INTRODUCTION — Opiates extracted from the poppy plant (Papaver somniferum) have been used recreationally and medicinally for millennia. Opiates belong to the larger class of drugs, the opioids, which include synthetic and semi-synthetic drugs, as well. Opioid abuse is a worldwide problem and deaths from opioid overdose are numerous and increasing [1-5]. This topic review will discuss the mechanisms, clinical manifestations, and management of acute opioid intoxication. A summary table to facilitate emergent management is provided (table 1). Issues related to opioid withdrawal, chronic opioid abuse, and general management of the poisoned patient are found elsewhere. (See "Opioid withdrawal in the emergency setting" and "Pharmacotherapy for opioid use disorder" and "Opioid use disorder: Epidemiology, pharmacology, clinical manifestations, course, screening, assessment, and diagnosis" and "General approach to drug poisoning in adults").

PHARMACOLOGY AND CELLULAR TOXICOLOGY — The opioid pharmaceuticals are analogous to the three families of endogenous opioid peptides: enkephalins, endorphins, and dynorphin. The most recent classification scheme identifies three major classes of opioid receptor, with several minor classes [6]. Within each receptor class there are distinct subtypes. Each subtype produces a variety of distinct clinical effects, although there is some overlap (table 2). For most clinicians, the nomenclature derived from the Greek alphabet is more familiar, although the International Union of Pharmacology (IUPHAR) Committee on Receptor Nomenclature has recommended a change from the original Greek system to make opioid receptor names more consistent with other neurotransmitter systems [6].

The opioid receptors are distinct in their locations and clinical effects, but they are structurally similar (table 2). Each consists of seven transmembrane segments, with amino acid and carboxy termini. Although the opioid receptors are all coupled to G proteins, they use a variety of signal transduction mechanisms [6]. These include reducing the capacity of adenylate cyclase to produce cAMP, closing calcium channels that reduce the signal to release neurotransmitters, or opening potassium channels to hyperpolarize the cell [6].

The end result of these mechanisms is to modulate the release of neurotransmitters. Opioid receptors exist throughout the central and peripheral nervous system and are linked to a variety of neurotransmitters, which explains the diversity of their clinical effects. The analgesic effects of opioids result from inhibition of nociceptive information at multiple points of its transmission from the peripheral nerve to the spinal cord to the brain. Euphoria results from increased dopamine released in the mesolimbic system [7]. Anxiolysis results from effects on noradrenergic neurons in the locus ceruleus [8].

KINETICS — The vast number of opioids precludes presenting pharmacokinetic data for each one, but a few clinically important generalizations can be made. The majority of opioids have volumes of distribution of 1 to 10 L/kg, which makes removal of a significant quantity of drug by hemodialysis impossible. They have variable protein binding (from 89 percent for methadone to 7.1 percent for hydrocodone) and are renally eliminated. Many opioids are metabolized by the liver to active metabolites. Examples include hydrocodone (metabolized to hydromorphone by Cytochrome [CYP] 2D6) and morphine (metabolized to morphine-6-glucuronide). Cytochrome P polymorphisms cause variations in clinical effect.

The most clinically important pharmacokinetic difference is a wide variation in serum half-life (table 3). The half-life data in these tables, taken from healthy subjects receiving therapeutic doses, should serve only as a rough guide to
duration of clinical effect. Actual effects are influenced by dose, an individual's tolerance, and the presence of active metabolites.

In overdose, the apparent half-life may vary significantly from therapeutic dosing. If many tablets are taken, dissolution and absorption will be delayed, prolonging the apparent half-life. Duration of action may also be shortened in overdose. As an example, when a sustained-release formulation of oxycodone is crushed before ingestion, the drug is rapidly absorbed. While the user's intent may be to increase euphoria, the chance of significant morbidity is increased as well.

Although active metabolites of some opioids (eg, morphine) may accumulate in patients with impaired kidney function, such metabolites are not dialyzable and management is unchanged [9].

**CLINICAL FEATURES OF OVERDOSE** — Important clinical features related to opioid intoxication are discussed here. A general approach to the overdose patient is found elsewhere. (See "General approach to drug poisoning in adults".)

**History** — The clinician should attempt to identify the specific drug, dose, and formulation to which the patient was exposed, the presence of nonopioid co-exposures, and the individual's prior history of opioid use. One review found the "typical" heroin death to involve experienced users in their 20s to 30s using coingestants [10]. Recently released prisoners are at higher risk of opioid overdose in the post-release period because of lost tolerance during incarceration [11,12].

While not essential for management, historical features may help predict the expected duration of poisoning. History should also determine the reason for poisoning, as the patient's intention will influence post-overdose management. Generally, opioid exposures will fall into one of several categories: therapeutic use, recreational use, intended self-harm, attempt to hide drugs from law enforcement out of fear of arrest ("body stuffing"), swallowing large quantities of packaged drugs in order to transport them across borders ("body packing"), and unintentional pediatric exposures.

**Physical examination** — Physical examination helps to confirm the diagnosis of opioid poisoning, determine the extent of intoxication, identify other conditions requiring treatment, and prevent further exposure (table 4).

The classic signs of opioid intoxication include:

- Depressed mental status
- Decreased respiratory rate
- Decreased tidal volume
- Decreased bowel sounds
- Miotic (constricted) pupils

Normal pupil examination does not exclude opioid intoxication. Users of meperidine [13] may present with normal pupils, and the presence of coingestants (such as sympathomimetics or anticholinergics) may make pupils appear normal or large. The best predictor of opioid poisoning is a respiratory rate <12/minute, which predicted response to naloxone in virtually all patients in one series [14]. The clinician should measure the respiratory rate and pay close attention to chest wall excursion, as subtle changes may not be identified in triage vital signs.

While decreased respiratory rate is the most notable vital sign abnormality, heart rate ranges from normal to low, although this is not usually consequential. Mild hypotension (from histamine release) may also be present [15]. Pulse oximetry should be performed in every patient, although the clinician should be wary that hypercapnia can be present in the setting of normal oxygen saturation, particularly when the patient is placed on supplemental oxygen.

Obtain a core temperature from any patient more than mildly intoxicated. Hypothermia, which results from a combination of environmental exposure and impaired thermogenesis, may be present. In a severely obtunded patient, room temperature may produce significant hypothermia. Elevated temperature may suggest early aspiration pneumonia or complications of injection drug use, such as endocarditis.

Mental status can range from euphoria to coma, or may be nearly normal. Seizures can occur in the setting of tapentadol, tramadol, or meperidine overdose, or as a result of hypoxia from any opioid.

During the secondary survey, look for signs of trauma, particularly to the head. Not only do opioids predispose the
patient to trauma, but obtundation from traumatic brain injury can be misidentified as drug intoxication. Pulmonary
findings, such as rales, can indicate the presence of aspiration or acute respiratory distress syndrome. If the patient
is suspected of attempting to hide drugs out of fear for arrest, rectal and vaginal examination should be performed
with the patient's permission. If the patient cannot give consent because of poisoning, consent is inferred based on
medical necessity. Examination of the skin may identify medication patches that must be removed, track marks
suggesting history of chronic injection drug use, or coexisting soft tissue infections (picture 1).

Toxicities of specific agents — In addition to the general features described above, some agents have specific
toxicities. A brief description of the notable, albeit infrequent, effects and characteristics of several opioids commonly
encountered in the overdose patient follows:

- **Buprenorphine** — Partial opioid agonist; may induce withdrawal in opioid-dependent patients
- **Dextromethorphan** — Serotonin toxicity; at high doses exhibits some \( \mu \) effects of opioids (miosis, respiratory
  and CNS depression) but is not a pure opioid agonist
- **Fentanyl** — Very short acting
- **Hydrocodone** — Often combined with acetaminophen
- **Loperamide** — Wide-complex tachycardia; loses specificity for gastrointestinal tract in supratherapeutic dosing
  [16,17]
- **Meperidine** — Seizure, serotonin toxicity (in combination with other agents) (see "Serotonin syndrome
  (serotonin toxicity)"
- **Methadone** — Very long-acting; QTc prolongation, Torsades de Pointes (see 'Electrocardiography' below)
- **Oxycodone** — Often combined with acetaminophen; possible QTc interval prolongation
- **Tramadol** and tapentadol — Seizure

DIFFERENTIAL DIAGNOSIS — The differential diagnosis of opioid intoxication includes toxic and nontoxic
conditions.

There are myriad drugs that can produce coma (table 5). Ethanol, clonidine, and sedative-hypnotics (eg,
benzodiazepines) may be the most clinically-relevant toxic agents in the differential diagnosis, because they occur
frequently. While clonidine may produce miosis and obtundation, bradycardia, and hypotension are more prominent.
Ethanol intoxication produces little to no miosis and no change in bowel sounds. The sedative-hypnotic agents result
in much less respiratory depression than the opioids, especially when taken orally. (See "Ethanol intoxication in
adults".)

The presence of coingestants often confounds the diagnosis of opioid intoxication. While it is frequently impossible
to determine the exact substances to which the patient was exposed, a careful history, physical examination, and
judicious use of laboratory studies can determine the correct course of management. The sine qua non of opioid
intoxication is clinical response to an antagonist, although giving large doses of antagonist to establish the diagnosis
of opioid poisoning is usually not helpful and potentially dangerous, and therefore not recommended. (See
'Management' below and "General approach to drug poisoning in adults".)

Any medical condition that can produce coma may be mistaken for (or occur in conjunction with) opioid poisoning.
The most important conditions to exclude are those in which delay of diagnosis will delay definitive care, such as
cerebrovascular accident, electrolyte abnormality, and sepsis (table 6). (See "Stupor and coma in adults".)

LABORATORY EVALUATION AND ANCILLARY STUDIES

**Laboratory evaluation** — A rapid serum glucose concentration should be obtained in all suspected cases of opioid
overdose. Hypoglycemia is prevalent, easily detectable, rapidly correctable, and potentially confused with opioid
poisoning. Most patients with mild or moderate unintentional or recreational poisoning can be managed successfully
without any further laboratory investigation.

After any overdose in which the opioid is formulated with acetaminophen, or any overdose that is the result of
intended self-harm, serum acetaminophen concentration should be obtained. In one series, 1 in 365 individuals with suicidal ingestion and history negative for acetaminophen ingestion had a potentially hepatotoxic acetaminophen concentration [18]. It is not essential to obtain a salicylate concentration in the absence of clinical suspicion or signs of overdose (eg, tachypnea or increased anion gap). (See "Acetaminophen (paracetamol) poisoning in adults: Treatment" and "Salicylate (aspirin) poisoning in adults".)

To exclude rhabdomyolysis in the patient presenting after prolonged immobilization, serum creatine phosphokinase concentration should be obtained. Further testing, such as serum creatinine and electrolytes, may be needed depending on clinical circumstances. (See "Clinical manifestations and diagnosis of rhabdomyolysis" and "Clinical features and diagnosis of heme pigment-induced acute kidney injury (acute renal failure)". section on 'Clinical manifestations'.)

Urine toxicologic screens should NOT be routinely obtained. Acute opioid poisoning is a clinical diagnosis; the management of a patient with an opioid toxidrome is unchanged by the result of a urine opioid screen. A positive test may indicate recent use but not current intoxication, or may even represent a false positive. Conversely, many opioids, especially the synthetic drugs, will produce false-negative results in many commonly available urine screens. Commonly available laboratory assays (eg, for phenytoin) can be performed if the history or examination suggests coingestion.

Electrocardiography — An electrocardiogram (ECG) should be obtained when the patient is suspected of intended self-harm or a coexposure likely to cause cardiovascular complications is possible (eg, cocaine or a cyclic antidepressant). With a few exceptions, electrocardiography can be omitted in other types of opioid exposure. Loperamide has been associated with cardiac conduction disturbances ranging in severity from simple QRS widening to ventricular tachycardia (polymorphic and monomorphic) and idioventricular rhythm [19]. Methadone can cause QTc interval prolongation and Torsade de Pointes. This phenomenon more commonly occurs in patients taking high daily doses of the drug [20]. However, the observations that most people who take very large doses of methadone tolerate it well and that some have developed QT prolongation from lower doses suggest individual susceptibility to the condition varies. There may also be an association with oxycodone toxicity and QT prolongation [21].

The benefit of performing an ECG on every individual with a history of methadone, loperamide, or oxycodone exposure is unstudied and cannot be recommended. Rather, the test should generally be reserved for those patients presenting after a large dose increase or with complaints suggesting a dysrhythmia, such as palpitations or syncope. (See 'Toxicity of specific opioids including conduction disturbances' below and "Acquired long QT syndrome".)

Imaging — Chest radiography is reserved for those patients with adventitious lung sounds or hypoxia that does not correct when ventilation is addressed. Abnormal lung sounds may represent aspiration pneumonia or acute respiratory distress syndrome. (See 'Lung injury and ARDS' below and "Acute respiratory distress syndrome: Clinical features and diagnosis in adults".)

Imaging of drug packets is discussed below. (See 'Body packing and body stuffing' below.)

MANAGEMENT

Basic measures and antidotal therapy — General management of the overdose patient is discussed elsewhere. (See "General approach to drug poisoning in adults".) Specific management strategies for opioid overdose are discussed below. A summary table to facilitate emergent management is provided (table 1).

Once opioid poisoning is suspected, initial management should focus on support of the patient's airway and breathing. Attention should be paid to the depth and rate of ventilation. While pulse-oximetry is useful in monitoring oxygenation, it may not be useful in gauging ventilation when supplemental oxygen is being given. While not yet widely used for this purpose, capnography may be an excellent tool to monitor the ventilatory effort of opioid-poisoned patients. Several studies in patients undergoing procedural sedation show that ventilatory difficulty manifests as elevations in end-tidal CO2 earlier than declines in oxygenation by pulse oximetry. (See "Carbon dioxide monitoring (capnography)".)

Administer naloxone, a short-acting opioid antagonist, preferably by the intravenous route. The apneic patient and
patients with extremely low respiratory rates or shallow respirations should be ventilated by bag-valve mask attached to supplemental oxygen prior to and during naloxone administration to reduce the chance of acute respiratory distress syndrome [22]. Apneic patients should receive higher initial doses of naloxone (0.2 to 1 mg). Patients in cardiorespiratory arrest following possible opioid overdose should be given a minimum of 2 mg of naloxone [23,24]. (See "Basic airway management in adults" and 'Lung injury and ARDS' below and "Acute respiratory distress syndrome: Clinical features and diagnosis in adults".)

When spontaneous ventilations are present, an initial dose of 0.04 to 0.05 mg is an appropriate starting point, and the dose should be titrated upward every few minutes until the respiratory rate is 12 or greater [25]. The goal of naloxone administration is NOT a normal level of consciousness, but adequate ventilation. In the absence of signs of opioid withdrawal, there is no maximum safe dose of naloxone. However, if a clinical effect does not occur after 5 to 10 mg, the diagnosis should be reconsidered.

Naloxone may be given nasally, subcutaneously, or intramuscularly if there is a delay in securing intravenous access. When given by these routes, there is slower absorption and delayed elimination, making the drug much more difficult to titrate. Naloxone can be absorbed in the respiratory tract, and thus, can be administered into an endotracheal tube or nebulized. Conceptually, there is little role for nebulized or nasal naloxone in the hospital setting because the dose administered is determined by the patient's ventilation, thus the most severely poisoned patients will absorb the least amount of antidote [26]. The respiratory route and other routes of administration are less predictable. In addition, intravenous access is required in these patients as other medications (such as hypertonic dextrose) may be needed.

If the clinician "overshoots" the appropriate dose of naloxone in an opioid-dependent individual, withdrawal will ensue. Symptoms of withdrawal should be managed expectantly only, NOT with additional opioids. To overcome naloxone antagonism requires a large dose of opioids. More importantly, because naloxone has a short duration of action, any opioid administered will result in even more sedation once the effects of naloxone subside. (See "Opioid withdrawal in the emergency setting".)

After ventilation is restored with naloxone, repeat doses may be required, depending on the quantity and duration of action of the opioid. As an alternative to repeat dosing, a naloxone infusion can be prepared by determining the total initial dose required to reinstate breathing, and delivering two thirds of that dose every hour [27]. If the patient develops withdrawal signs or symptoms during the infusion, stop the infusion. If intoxication returns, restart the infusion at half the initial rate. If the patient develops respiratory depression during the infusion, re-administer half the initial bolus every few minutes until symptoms improve, then increase the infusion by half the initial rate.

GI decontamination — Activated charcoal and gastric emptying are almost never indicated in opioid poisoning. Gastrointestinal decontamination has some risk and opioid poisoning is readily treatable by other means. While orogastric lavage could remove tablets still in the stomach, and activated charcoal binds opioids, each of these therapies produces a risk of aspiration, especially in the obtunded, opioid-poisoned patient. Gastrointestinal decontamination should be reserved for patients presenting with potentially life-threatening coingestants, not for opioids alone, and should be performed only if the airway is secure. (See "Gastrointestinal decontamination of the poisoned patient".)

Extracorporeal removal — The large volume of distribution of the opioids precludes removal of a significant quantity of drug by hemodialysis.

Body packing and body stuffing — Body packing is described as the act of swallowing packets or containers of drug for the purposes of smuggling. Body packers are generally participants in international drug networks who are transporting drugs across international borders. Heroin and cocaine are more frequently implicated than other drugs [28]. The smugglers carry massive amounts of well-packaged drugs. While the majority of body packers do not present to health care, those who do should be evaluated for signs of intoxication (from ruptured or leaking packets), obstruction, or rarely, gastrointestinal perforation. A detailed discussion of body packing is found elsewhere. (See "Internal concealment of drugs of abuse (body packing")

Plain radiography has a sensitivity of 85 to 90 percent for finding packets [29]. Computed tomography of the abdomen will be more sensitive, as well as offer the ability to identify complications, such as obstruction or perforation. A negative urine screen may be useful to exclude the presence of ruptured packets.
If the history reveals that the patient has smuggled packets of heroin, the goals of management are to support the airway and assist in elimination of the packets. Intravenous naloxone should be given until ventilation is adequate. The total dose required should be given hourly to preserve the effect. The dose requirement may increase if further packet rupture or leakage occurs.

After confirming bowel sounds, polyethylene glycol electrolyte lavage solution (PEG-ELS) should be administered orally at a rate of 2 L/h until all packets have been passed. Though placement of a nasogastric tube is not necessary (and should be avoided in the patient with a depressed mental status), it may facilitate administration of the solution.

Operative management will be required only if gastrointestinal obstruction or perforation occur.

"Body stuffing" refers to the swallowing of a smaller quantity of drug because of fear of arrest. Compared with body packers, body stuffers are carrying a far smaller quantity of drug and the drug is more poorly packaged. In contrast to the "body packer", it may not be necessary to routinely administer PEG-ELS to the opioid "body stuffer". While the regimen could theoretically cause some packages to pass before drug is absorbed, the clinician may elect to manage the patient by close observation and administration of naloxone if symptoms arise. Oral activated charcoal alone may be sufficient.

The body stuffer should be observed for signs of intoxication. The ideal length of time is not known, but 6 to 12 hours is reasonable. If signs of opioid poisoning develop, the patient can be managed as described above. (See 'Management' above.)

**Lung injury and ARDS** — Acute Respiratory Distress Syndrome (ARDS) is a potential adverse effect of morphine, heroin, methadone, and other opioids [30-32]. The signs, which typically include rales, hypoxia, and occasionally frothy sputum, often occur as a patient is recovering from opioid-induced respiratory depression. The pathophysiology is unclear, but in some cases ARDS occurs in the setting of iatrogenic reversal of opioid toxicity (such as with naloxone). In such cases, rapid precipitation of withdrawal in the setting of elevated PCO2 may cause a surge in catecholamine concentrations, thereby increasing afterload, which causes interstitial edema followed by alveolar filling [22]. Because of this, very small doses of naloxone (0.04 to 0.05 mg to start) should be used on those patients with marked hypoventilation and they should be ventilated with a bag-valve mask prior to administration of naloxone. (See 'Basic measures and antidotal therapy' above and "Basic airway management in adults".)

Management of opioid and naloxone-related ARDS is supportive and the prognosis is generally good if it is identified and addressed promptly. The clinical manifestations and management of ARDS are discussed elsewhere. (See "Acute respiratory distress syndrome: Clinical features and diagnosis in adults" and "Mechanical ventilation of adults in acute respiratory distress syndrome" and "Acute respiratory distress syndrome: Supportive care and oxygenation in adults".)

**Toxicity of specific opioids including conduction disturbances** — Several opioids possess uncommon toxicities requiring specific management. In extreme supratherapeutic dosing, loperamide is associated with ventricular conduction disturbances including QRS prolongation, idioventricular rhythm, and ventricular tachycardia (monomorphic and polymorphic). Sodium bicarbonate is recommended for management of other drug-induced sodium channel toxicity [33]. The clinical benefit of this intervention is unknown, but if QRS prolongation is encountered it seems reasonable to administer a bolus of 1 to 2 mEq/kg of sodium bicarbonate intravenously in the absence of contraindications. If the complex narrows, a bicarbonate infusion can be performed. We mix 132 mEq of NaHCO3 in 1 liter of D5W, and infuse at 250 mL/hour. Since loperamide also causes QT prolongation, it is important to monitor potassium and magnesium if bicarbonate is given as depletion may increase the risk of QT prolongation. Methadone can cause QT interval prolongation and Torsade de Pointes. If the QTc is determined to be greater than 480 msec, the patient should be observed on a cardiac monitor for a 24-hour period and hypocalcemia, hypokalemia, and hypomagnesemia should be corrected when present [34]. The clinician should consider either stopping methadone therapy, or switching to buprenorphine, if the patient's psychosocial situation permits this. (See 'Electrocardiography' above and "Acquired long QT syndrome").

**Opioid adulterants, including krokodil** — Illicitly-purchased drugs frequently contain adulterants, some of which may cause clinical problems distinct from the desired compound. From the perspective of the drug seller, the ideal adulterant would be inexpensive, appear and taste similar to the desired drug, and not harm the user. Nonetheless, opioids containing harmful adulterants are common.
One example is “krokodil” (from the Russian word for crocodile), a homemade formulation of the potent, short-acting opioid desomorphine [35,36]. Derived from codeine, which is available without prescription in Russia, krokodil is reported to contain solvents, such as gasoline and lighter fluid. Other potential contaminants include iodine, hydrochloric acid, and red phosphorous. Subcutaneous injection has resulted in local tissue damage, including ulcers, skin necrosis, and infection. The name of the drug is derived from the scaly skin lesions observed in some users. Such lesions are likely the result of infection and/or direct tissue injury from adulterants, as desomorphine itself would not be expected to cause tissue toxicity, and similar findings were commonly seen with subcutaneous injection of impure heroin in the 1980's in the United States. Although there has been an epidemic of cases of tissue damage from krokodil injection in former Soviet republics, cases outside this region are uncommon [35].

Alkaloids, such as quinine and strychnine, are additional examples of harmful adulterants that have been implicated in heroin-related deaths [37]. Heroin has also been tainted with the anticholinergic scopolamine and the beta-adrenergic agonist clenbuterol, both of which have caused widespread toxicity [38,39]. (See "Strychnine poisoning" and "Anticholinergic poisoning").

**Buprenorphine and naloxone** — Buprenorphine is a partial agonist at the opioid receptor. When taken alone, buprenorphine can cause respiratory depression, but likely to a limited degree. Although most fatalities associated with buprenorphine have occurred in the setting of mixed overdose where the coingestant may produce or contribute to respiratory depression (eg, alcohol or benzodiazepines), fatalities may occur from buprenorphine alone [40]. Buprenorphine binds to the opioid receptor with high affinity. In experimental models, high doses of naloxone were needed to reverse respiratory depression. Interestingly, because of complex physiology, respiratory depression can recur with very high doses of naloxone. This effect has been described as a "bell-shaped" dose-response curve and may be a result of the high affinity of buprenorphine for the opioid receptor compared to naloxone [41].

Such research has led some to conclude that respiratory depression from buprenorphine may be difficult to reverse with naloxone. In observational studies of buprenorphine toxicity, the response to naloxone is mixed. In a case series of patients with buprenorphine overdose, none of the 19 patients administered 0.4 to 0.8 mg of naloxone had an adequate response [42]. In contrast, standard naloxone doses were adequate for reversal of buprenorphine effects in a small series of pediatric patients treated in an intensive care unit for buprenorphine toxicity [43].

We suggest that clinicians start with standard naloxone doses (0.04 to 0.05 mg IV) when treating patients with buprenorphine-associated respiratory depression, but be prepared to titrate to higher doses (single doses of up to 2 mg, for a total of 10 mg) than are typically required to treat respiratory depression from other opioids. After initial reversal is achieved, a naloxone infusion may be preferable to serial boluses. Infusion dosing is described above. (See ‘Basic measures and antidotal therapy’ above.)

**Disposition** — With the exception of overdoses involving the long-acting opioid methadone, most opioid poisonings can be managed in the emergency department without need for hospital admission. Generally, the patient may be discharged or transferred for psychiatric evaluation once respiration and mental status are normal and naloxone has not been administered for two to three hours. Although the half-life of naloxone is just over one hour, the duration of the drug's effect is shorter. Therefore, a two to three hour period of observation is generally sufficient.

Management of opioid intoxication in children is discussed elsewhere. (See "Opioid intoxication in children and adolescents").

**Harm reduction and take-home naloxone** — Bystander-administered naloxone by the intramuscular and intranasal routes can be used successfully to resuscitate opioid overdose patients [44,45]. Providing opioid users, family members, and friends with naloxone, accompanied by teaching them how to recognize opioid overdose, may reduce overdose mortality [46]. Following implementation of a comprehensive opioid overdose prevention program that included take-home naloxone, overdose deaths decreased from 46.6 to 29.0 per 100,000 [47]. Professional societies recommend prescription of naloxone to third parties (bystanders) as part of a harm reduction program [46].

**ADDITIONAL RESOURCES** — Regional poison control centers in the United States are available at all times for consultation on patients who are critically ill, require admission, or have clinical pictures that are unclear (1-800-222-1222). In addition, some hospitals have clinical and/or medical toxicologists available for bedside consultation and/or inpatient care. Whenever available, these are invaluable resources to help in the diagnosis and management of
ingestions or overdoses. The World Health Organization provides a listing of international poison centers at its website: www.who.int/gho/phe/chemical_safety/poisons_centres/en/index.html

**SUMMARY AND RECOMMENDATIONS**

**Pharmacology and presentation**

- There is a wide variation in the serum half-life of opioids (table 3). Actual drug effects are influenced by dose, an individual's tolerance, and the presence of active metabolites. In overdose the apparent serum half-life may vary significantly from therapeutic dosing. (See 'Pharmacology and cellular toxicology' above and 'Kinetics' above.)

- The classic signs of opioid intoxication include: depressed mental status, decreased respiratory rate, decreased tidal volume, decreased bowel sounds, and miotic pupils (table 4). The best predictor of opioid poisoning is a respiratory rate <12. Normal pupil examination does NOT exclude opioid intoxication. Users of meperidine and propoxyphene may present with normal pupils; the presence of coingestants (such as sympathomimetics or anticholinergics) may make pupils appear normal or large. (See 'Physical examination' above.)

- Although suppression of respiratory drive is most prominent, opioid intoxication can also be complicated by hypothermia, coma, seizure, head trauma, aspiration pneumonia, and rhabdomyolysis. Coingestants are frequently present. (See 'Clinical features of overdose' above.)

- Any medical condition that can produce coma may be mistaken for (or occur in conjunction with) opioid poisoning. The most important conditions to exclude are those in which delay of diagnosis will delay definitive care, such as intracranial hemorrhage, electrolyte abnormality, and sepsis. (See 'Differential diagnosis' above.)

- A rapid serum glucose concentration should be obtained in all suspected cases of opioid overdose. Most patients with mild or moderate unintentional poisoning can be managed successfully without any further laboratory investigation. (See 'Laboratory evaluation' above.)

- An electrocardiogram (ECG) should be obtained when the patient is suspected of intended self-harm or a coexposure likely to cause cardiovascular complications is possible. Loperamide can cause QRS and QT prolongation; methadone can cause QT prolongation. (See 'Electrocardiography' above.)

- Initial management should focus on support of the patient's airway and breathing. (See 'Basic measures and antidotal therapy' above.)

- In cases of suspected opioid overdose, we recommend the short-acting opioid antagonist naloxone be given (Grade 1B). While the intravenous (IV) route is preferred, naloxone may be given nasally, subcutaneously or intramuscularly if IV access is unavailable.

- When spontaneous ventilations are present, an initial naloxone dose of 0.05 mg is an appropriate starting point, and the dose should be titrated upward every few minutes until the respiratory rate is 12 or greater. Bag mask ventilation should be performed prior to and during administration of naloxone in apneic patients and patients with very low respiratory rates or shallow respirations. Apneic patients should receive higher initial doses of naloxone (0.2 to 1 mg). Patients in cardiac arrest should receive a dose no less than 2 mg. (See 'Basic measures and antidotal therapy' above.)

- The goal of naloxone administration is NOT a normal level of consciousness, but adequate ventilation. In the absence of signs of opioid withdrawal, there is no maximum safe dose of naloxone. If a clinical effect does not occur after 5 to 10 mg, the diagnosis should be reconsidered. (See 'Basic measures and antidotal therapy' above.)

- If the clinician "overshoots" the appropriate dose of naloxone in an opioid-dependent individual, withdrawal will ensue. Symptoms of withdrawal should be managed expectantly only, NOT with opioids. (See "Opioid withdrawal in the emergency setting").
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