine and heroin were involved in 1 million visits in both 2004 and 2008, whereas prescription or over the counter drugs used non-medically were involved in 0.5 million visits in 2004 and 1 million visits in 2008.[3,4] The estimated number of ED visits involving nonmedical use of opioid analgesics increased from 144,600 in 2004 to 305,900 in 2008, whereas prevalence of non-medical use increased from 49.4 to 100.6 per 100,000, an increase of 104%.[5,6] The non medical use of prescription opioids is a growing and deadly problem. Martyres et al[5] reported in an Australian cohort of young people who died of heroin related overdose that doctor shopping in the years before heroin related death was associated with misuse of prescription drugs such as benzodiazepines and opioids. The prevalence of mortality related to prescription opioid overdose increased drastically in the US between 1999 and 2006.[6,7]

## Mechanism of action, metabolism and pharmacokinetic profile

Opioid drugs act by binding to certain receptors in the brain which lead to specific actions based on the type of the receptor involved. There are 4 types of opioid receptors including mu, kappa, delta, and orphanin FQ nociceptin. The opioid receptors are also the binding sites for endogenous peptides which play an important role in modulating the response to pain, regulation of body temperature, respiration, endocrine and gastrointestinal activity, mood, motivation and other functions.[8] Exogenous opioids may act as agonists, partial agonists or antagonists to these receptors. Most of the opioids with addictive potential are agonists at the mu receptor. Those drugs activate the mesocorticolimbic dopaminergic system through their mu agonist property leading to euphoria, positive reinforcement and drug seeking behavior. When opioid receptors are activated by an agonist (endogenous or exogenous), a cascade of intracellular changes involving second and third messenger systems is set in motion. These changes not only produce immediate changes in the responsiveness of the opioid receptor-bearing neurons but also lead to adaptive changes in other neuronal systems that interact with them. Some of these intracellular changes are related to the development of tolerance (decreased responsiveness to the same concentration of the opioid at the receptor) and altered excitability (withdrawal) when the agonist is removed after a period of receptor occupancy.[9,10] The interaction between the environment and the individual may play an important role for the drug seeking behavior and elicit triggers for drug use. In other words, the neurobiologic mechanism of action of opioids may represent the interaction between the environment as a trigger for illicit drug use and the individual as the subject who would experience drug craving in response to the environmental cues.[11]

Opioids are classified into natural and synthetic subclasses. Morphine is a natural short acting opioid and can be detected in urine by immunoassay screening

tests. Heroin (diacetalymorohine) is an illicit synthetic opioid. It is rapidly hydrolyzed to 6-monacetylmorphine (half life 3–6 minutes) as a result of spontaneous hydrolysis and hydrolysis by cholinesterase, which in turn is hydrolyzed to inactive morphine 3-glucouronide and the active morphine-6-glucouronide following intravenous administration in humans.[12,13] Duration of action of heroin is usually short, but elimination of its metabolite (morphine) depends on route of administration, drug dose, body weight, time elapsed since the last dose, and inter-individual pharmacokinetics.[14] Heroin is mainly excreted in the urine as free and conjugated morphine.

The metabolism of the short acting synthetic opioids (eg, oxycodone and hydrocodone) is different from heroin. After a dose of conventional oral oxycodone, peak plasma levels of the drug are attained in approximately one hour; in contrast, after a dose of OxyContin (an oral continuous release formulation), peak plasma levels of oxycodone occur in about three hours. Oxycodone is metabolized to α and β oxycodol; oxymorphone, then α and β oxymorphol and noroxymorphone; and noroxycodone, then α and β noroxycodol and noroxymorphone (N-desmethyloxycodone). Unlike morphine and hydromorphone, oxycodone is metabolized by the cytochrome P450 enzyme system in the liver, making it vulnerable to drug interactions. Some people are fast metabolizers resulting in reduced analgesic effect but increased adverse effects, while others are slow metabolisers resulting in increased toxicity without improved analgesia. Unlike morphine and hydromorphone, oxycodone is metabolized by the cytochrome P450 enzyme system in the liver, making it vulnerable to drug interactions. Oxycodone and its metabolites are mainly excreted in the urine and sweat.[15–17]

Methadone is a long acting synthetic opioid. It is extensively metabolized in the body mainly in the liver but also by intestinal cytochrome P450 3A4 enzymes. The main metabolite of methadone (2-ethylidene-1,5-dimethyl 1-3,3-diphenylpyrrolidine; EDDP) is inactive. In addition to methadone nine metabolites including EDDP, have been identified in urine and three in feces.[18–20]

Heroin has been the main source of illicitly used opioids for decades. Sniffing, smoking and IV administration are common routes for illicit heroin use. Recently a new epidemic of non medical use of prescribed opioids emerged in the US. New routes of administration of prescribed opioids have been reported in order to achieve euphoria by illicit users. These routes include chewing, crushing and IV use of controlled release oxycodone (oxycontin), and licking of fentanyl patches and also oral ingestion of prescribed opioids for non medical use.

## Signs and symptoms of intoxication, overdose and withdrawal

Cardinal signs of opioid intoxication and overdose include a reduced level of consciousness which may range from drowsiness to a stuporous state to a coma. Other cardinal signs include pinpoint pupils and a depressed respiratory rate. Cyanosis, hypotension, bradycardia, and hypothermia may also be present. Death is usually from respiratory depression.[13] Some case reports describe non fatal heroin overdoses associated with significant morbidity.[21] The most commonly reported signs and symptoms of overdose morbidity are pulmonary conditions such as edema and pneumonia[22–25] and muscular complications such as rhadomyolysis[26,27] from prolonged pressure on muscles during coma and renal failure from lysis of muscle tissue.[21] Cardiovascular[28–30] and cognitive impairment have been reported.[31,32] Warner Smith et al[21] also report overdose related morbidity including peripheral neuropathy, vomiting, temporal paralysis of limbs, chest infection and seizures.

Opioid withdrawal is a syndrome related to sudden discontinuation of opioids after prolonged period of use. Short acting opioids such as heroin usually exhibit signs and symptoms of withdrawal within 8–12 hours after the last dose. If untreated, it reaches a peak within 36–72 hours and usually subsides substantially within 5 days. For long acting opioids like methadone, withdrawal may reach a peak between 5–6 days, and the syndrome will not usually subside for 14–21 days. The signs and symptoms of opioid withdrawal may be classified as objective and subjective.[33] Objective signs include vomiting, lacrimation, rhinorrhea, pupillary dilatation, piloerection, sweating, diarrhea, yawning, fever, elevated pulse and blood pressure. Subjective symptoms may include dysphoric mood, insomnia, muscle aches and cramps, abdominal pain and colic. The Clinical

Opiate Withdrawal Scale (COWS) is usually used to classify the severity of opioid withdrawal based on the generated score.[34]

## Diagnosis of intoxication and overdose

Opioid drugs have a wide biodistribution and can be identified in virtually all parts of the body and in all body fluids. The drugs are typically metabolized by the liver, producing metabolites that are often longer lasting and detectable at higher levels than the parent drug. Several laboratory tests can identify the presence of opioids or their metabolites in the blood, urine, hair or saliva. Inexpensive immunoassay screening tests are usually used to detect the presence of opiates (derivatives of the opium poppy) or their metabolites in the blood, urine, hair or saliva. The presence of opioids or their metabolites may be detected in the blood up to 3–12 hours, in urine up to 1–3 days, in hair up to 7–90 days, and in saliva up to 3–24 hours. Gas chromatography/mass spectrometry is a more expensive laboratory test that is available for confirmation of the results and/or detection of synthetic opioids not usually included in screening immunoassays.[35]

## Treatment and prevention of intoxication and overdose

Naloxone is the standard treatment for opioid overdose (Fig. 1). It is a short acting mu receptor antagonist. Its active metabolite, 6-alpha-naloxol has a much longer half-life than naloxone.[36] It is usually given intravenously (IV), subcutaneously (SC) or by intramuscular injection (IM). Some reports indicate that the IM administration may prolong the effect of naloxone.[37] It is usually administered by paramedics before transferring the patient to the ED. There is evidence that it antagonizes the respiratory depressant effect of morphine up to six hours.[38] The starting dose is usually 0.4 mg IV/SC/IM. It can be repeated until the patient responds. Some studies reported a total dose range between 2–6 mg depending on the half- life of the opioid involved in the overdose.[39–42] Other factors may also be associated with the need for higher doses of naloxone for resuscitating overdose patients such as concomitant use of alcohol with opioids.[43]

There have been controversies about the suggested post opioid overdose period of observation. Several factors need to be considered for this observation period. Opioids with short duration of action such as heroin may need a short period of observation[44–46] while the long acting opioids such as methadone may need a longer period of observation.[47,48] Response to initial doses of naloxone also plays an important factor in determining the duration of observation and the need for an inpatient admission. Signs of pulmonary edema, hypoventilation, aspiration pneumonia and somnolence may warrant longer periods of observation up to 12–24 hours and in some cases an inpatient or intensive care unit (ICU) admission for further evaluation and respiratory support. Patients who overdose on short acting opioids (eg, IV heroin) with good response to initial doses of naloxone before arriving to the ED and no respiratory complications may need to be observed for 1–4 hours before discharge from the ED.[38] Boyd et al[39] reported recently that in their study population, allowing presumed heroin overdose patients to sign out after pre-hospital care with naloxone appears to be safe. When transported to an ED, and if no adverse events related to heroin use are evident on arrival, a 1-h observation period after naloxone administration seems to be adequate for recurrent heroin toxicity. In an older study, Smith et al[36] found on retrospective review that complications after an IV heroin overdose are relatively few in number and usually evident on or soon after presentation of the patient in the ED. They reported that in most cases, there is no evidence to support 12 to 24 hours of observation or hospitalization for patients who are awake, alert, and who lack evidence of pulmonary complications after a brief observation period of two to four hours. Opioid intoxication associated with alcohol or other drugs may require longer periods of observation. Patients who do not fully regain consciousness or are confused or otherwise mentally incompetent should not be allowed to leave or sign out of the hospital against medical advice.

Some states developed harm reduction programs to reduce the growing rate of overdose mortality. Since the 1990s the Chicago Recovery Alliance program developed anti-overdose kits of naloxone injections to be administered by opiate addicted individuals in case of accidental opioid overdose. Those kits are distributed through needle exchange programs. This program has led to at least 1,000 successful overdose reversals in Chicago city since 2001. Other states
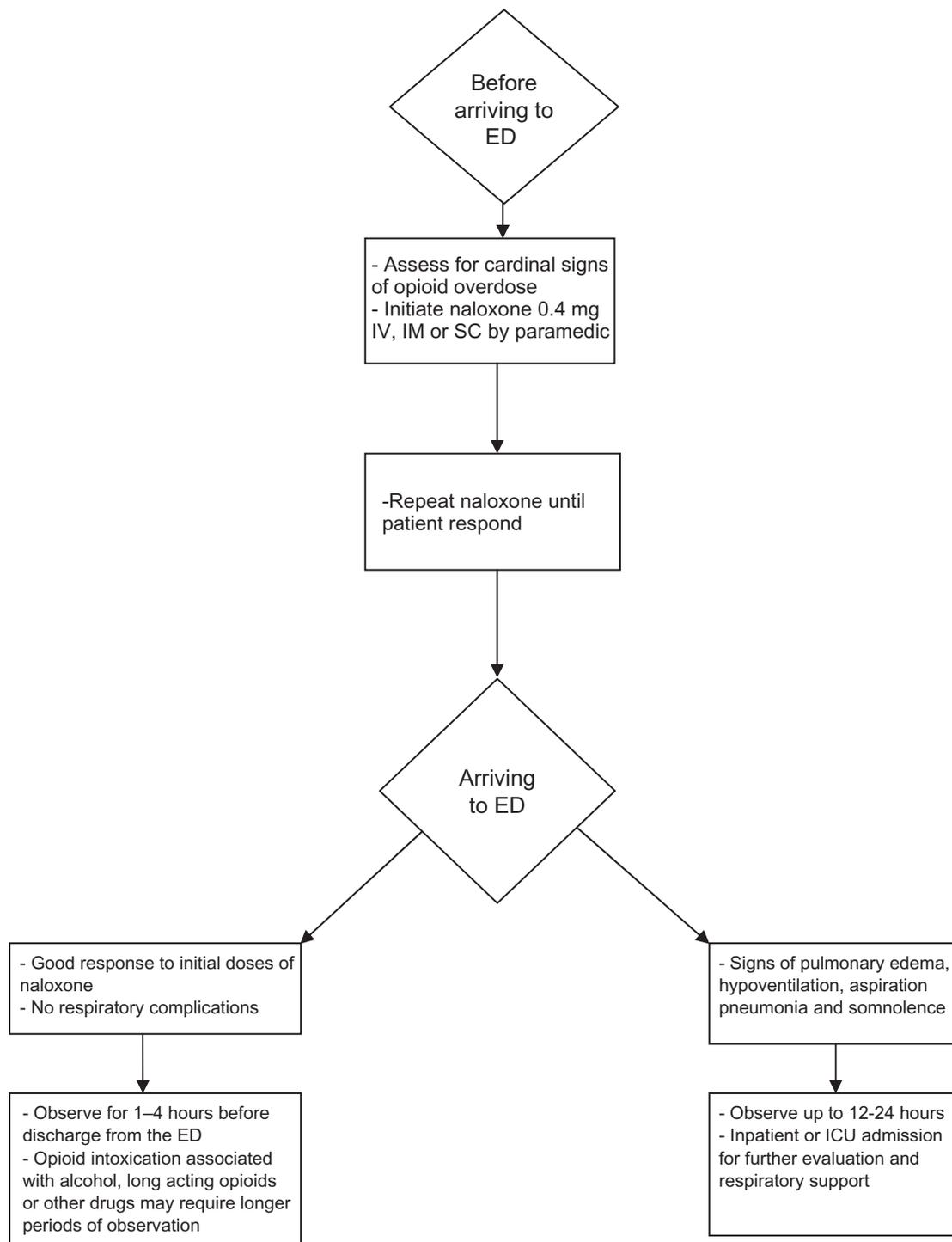
**Figure 1.** Management of acute opioid intoxication and overdose.

developed similar programs to fight the growing incidents of drug overdose.[49] There has been controversy about whether it is good public health policy to allow distribution and use of naloxone without medical supervision. On the other hand, those programs could be live saving for many individuals with opioid addiction.[49]

Naloxone injection may induce opioid withdrawal which may require treatment post overdose. Opioid withdrawal is usually not life threatening

but may trigger opioid use and relapse. Ambulatory opioid detoxification is the standard treatment for opioid withdrawal. Substitution with a long acting mu opioid receptor agonist such as buprenorphine[50] or methadone[51] with gradual taper over a few days may block withdrawal signs and symptoms and minimize the patient's suffering. Symptomatic treatment with an alpha 2 receptor agonist such as clonidine or lofexidine decreases noradrenergic activity and reduces some signs and symptoms of opioid withdrawal. However, several studies reported that this option is not as effective as substitution with mu receptor agonists in reducing the severity of the withdrawal syndrome.[52–54]

Some studies report that non-fatal illicit drug overdose significantly predicted subsequent drug overdose.[55–57] Therefore prevention of future opioid overdose in high risk patients may reduce mortality and morbidity in this population. Several studies reported that methadone maintenance treatment (MMT) can reduce the risk of overdose and mortality in this population.[58–62] Brugal et al[63] recently reported that the life expectancy of their cohort of heroin users in MMT increased by 21 years during the period of the study. Factors contributing to increased life expectancy included a reduced incidence of acquired immune deficiency syndrome (AIDS) and reduction of death related to drug overdose. Caplehorn et al[64] performed a meta-analysis to study the relationship between being in MMT and the risk of drug related mortality. They found that MMT reduces the risk of overall mortality in this population by 25%, primarily due to reduction of the risk of accidental overdose (heroin in particular). Conversely, dropping out of MMT increases the risk of drug overdose and mortality. Langendam et al[65] reported that in their cohort of drug users, participation in harm-reduction MMT reduced the risk of overdose death, whereas leaving treatment was associated with increased risk. On the other hand, several studies have reported an increased risk of fatal drug overdose during the first few weeks of initiating MMT.[65–69] Therefore the induction period for MMT may constitute high risk for drug related overdose. Illicit use of central nervous depressants such as benzodiazepines or alcohol during this period may increase the risk for overdose and mortality.[5] Increased patient monitoring and education during the induction phase of MMT may attenuate the risk

of non opioid drug-related mortality and morbidity. Buprenorphine maintenance treatment (BMT) may be an alternative to MMT for certain high risk patients. Buprenorphine has an improved safety profile compared to methadone due to its pharmacokinetic and pharmacodynamic properties.[50] It is a partial agonist of the mu opiate receptor and has a ceiling effect which may reduce the risk for drug overdose.[50] It is also safer than methadone as regards its cardiotoxic effect.[70] Bell et al[71] reported that the risk of overdose death during the 9-month period of their study was significantly lower for patients receiving BMT compared to patients on MMT. In another study, Bell et al[72] reported that BMT was associated with less mortality during the induction phase of treatment but shorter retention in treatment compared to MMT. Overall, one may understand from these data that opioid maintenance treatment may improve the risk of illicit opioid overdose and should be considered as a preventive measure for high risk patients.

A new interest in using a sustained release naltrexone implant as prophylaxis against heroin overdose has gained some popularity in Australia.[69,73,74] Hulse et al[73] found a lower rate of hospitalization for accidental overdose in patients receiving the implant treatment. Ngo et al[74] reported that naltrexone implants, but not methadone maintenance, have long-term benefits in reducing opioid related hospital morbidity. However, long-lasting and increased nonopioid drug–related morbidity following naltrexone implantation is particularly concerning. They attributed the nonopioid drug related morbidity to the switching of the drug of choice in those patients to nonopioid drugs. The switch of the drug of choice is probably due to the lack of the expected pleasurable effects upon using opioids. Also, there are some reports[75,76] about the increased risk of drug overdose following naltrexone treatment due to decreased opioid tolerance after treatment. More studies are needed to confirm the safety and efficacy of naltrexone implant for prevention of opioid overdose.

In addition to psychopharmacologic intervention for the prevention of illicit opioid overdose, psychotherapeutic intervention is also important. ED and primary care visits represent an opportunity for educational interventions and referral for substance use disorder (SUD) treatment. Brief interventions may be useful for primary care and ED settings but intensive

behavioral treatments are preferred for long term management. Brief motivational interviewing (MI) has been implemented in primary care and proved to be an effective intervention for patients with alcohol disorders.[77] Recent reports about implementing MI by ED staff and offering referral to SUD treatment programs for patients with alcohol related injuries seem promising.[78–81] There are limited data about using MI for patients presenting to ED due to opioid intoxications or overdose. Early intervention after reviving those patients may decrease the burden on ED and prevent future episodes of illicit opioid intoxications and overdose. There is a need to study whether MI and offering referral to SUD treatment by ED staff is effective in preventing future illicit opioid intoxications and overdose.

## Conclusions and Future Directions

There are a number of different intoxicants that may be seen in the ED with different presentations and interventions. Opioid intoxications and overdose in particular can be life threatening. Naloxone is the standard treatment for acute opioid overdose and can be life saving if it is given soon enough to revive individuals with opioid overdose. Opioid maintenance treatment may prevent opioid overdose and decrease the risk of mortality for high risk patients. The induction phase of MMT warrants frequent monitoring and education for high risk patients to limit the risk of drug overdose during the first few weeks. Buprenorphine treatment may offer a better safety profile compared to methadone. The naltrexone implant is promising for the prevention of overdose mortality for some patients with opioid dependence but more research is needed to confirm its safety and efficacy. Motivational interviewing and referral to SUD treatment by ED staff are non-pharmacologic interventions for individuals who survive opioid overdose.

## Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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