INTRODUCTION — Cocaine, purported to be the most potent stimulant of natural origin, is extracted from the leaves of the coca plant (Erythroxylum coca), which is indigenous to the Andean highlands of South America. Natives in this region chew or brew coca leaves into a tea for refreshment and to relieve fatigue, similar to the customs of chewing tobacco and drinking tea or coffee in other cultures.

Pure cocaine was first isolated in the 1880s and was first used as a local anesthetic in eye surgery. It was particularly useful in surgery of the nose and throat because of its ability to provide anesthesia and constrict blood vessels, thereby limiting bleeding. Cocaine was legal and widely used in the United States during the second half of the 19th century and was a main ingredient of the original Coca-Cola. Despite legislative attempts dating from the early 20th century to eradicate its use, cocaine remains a common and dangerous drug of abuse.

This topic review will discuss the basic pharmacology, clinical presentation, and management of acute cocaine intoxication. Treatment for chronic cocaine abuse, general management of acute drug overdose, and other aspects of drug abuse are discussed elsewhere. A summary table to facilitate emergent management is provided (table 1).

(See "Cocaine use disorder in adults: Epidemiology, pharmacology, clinical manifestations, medical consequences, and diagnosis" and "Evaluation and management of the cardiovascular complications of cocaine abuse" and "Pulmonary complications of cocaine abuse" and "General approach to drug poisoning in adults".)

EPIDEMIOLOGY — Other than alcohol, cocaine is the most common cause of acute drug-related emergency department (ED) visits in the United States. It accounts for more reports to the Drug Abuse Warning Network (DAWN) than marijuana, synthetic marijuana, or hashish the next leading causes [1]. Death from unintentional cocaine overdose and cocaine-related violence occurs throughout the world [2-5].

PHARMACOLOGY — Cocaine is well-absorbed following contact with the oral, nasal, gastrointestinal, rectal, and vaginal mucosa, or via the pulmonary alveoli following inhalation. Cocaine’s vasoconstrictive properties prolong the rate of absorption and delay its peak effect when absorbed from mucosal surfaces. The bioavailability of cocaine is approximately 90 percent when smoked and about 80 percent after intranasal use. Bioavailability is decreased when cocaine is ingested, though this is not well studied [6].

The alkaloidal form of cocaine is extracted from the coca leaf by mechanical degradation in the presence of a hydrocarbon solvent. The resultant product is converted into a hydrochloride salt and extracted into an aqueous phase, from which water is subsequently evaporated to yield a white powder (cocaine hydrochloride).

Smokeable cocaine is formed by dissolving the hydrochloride form of cocaine in water and adding a strong base. A hydrocarbon solvent is then added, the cocaine base is extracted into the organic phase, and the solvent then evaporated. "Free-basing" is a term used to refer to smoking or inhaling cocaine base following extraction, and "crack" is an analogous compound used in solid form.

KINETICS — A table summarizing the time of onset, time to peak action, and duration of action for various routes of exposure is provided (table 2). These parameters were determined in volunteers with a history of cocaine use, by administering cocaine via the various routes and measuring serum levels [6].

- Metabolites – There are three major metabolites of cocaine: benzoylecgonine (BE) formed from spontaneous hydrolysis (>50 percent), ecgonine methyl ester (EME) formed from metabolism by plasma
A transesterification reaction between ethanol and cocaine produces a unique agent, benzoylmethylecgonine, also called cocaethylene or ethyl cocaine [12]. In healthy volunteers given cocaine and ethanol, cocaethylene accounted for up to 17 percent of the metabolites [13]. Cocaethylene has a long duration of action (up to 13 hours depending on the route of administration [14]), and like cocaine, is vasoconstrictive, cardiototoxic, dysrhythmogenic, and neurotoxic [15,16]. Cocaethylene is as potent as cocaine at inhibiting dopamine reuptake [17].

The serum concentration of cocaethylene varies by the route of administration of cocaine. Approximately 24 percent of cocaine is converted to cocaethylene when administration is intravenous, 18 percent when the drug is insufflated and 34 percent when cocaine is used orally. The physiologic effects of cocaethylene typically outlast the effects that would have been observed if cocaine alone was used by any of the common routes of administration [14].

Cocaine's volume of distribution is about 2.7 L/kg, and it is about 90 percent protein bound. It is unclear whether these values change in overdose states [6]. The serum half-life of cocaine is 0.5 to 1.5 hours. A minor amount is excreted unchanged in the urine [18]. BE and EME are excreted in the urine, and have serum half-lives of 5 to 8 hours and 3.5 to 6 hours, respectively [7].

PATHOPHYSIOLOGY — Cocaine's effects occur primarily via three mechanisms, which are discussed below.

- Blockade of reuptake of biogenic amines – Cocaine is an indirect sympathomimetic agent, which increases the availability of biogenic amines at adrenergic receptors by blocking their presynaptic reuptake. These effects are described in neurons containing serotonin and catecholamines (ie, dopamine, norepinephrine, and epinephrine) [19,20].

Cocaine stimulates alpha-1, alpha-2, beta-1, and beta-2 adrenergic receptors through increased levels of norepinephrine, and to a lesser extent epinephrine. Cocaine has preferential alpha-receptor activity on the cardiac and peripheral vasculature and additional cardiac effects through beta-adrenergic agonism. The alpha-adrenergic agonist effects of norepinephrine cause vasoconstriction in both cardiac and peripheral vasculature.

The euphoric properties of cocaine derive from the inhibition of neuronal serotonin reuptake in the CNS, while addiction has been linked to effects on dopamine reuptake. In animal studies, effects on the dopamine-containing neuronal systems traveling from the limbic region to the frontal cortex are strongly associated with cocaine addiction [21].

- Sodium (Na+) channel blockade – Cocaine slows or blocks nerve conduction and acts as a local anesthetic by altering the recovery of the neuronal Na+ channels. Local anesthetics block conduction by decreasing or preventing the large transient increase in the permeability of excitible membranes to Na+ that normally is produced by a slight depolarization of the membrane. Cocaine has similar effects on cardiac Na+ channels and is able to slow Na+ current in cardiac myocytes. With severe overdose, these cardiac Na+ channel effects manifest on an electrocardiogram as prolongation of the QRS complex, and clinically as negative inotropy.

- Excitatory amino acid stimulation – Cocaine increases the concentration of the excitatory amino acids glutamate and aspartate in the brain, particularly in the nucleus accumbens [22]. Glutamate is the main excitatory neurotransmitter of the central nervous system (CNS) [23]. Aspartate has similar actions, although its exact role as a neurotransmitter is not as well defined; it is only active at certain subtypes of glutamate receptors [24]. Aspartate also serves as a precursor for glutamate.

CLINICAL MANIFESTATIONS — Cocaine produces a dose-dependent increase in heart rate and blood pressure...
accompanied by increased arousal, improved performance on tasks of vigilance and alertness, and a sense of self-confidence, euphoria, and well-being. Use is typically followed by a craving for more of the drug. Cocaine produces end-organ toxicity in virtually every organ system in the body, primarily through its hemodynamic effects.

**Cardiovascular** — Acute cocaine use is associated with arterial vasoconstriction and enhanced thrombus formation [25-27]. It causes tachycardia, hypertension, increased myocardial oxygen demand, and increased vascular shearing forces. Cocaine causes coronary vasoconstriction in a dose-dependent fashion and is associated with cardiac ischemia in 5 to 6 percent of patients with cocaine-related visits to the emergency department [28]. At high blood concentrations, cocaine’s negative inotropic effects may cause acute depression of left ventricular function and heart failure [29]. Cocaine can cause supraventricular and ventricular dysrhythmias through direct actions at myocardial receptors or as a complication of myocardial ischemia. Aortic dissection and rupture occur rarely after cocaine use [30]. (See 'Pathophysiology' above.)

Chronic cocaine use can cause accelerated atherogenesis [31,32] and left ventricular hypertrophy, which increase the risk of myocardial ischemia or infarction, and can lead to dilated cardiomyopathy. (See "Evaluation and management of the cardiovascular complications of cocaine abuse".)

**Central nervous system** — Cocaine can cause a variety of central nervous system (CNS) complications including psychomotor agitation, seizures, coma, headache, intracranial hemorrhage, and focal neurologic symptoms [15]. Cocaine-induced psychomotor agitation can cause hyperthermia when peripheral vasoconstriction prevents the body from dissipating the heat being generated from persistent agitation. Mortality can be as high as 33 percent when hyperthermia develops in the setting of cocaine intoxication [33].

Psychomotor agitation occurs via several mechanisms. Cocaine causes an increase in the CNS excitatory amino acids glutamate and aspartate, and release of the excitatory neurotransmitters norepinephrine, serotonin, and dopamine. The hyperthermia seen in cocaine-intoxicated patients is directly related to the extent of their psychomotor agitation and the ambient temperature [33]. (See 'Pathophysiology' above.)

Seizures occur in approximately 3 to 4 percent of cocaine-related emergency department visits following acute or chronic use [29,34]. Seizures may occur after large doses in patients without an underlying seizure focus [29]. Headaches occur often and are likely due to neurotransmitter dysregulation or hemodynamic alterations [15].

Cocaine is associated with both focal neurologic deficits and coma. Possible etiologies include vasoconstriction (ie, transient ischemic attack or ischemic stroke) and intracerebral hemorrhage. Numerous reports describe patients with subarachnoid, intraventricular, and intraparenchymal bleeding associated with cocaine use [35-38]. Other neurologic complications, such as paralysis from vasospasm-induced anterior spinal cord syndrome, occur rarely [35].

**Pulmonary** — Crack cocaine requires high temperatures to be vaporized and smoked. Angioedema and pharyngeal burns can occur when crack is smoked. Injury to the upper and lower airway occurs primarily from inhalation of heated fumes and is not a direct toxic effect of the drug.

Intranasal and inhalational cocaine use is associated with pneumothorax, pneumomediastinum, and pneumopericardium [39-41]. These complications result from the Valsalva maneuver applied by the user to avoid exhaling the drug. (See "Pulmonary complications of cocaine abuse".)

Cocaine is associated with exacerbations of reversible airway disease and bronchospasm [42-44]. Crack lung can also cause shortness of breath. (See 'Crack lung' below.)

Cocaine use is associated with vasoconstriction [25], vasospasm, and enhanced thrombus formation [26]. This predisposes patients who use cocaine to pulmonary infarction. Patients with this complication usually present with shortness of breath and pleuritic chest pain, as well as the other findings that may be confused with pulmonary embolism [45,46]. It is not known whether the risk of pulmonary embolism is increased among cocaine abusers.

**Gastrointestinal and renal** — Cocaine users have a disproportionate incidence of perforated ulcers. Possible mechanisms include increased sympathetic tone causing increased gastric acid production or local ischemia in the gastrointestinal tract [47-49]. Cocaine is also implicated in cases of ischemic colitis, intestinal infarction, and
metabolic acidosis. Patients presenting with signs and symptoms of bowel obstruction may be engaged in body packing (see 'Body packers and stuffers' below) [15].

Although less common, splenic and renal infarction can occur from cocaine use [50,51]. In cocaine users, minor abnormalities of liver enzymes are common and rarely associated with symptoms [52]. More severe hepatic failure can be seen following hyperthermia due to psychomotor agitation. (See CNS manifestations above in this section).

Other organ systems

- Musculoskeletal – Patients with cocaine toxicity can present with a spectrum of musculoskeletal concerns. Signs can range from mild creatinine phosphokinase and myoglobin elevation to electrolyte alterations (hyperkalemia, hypocalcemia) seen with rhabdomyolysis. Patients can demonstrate a range of complications from localized or diffuse muscle pain to frank compartment syndrome [15,53]. Patients with severe rhabdomyolysis may have a lactic acidosis, life-threatening hyperkalemia, and renal failure (see "Clinical manifestations and diagnosis of rhabdomyolysis"). For treatment (see "Prevention and treatment of heme pigment-induced acute kidney injury (acute renal failure)"), section on 'Treatment').

- Ophthalmologic – Sympathetic stimulation causes mydriasis through activation of the dilator fibers of the iris. The pupil usually maintains its ability to constrict to light. Cocaine, like other mydriatic agents, can cause acute angle-closure glaucoma, and vasospasm of the retinal vessels can produce unilateral or bilateral vision loss [54,55]. Patients who smoke crack cocaine may develop mydriasis (unilateral or bilateral), suffer corneal epithelial destruction, or singe their eyebrows and lashes (madarosis) due to heat or direct topical effects [15,56].

- Pregnancy (pre and postnatal exposure) – Chronic cocaine use during pregnancy is associated with problems in fetal development [57]. Acute cocaine exposure in pregnancy is associated with abruptio placentae [58]. The effects of in-utero cocaine exposure are discussed more extensively elsewhere. (See "Overview of substance misuse in pregnant women", section on 'Cocaine' and "Infants of mothers with substance use disorder", section on 'Cocaine'.)

- Passive cocaine exposure – Children and elderly patients can present with signs and symptoms of cocaine intoxication and/or complications of cocaine exposure by proximity to users of inhalational cocaine. Cocaine exposure can also occur via ingestion of cocaine or crack, typically when cocaine is left within a child’s reach. The incidence of unintentional cocaine exposure may be as high as 5 percent among all children presenting to urban emergency departments [59]. (See 'Pediatric considerations' below.)

- Hematologic and other effects of adulterants – Levamisole, an immunomodulator, has been found in cocaine and can cause agranulocytosis, leukoencephalopathy, and cutaneous vasculitis, possible leading to cutaneous necrosis. Clenbuterol, another adulterant, can cause tachycardia, hyperglycemia, palpitations, and hypokalemia. (See 'Adulterants and their effects' below.)

ADULTERANTS AND THEIR EFFECTS

**Levamisole** — Levamisole is a common adulterant of cocaine that can cause agranulocytosis, leukoencephalopathy, or cutaneous vasculitis, possibly leading to cutaneous necrosis [60-66]. A review of published cases of levamisole-related toxicity noted that 52 percent of these patients presented with oropharyngeal complaints, while 27 percent presented with soft tissue infections or purpura [67]. Exposure to cocaine adulterated with levamisole should be suspected in patients with these entities or complaints. Levamisole was used as an adjuvant treatment for colon cancer and an immunomodulator for various conditions and is now used primarily in veterinary practice as an anthelmintic agent [68]. A small case series describes an association between levamisole and hyponatremia, but this phenomenon has yet to be formally studied [69].

The United States Drug Enforcement Agency first noted levamisole mixed with cocaine in 2003 and beginning in 2008 investigators in New Mexico reported that some patients who had been exposed to cocaine were developing agranulocytosis (confirmed by bone marrow histopathology). In 2008, levamisole was found in about 44 percent of seized cocaine, and by 2009, this amount rose to 69 to 73 percent [68]. In 2010, investigators in Colorado found that 78 percent of patients with a urine drug screen positive for cocaine also tested positive for levamisole [60]. In Europe as well, levamisole has been detected in the urine samples of patients testing positive for cocaine [70].
Clenbuterol — Clenbuterol, a beta adrenergic agonist, has been found as an adulterant in cocaine and heroin. It can cause hyperglycemia and hypokalemia.

In early 2005, cases were reported in the northeastern and southern United States describing a number of patients with atypical presentations following heroin or cocaine use [71]. The most common findings were tachycardia (89 percent), hyperglycemia (78 percent), palpitations (78 percent), and hypokalemia (78 percent). In one case series, 67 percent of the patients had all four findings. Other common findings included nausea, hypotension, chest pain, venous hyperoxia, lactic acidosis, agitation, and anxiety. Investigators attributed these symptoms to the heroin and cocaine supply being adulterated with clenbuterol.

Differential Diagnosis — Psychomotor agitation is a common, important feature of many overdose and disease states, including:

- Amphetamine abuse
- Phencyclidine abuse
- Hypoglycemia (see "Hypoglycemia in adults: Clinical manifestations, definition, and causes")
- Hypoxia (see "Oxygenation and mechanisms of hypoxemia")
- Alcohol and sedative-hypnotic withdrawal syndromes (see "Management of moderate and severe alcohol withdrawal syndromes")
- Serotonin syndrome (see "Serotonin syndrome (serotonin toxicity")
- Neuroleptic malignant syndrome (see "Neuroleptic malignant syndrome")
- Heat-related illness (see "Severe nonexertional hyperthermia (classic heat stroke) in adults")
- Thyroid storm (see "Thyroid storm")
- Subarachnoid hemorrhage (see "Treatment of aneurysmal subarachnoid hemorrhage")
- Infections of the central nervous system (ie, meningitis and encephalitis) (see "Clinical features and diagnosis of acute bacterial meningitis in adults")
- Seizures (see "Overview of the management of epilepsy in adults").
- Several psychiatric diseases

The majority of these diagnoses are determined from the patient's medical history. A review of the patient's medications and a detailed account of their substance abuse preferences through family, friends, and first-responders, may provide valuable clues. Diagnostic testing may include CT scan of the head and lumbar puncture as appropriate. We discourage indiscriminate drug testing as a means to differentiate diagnostic possibilities because of the high rate of false positive results. (See "General approach to drug poisoning in adults".)

Other diagnostic possibilities include cardiopulmonary disease, such as acute coronary syndrome, pulmonary embolus, aortic dissection, and pneumothorax. These diagnoses are generally identified through standard tests such as an electrocardiogram, chest radiograph, echocardiography, chest CT, or cardiac biomarkers. (See "Initial evaluation and management of suspected acute coronary syndrome (myocardial infarction, unstable angina) in the emergency department" and "Overview of acute pulmonary embolism in adults" and "Clinical features and diagnosis of acute aortic dissection" and "Primary spontaneous pneumothorax in adults".)

In most situations, general supportive care with sedation, cooling, and intravenous fluids is appropriate while diagnostic testing is performed.

Laboratory and Radiographic Evaluation

- General testing – Routine laboratory evaluation in the potentially poisoned patient should include the following:
  - Fingerstick glucose, to rule out hypoglycemia as the cause of any alteration in mental status
  - Acetaminophen and salicylate levels, to rule out these common coingestions
  - Electrocardiogram, to rule out conduction system poisoning by drugs that effect the QRS or QTc intervals
  - Pregnancy test in women of childbearing age
- Specific testing – Benzoylcegonine (BE), the major urinary metabolite of cocaine, is the analyte usually tested
Radiographs can play a role in the detection of body stuffing and packing. (See 'Body packers and stuffers' below.)

Additional laboratory and radiographic testing can be helpful depending on the clinical setting. As examples, a troponin, creatine kinase, electrocardiogram, and chest radiograph are obtained in a patient with chest pain, creatine kinase and urine myoglobin are obtained in a patient at risk for rhabdomyolysis, and a CT of the head, followed by cerebrospinal fluid analysis if the CT is nondiagnostic, is obtained in a patient with symptoms concerning for intracranial hemorrhage.

INITIAL MANAGEMENT — General management of the overdose patient is discussed elsewhere (see "General approach to drug poisoning in adults"). Specific management strategies for cocaine overdose are discussed below. A summary table to facilitate emergent management is provided (table 1). The management of myocardial infarction diagnosed in the setting of cocaine intoxication is reviewed elsewhere. (See "Evaluation and management of the cardiovascular complications of cocaine abuse").

Airway and breathing — Supplemental oxygen should be administered as needed. If rapid sequence tracheal intubation is necessary, we suggest that succinylcholine not be used. Plasma cholinesterase (PChE) metabolizes both succinylcholine and cocaine, and coadministration of succinylcholine can prolong the effects of cocaine and the paralysis from succinylcholine [15]. In the setting of rhabdomyolysis and hyperthermia, succinylcholine may worsen hyperkalemia and cause life-threatening arrhythmias [15]. We suggest using a nondepolarizing neuromuscular blocker, such as rocuronium, if paralysis is indicated. Acceptable induction agents in cocaine-intoxicated patients include: benzodiazepines, etomidate, or propofol. (See "Rapid sequence intubation for adults outside the operating room" and "Rapid sequence intubation (RSI) in children").

Cardiovascular complications — Since most cardiovascular stimulation from cocaine is centrally mediated via the sympathetic nervous system, sedation with a benzodiazepine, using an appropriate dose and route of administration, is generally sufficient to alleviate cardiovascular symptoms. Benzodiazepine dosing for psychomotor agitation is described below. (See 'Psychomotor agitation' below.) In patients with severe, refractory, or symptomatic cocaine-induced hypertension, phentolamine can be used to counteract the alpha-adrenergic effects of cocaine (caused by norepinephrine release). Phentolamine is given as an intravenous bolus. The usual dose is 5 to 10 mg every 5 to 15 minutes as necessary. Chest pain associated with acute cocaine intoxication is discussed below. (See 'Chest pain' below.)

We recommend that beta-adrenergic antagonists (ie, beta blockers) not be used in the treatment of cocaine-related cardiovascular complications because they may create unopposed alpha-adrenergic stimulation and are associated with coronary vasoconstriction and end-organ ischemia [25,72]. This proscription includes labetalol, which has predominantly beta-blocking effects. In the rare circumstance when beta blockers must be used, their administration should be preceded by that of phentolamine to prevent unopposed alpha-adrenergic stimulation. The use of beta blockers is discussed further below. (See 'Use of beta blockers' below.)

Hypertensive emergencies can be seen in the setting of acute cocaine intoxication and are usually defined as an elevated blood pressure associated with end-organ damage. There are no treatment goals specifically defined for cocaine-related hypertensive emergencies, but the initial aim of treatment in general hypertensive crises is to rapidly
lower the diastolic pressure to about 100 to 105 mmHg; this goal should be achieved within two to six hours, with the maximum initial fall in mean arterial blood pressure not exceeding 25 percent of the presenting value. Cocaine-related hypertension should be treated judiciously given its usually self-limited nature (hypertension generally resolves when cocaine is metabolized) and the importance of avoiding hypotension. Treatment with benzodiazepines, and possibly phentolamine, as described above, is sufficient in most cases. Hypertensive emergencies are discussed separately. (See "Moderate to severe hypertensive retinopathy and hypertensive encephalopathy in adults", section on 'Goal of therapy' and "Evaluation and treatment of hypertensive emergencies in adults").

If a patient no longer appears acutely agitated and other signs of sympathetic excess (e.g., tachycardia, diaphoresis) have resolved but significant hypertension persists, acute cocaine exposure is unlikely to be the cause. In such cases, hypertension should be managed based upon the patient's medical comorbidities and clinical status.

Cocaine toxicity usually causes hypertension, but massive toxicity may result in hypotension due to sodium-channel blockade, cardiac dysrhythmias, or cardiac ischemia. Patients with hypotension are treated with intravenous isotonic saline. If hypotension persists after 2 to 3 L of rapidly infused isotonic saline, direct-acting vasopressors such as norepinephrine or phenylephrine can be given and titrated to effect. An electrocardiogram (ECG) should be obtained, and if there are signs of QRS widening (suggesting sodium channel blockade), hypertonic sodium bicarbonate should be administered at a dose of 1 to 2 mEq/kg by bolus via a large bore IV. A repeat ECG should be obtained to evaluate whether QRS narrowing has occurred in response to treatment. (See "Tricyclic antidepressant poisoning", section on 'Sodium bicarbonate for cardiac toxicity'.)

Management of patients suspected to be body packers or stuffers is discussed briefly below and in detail elsewhere. (See 'Body packers and stuffers' below and "Internal concealment of drugs of abuse (body packing)").

**Use of beta blockers** — The use of beta-adrenergic antagonists (i.e., beta blockers) to treat cocaine-related cardiovascular complications is controversial, but we recommend that they **NOT** be used. Although early reports suggested that beta blockade of cocaine-intoxicated patients was beneficial [73, 74], further work has led many to question the safety and efficacy of this practice. We believe that optimal therapy for patients experiencing cardiovascular complications in the setting of acute cocaine intoxication begins with reduction in central nervous system catecholamine release rather than peripheral antagonism of released catecholamines, and that benzodiazepines have a proven role in this regard [75, 76]. (See 'Psychomotor agitation' below.)

In cases of potential myocardial ischemia, the balance between myocardial oxygen demand and delivery is tenuous. Some conceive of this balance in terms of the patient's blood pressure, which reflects myocardial oxygen demand, and blood flow through the coronary arteries, which determines oxygen supply. Since beta blockers exert unpredictable effects on both of these measures, their primary use, certainly before adequate sedation, cannot be recommended.

In humans given cocaine while undergoing cardiac catheterization, the non-selective beta blocker propranolol worsened cocaine-associated coronary-artery vasoconstriction and did not improve cocaine-induced hypertension [77]. The beta 1-selective antagonists esmolol and metoprolol have been associated with paradoxical hypertension [78] and abrupt deterioration [79], respectively, soon after administration. In another human cardiac catheterization study, the mixed alpha-beta antagonist labetalol did not reverse cocaine-associated coronary artery vasoconstriction, although it did lower blood pressure [80]. Of note, the alpha-blocking effect of labetalol is minor compared to its beta-blocking effect (alpha:beta antagonism ratio 1:7) [81].

The above data emphasizes the risks associated with beta blockade in the absence of adequate alpha blockade. Beta blockers are associated with coronary artery and peripheral vasoconstriction, likely caused by a reduction in beta-2 mediated vasodilation; alpha adrenergic antagonism with phentolamine can prevent this [25, 82].

Several reports have suggested an adequate safety profile and/or improved outcomes with the use of beta-blockade in the setting of cocaine-associated chest pain [83-86]. However, these studies suffer from significant methodological shortcomings, including retrospective design, lack of evidence of clinical intoxication at the time of beta blocker administration, potential selection bias of patients receiving beta blockers, and asymmetrical use of ancillary medications (such as nitroglycerin and aspirin) between groups [87-91]. Conversely, another report has suggested an increased risk of harm with beta blockade in the setting of cocaine use [92], although that report is similarly...
In summary, human studies document that administration of beta blockers worsens or does not change cocaine-induced coronary artery vasoconstriction, has been associated with poor outcomes in case reports, and lacks methodologically sound evidence in support of its safety or efficacy. For these reasons, we believe that cocaine-related cardiovascular complications should initially be managed using alternative pharmacological agents such as benzodiazepines, and that beta blockade should be performed cautiously (if at all), generally in combination with alpha antagonists, and under close observation.

**Psychomotor agitation** — Agitated patients are sedated as needed with benzodiazepines, after ensuring they are not hypoglycemic or hypoxic. We suggest diazepam be given in an initial dose of 10 mg IV, then 5 to 10 mg IV every three to five minutes until agitation is controlled. Monitor patients for respiratory depression and hypotension. Intramuscular lorazepam can be used if IV access is unavailable, but its peak effect is typically delayed (10 to 20 minutes).

Hyperthermic patients should be cooled rapidly, optimally in 30 minutes or less, to a goal core body temperature of <102°F. Immersion in ice or ice water is the most rapid cooling method for severely hyperthermic patients; cooling via evaporative spray may be sufficient in moderately hyperthermic patients [93-95]. (See "Severe nonexertional hyperthermia (classic heat stroke) in adults").

**Gastrointestinal decontamination** — Since the popular methods of cocaine use are nonenteral (ie, inhalational, intravenous, and intranasal), the majority of patients who present with cocaine intoxication will not require gastrointestinal decontamination [34]. Decontamination should be performed, if required, by removing any cocaine powder from nares, mouth, or oropharynx. Gentle nasal irrigation with 0.9 percent (isotonic) saline could be used if the patient presents with a visible white powder presumed to be cocaine [18]. Activated charcoal reduces the lethality of oral cocaine [96]. The dose of activated charcoal is 1 g per kg body weight (up to 50 g), and should be administered by mouth every four hours for several doses. Body packing and stuffing is discussed elsewhere. (See "Internal concealment of drugs of abuse (body packing)").

**SPECIFIC SYNDROMES**

**Chest pain** — Cocaine-associated chest pain (CACP) accounts for approximately 40 percent of all cocaine-related visits to the emergency department (ED) [34]. Acutely, cocaine causes vasoconstriction and enhances thrombus formation, increasing the risk of myocardial ischemia [25,26]. Approximately 6 percent of patients presenting with CACP manifest elevations in biomarkers consistent with myocardial injury [28,97]. The management of myocardial infarction diagnosed in the setting of cocaine intoxication is reviewed separately. (See "Evaluation and management of the cardiovascular complications of cocaine abuse").

Although acute coronary syndrome remains an important concern, ED clinicians should avoid prematurely discounting alternative diagnoses in patients with CACP but no clear evidence of myocardial infarction. Pneumothorax and crack lung can also present as chest pain following cocaine abuse. (See 'Crack lung' below.)

According to one retrospective cohort study, patients with CACP most commonly complain of: substernal chest pain (76 percent), shortness of breath (62 percent), tightness/pressure/squeezing (55 percent), and diaphoresis (48 percent) [97].

Evaluation of patients with suspected CACP pain includes an ECG, chest radiograph, and biomarkers to exclude myocardial infarction. Two prospective observational studies suggest the ECG has limited accuracy in the setting of CACP, and ECG evidence of ischemia or infarction may not correlate with myocardial infarction, as diagnosed by an elevation in cardiac biomarkers [28,98]. According to these studies, the sensitivity and specificity of the ECG are approximately 36 and 90 percent respectively. However, the number of patients diagnosed with myocardial infarction in each study was small so the accuracy of the ECG in CACP remains unclear.

Early management of patients with CACP includes the administration of oxygen and reduction of sympathetic outflow using benzodiazepines given intravenously (IV). We suggest benzodiazepines be given to patients who are anxious, agitated, hypertensive, or tachycardic; we suggest nitroglycerin be given in addition to patients with hypertension. We give diazepam (5 mg IV every three to five minutes) or lorazepam (1 mg IV every 5 to 10 minutes) until sedation is achieved. We give nitroglycerin 0.4 mg sublingual every five minutes as needed for a maximum of three doses. If
additional nitroglycerin is needed, an infusion can be started with the dose titrated to effect.

No study has clearly demonstrated whether benzodiazepines or nitrates are more efficacious in the management of CACP [75,76]. In one prospective controlled trial, 12 patients with CACP randomly assigned to receive sublingual nitroglycerin (NTG) and lorazepam had significantly more rapid and more complete relief of pain than the 15 patients assigned to treatment with NTG alone [75].

The pharmacologic treatment of patients with CACP differs in several important ways from the standard treatment of myocardial ischemia from atherosclerotic coronary artery disease. Beta blockers are contraindicated in patients who have recently used cocaine (<24 hours), and in patients with CACP. Beta blockers may lead to unopposed alpha adrenergic stimulation which can cause coronary arterial vasoconstriction, ischemia, and infarction [77,80,87]. This proscription includes labetalol, which has predominantly beta-blocking effects.

Studies that advocate administration of beta-blockers to patients with CACP have predominantly been retrospective and unable to characterize when patients used cocaine [83,87,88,99]. Since the urine drug screen (testing for the cocaine metabolite benzoylecgonine (BE)) can be positive many days after cocaine was last used, it is likely that there is a period after which the use of beta-blockers is safe despite a positive immunoassay. However, in a patient presenting acutely with chest pain after cocaine use, the use of beta-blockers remains contraindicated. This approach is consistent with guidelines for the management of CACP promulgated by the American Heart Association [100].

Aspirin is contraindicated in patients suspected of having an aortic dissection, but can be given at standard doses to patients with CACP when myocardial ischemia is the suspected cause.

Phentolamine, an alpha-adrenergic antagonist, can be used to reduce cocaine-induced coronary artery vasoconstriction when managing CACP or hypertension that is unresponsive to benzodiazepines [25,72,101,102]. Phentolamine is given as an IV bolus of 1 to 2.5 mg every 5 to 15 minutes as necessary. In one prospective observational study, adult patients with no history of cocaine use were given a low dose (2 mg/kg) of intranasal cocaine while undergoing cardiac catheterization [25]. Cocaine caused an increase in heart rate, blood pressure, and coronary vascular resistance, and narrowing of the coronary artery diameter by 13 percent. Coronary artery diameter returned to baseline with the administration of phentolamine.

Crack lung — Crack lung is a syndrome of hemorrhagic alveolitis from inhalational cocaine use [103]. Cough and shortness of breath are common presenting symptoms. Additional signs and symptoms may include: acute lung injury, hypoxia, chest pain, hemoptysis, fever, focal infiltrates, and bronchospasm [42]. A chest radiograph and a history of cocaine use provide the basis for diagnosis. Patients may have an eosinophilia, which suggests an immune-mediated component [104].

Management includes maintenance of oxygenation, ventilation, and symptomatic care. Patients with airway compromise may require endotracheal intubation. Succinylcholine should not be used. (See 'Airway and breathing' above.)

Body packers and stuffers — Body packers have been called swallowers, internal carriers, couriers, or mules [105]. The term body packer is used to refer to persons who swallow large quantities of prepackaged drugs with the intention of smuggling these drugs across international borders. Body stuffers are persons who swallow relatively small quantities of drugs in poorly constructed packets (usually in haste) to avoid repercussions from law enforcement agents [105,106].

Body stuffers with symptoms of cocaine overdose (eg, tachycardia, hypertension, hyperthermia, agitation, seizures, or cardiac dysrhythmias) are treated in standard fashion. Management begins with stabilization of the airway, breathing, and circulation, and continues with gastrointestinal decontamination with either activated charcoal, whole bowel irrigation, or both. Presentation and management of body packers and stuffers is discussed in detail elsewhere. (See "Internal concealment of drugs of abuse (body packing)".)

Gastrointestinal decontamination is generally performed in patients suspected of body packing, body stuffers with a concerning ingestion, or symptomatic body stuffers, unless they are being prepared for surgery [105]. Activated charcoal reduces the lethality of oral cocaine [96]. The dose of activated charcoal is 1 g per kg body weight (up to 50 g), and should be administered by mouth every four hours for several doses. Whole bowel irrigation (WBI) with
polyethylene glycol-electrolyte lavage solution is recommended in body packers for gentle evacuation of the gastrointestinal tract. WBI is given (usually via a nasogastric tube) at a rate of 2 L per hour in adults until the gastrointestinal tract is clear. Use of oil-based laxatives is not recommended because they reduce the tensile strength of packets [105].

The majority of the patients who sustain adverse outcomes has symptoms at presentation or within the first few hours [106,107]. The most common issues include: cocaine-induced toxic effects, intestinal obstruction, and medical assessment following arrest. Symptomatic cocaine body packers usually require surgical intervention for immediate removal of the packets. Patients are also treated with benzodiazepines for agitation and seizures, sodium bicarbonate and lidocaine for ventricular dysrhythmias, and phentolamine or sodium nitroprusside for severe hypertension [105].

PEDIATRIC CONSIDERATIONS

Presentation — Children can present with signs and symptoms of cocaine intoxication or complications of cocaine exposure from being around adults who use cocaine [59,108-110]. Unintentional cocaine exposure in children may occur from passive inhalation of free-base cocaine vapors or ingestion. The incidence of unintentional cocaine exposure among all children treated in the emergency department may be as high as 6 percent, particularly in urban settings [59,108,110].

Observational data suggests that passive exposure to cocaine may manifest as more frequent respiratory symptoms in infants, with and without fever [108], and more frequent generalized and focal seizures in children below eight years [109]. Clinical findings in older children are similar to adults.

Fetal exposure to cocaine is discussed elsewhere. (See "Infants of mothers with substance use disorder", section on 'Cocaine' and "Overview of substance misuse in pregnant women", section on 'Cocaine'.)

Specific management — There are no special decontamination procedures in children who are exposed to cocaine. Management of children exposed to crack cocaine fumes or cocaine residue is symptomatic. In rare circumstances, children have been used to smuggle drugs from foreign countries by making them swallow packets of cocaine. (See 'Body packers and stuffers' above.)

Cocaine-exposed children may need to be admitted to the hospital. Social work and/or child protective services must be notified. The involvement of local law enforcement authorities follows local practices.

Decontamination — For those patients requiring decontamination, dosing is provided.

Pediatric doses

- Activated Charcoal (AC) – 0.5 to 1 g/kg of body weight with cathartic, for the initial dose.
- Multidose Activated Charcoal (MDAC) – 0.25 to 0.5 g/kg q 2 to 4 hours for 12 hours, without a cathartic.
- Whole Bowel Irrigation (WBI) – 0.25 mL/kg per hour. Administer orally or via nasogastric tube. Administer for four to six hours or until rectal effluent is clear. Children may tolerate polyethylene glycol (NuLYTLELY) better than other irrigation fluids because it contains 50 percent less total salt and may cause fewer electrolyte abnormalities.

DISPOSITION — Patients with severe complications of cocaine abuse are managed as described above and admitted to the hospital at the appropriate level of care. (See 'Initial management' above.)

In general, patients who present with acute symptoms from cocaine toxicity that resolve are observed for six to eight hours. Patients who have returned to their baseline level of function can generally be discharged after this period with appropriate referrals.

Patients who present with cocaine-associated chest pain (CACP) are observed for 8 to 12 hours while two sets of cardiac biomarkers and repeat electrocardiograms (ECG) are obtained. This assumes the patient is pain-free, or rapidly made pain-free, and has a normal initial ECG. Cardiac biomarkers are typically performed 8 to 12 hours apart. Although this is not the standard approach to the management of patients with suspected acute coronary syndromes (ACS) unrelated to cocaine, the incidence of myocardial infarction in patients with CACP is extremely low.
For patients with CACP at low risk for ACS, observation in a chest pain unit is reasonable. The results of an observational study of 59 patients with CACP at low risk for ACS suggest that such patients can be discharged safely after nonischemic ECGs, normal cardiac biomarkers, and a negative coronary computerized tomography angiography (CTA) study. However, further research is needed before such an approach can be recommended.

Patients in whom cocaine use is not the sole risk factor for ACS or who have a moderate or high TIMI risk score should be evaluated like any patient presenting to the emergency department with a possible ACS. (See "Initial evaluation and management of suspected acute coronary syndrome (myocardial infarction, unstable angina) in the emergency department".)

Patients who present with psychomotor agitation, hyperthermia, or other neurological complications of cocaine toxicity may require admission for monitoring and management of sequelae. If after six to eight hours of observation their symptoms are completely resolved, they are awake, alert, and ambulate without difficulty, and their reexamination reveals no concerning findings, they may discharged.

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

Assessment

- Cocaine produces end-organ toxicity in virtually every organ system in the body, primarily through its hemodynamic effects. Among its more important effects are hypertension, arterial vasoconstriction (eg, coronary arteries), thrombus formation, psychomotor agitation (neurologic effects can range from agitation to seizures to intracranial hemorrhage), severe hyperthermia, dyspnea (from pneumothorax, pulmonary infarction, or other pulmonary injury), and ischemic bowel. (See 'Clinical manifestations' above.)

- Numerous drugs and disease states can mimic the cardiovascular effects and/or psychomotor agitation of acute cocaine overdose. A discussion of these is provided. A thorough history, including medications and preferred drugs of abuse, is often the key to diagnosis. (See 'Differential diagnosis' above.)

- Benzoylecgonine (BE), the major urinary metabolite of cocaine, is the analyte usually tested for. Cocaine is rapidly metabolized and detectable in blood and urine only briefly (ie, several hours) after use. BE can be detected in the urine for several days following intermittent use and up to 10 days or more after heavy use. Therefore, a drug assay "positive for cocaine" does not necessarily connote acute cocaine use. Additional testing is performed based on clinical circumstances. (See 'Laboratory and radiographic evaluation' above.)

Management

- A detailed approach to management is provided above. A summary table to facilitate emergent management is provided (table 1). If rapid sequence tracheal intubation (RSI) is necessary, we suggest that succinylcholine not be used because it can prolong the effects of cocaine and cause other complications (Grade 2C). A nondepolarizing neuromuscular blocker, such as rocuronium, may be used if RSI is necessary. Acceptable induction agents include: benzodiazepines, etomidate, or propofol. (See 'Airway and breathing' above.)

- Most cardiovascular stimulation from cocaine is centrally mediated via the sympathetic nervous system. We suggest initial treatment with a benzodiazepine, using an appropriate dose and route to alleviate cardiovascular symptoms (Grade 2C). Suitable dosing is described above (see 'Psychomotor agitation' above). In patients with severe, refractory, or symptomatic cocaine-induced hypertension, we suggest phentolamine be used to counteract the alpha-adrenergic effects of cocaine (Grade 2C). Phentolamine is given as an intravenous bolus.
The usual dose is 5 to 10 mg every 5 to 15 minutes as necessary. We recommend that beta blockers, including labetalol, NOT be used in patients with acute cocaine toxicity because of the risk of cardiovascular complications from unopposed alpha-adrenergic stimulation (Grade 1C). (See 'Cardiovascular complications' above.)

- It is important to rule out hypoglycemia and hypoxia as the causes of psychomotor agitation. For cocaine-induced agitation, we suggest treatment with benzodiazepines (eg, diazepam 5 to 10 mg IV every three to five minutes until agitation is controlled) (Grade 2C). (See 'Psychomotor agitation' above.)

- Although chest pain is a common presentation of acute cocaine intoxication, myocardial infarction is uncommon. Early management of cocaine-associated chest pain includes the administration of oxygen and reduction of sympathetic outflow using benzodiazepines. We suggest benzodiazepines be given to patients who are anxious, agitated, hypertensive, or tachycardic (Grade 2C). We give diazepam 5 mg every 3 to 5 minutes or lorazepam 1 mg every 5 to 10 minutes as an intravenous dose until sedation is achieved. We suggest nitroglycerin be given in addition to patients with hypertension (Grade 2C). Beta blockers are contraindicated. (See 'Cardiovascular complications' above and 'Use of beta blockers' above and 'Chest pain' above.)

- Crack lung is a syndrome of hemorrhagic alveolitis from inhalational cocaine use. Cough and shortness of breath are common presenting symptoms. Patients with airway compromise may require tracheal intubation. (See 'Crack lung' above.)

- Passive exposure to cocaine may cause more frequent respiratory symptoms in infants, with and without fever, and more frequent generalized and focal seizures in children below eight years. Clinical findings in older children are similar to adults. There are no special decontamination procedures in children who are exposed to cocaine. Fetal exposure to cocaine is discussed separately. (See 'Pediatric considerations' above and "Infants of mothers with substance use disorder", section on 'Cocaine'.)

- Disposition strategies are discussed above. Body packers and stuffers are discussed briefly above and in detail separately. (See 'Disposition' above and "Internal concealment of drugs of abuse (body packing)".)

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12. Bourland JA, Martin DK, Mayersohn M. In vitro transesterification of cocaethylene (ethylcocaine) in the


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