Cocaine use disorder: Epidemiology, clinical features, and diagnosis

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INTRODUCTION

Cocaine is a tropane ester alkaloid found in leaves of the *Erythroxylum coca* plant, a bush that grows in the Andes Mountains region of South America [1]. Cocaine use can lead to addiction and adverse physical effects, such as stroke and cardiac arrest.

Cocaine is classified as a Schedule II medication under the Controlled Substances Act in the United States. Cocaine hydrochloride is still legally available in the United States as a 4 or 10 percent solution for use as a local or topical anesthetic, principally in ear, nose, and throat surgery. Cocaine has now largely been replaced in clinical practice by synthetic local anesthetics that are considered safer and have less misuse potential [2].

Common street names used in the United States for cocaine are shown in a table (table 1).

This topic addresses the epidemiology, pharmacology, clinical effects, and diagnosis of cocaine use disorder in adults. Acute intoxication from cocaine use, specific cardiovascular and pulmonary complications related to cocaine, and treatment of stimulant use disorder are discussed separately.

- (See "Cocaine: Acute intoxication".)
- (See "Pulmonary complications of cocaine use".)

- (See "Clinical manifestations, diagnosis, and management of the cardiovascular complications of cocaine abuse".)
- (See "Stimulant use disorder: Treatment overview".)
- (See "Stimulant use disorder: Psychosocial management".)

EPIDEMIOLOGY

Cocaine use

- **Prevalence** – In an annual world drug report, cocaine is estimated to have been used by approximately 20 million (95% CI 16.6-24.6 million) people worldwide, or approximately 0.4 percent (95% CI 0.33-0.49) of the global population age 15 to 64 years [3].

  Use is most prevalent in North and South America, Western and Central Europe, and Oceania [4,5]. Use is least prevalent in Africa, Asia, and Eastern and Southeastern Europe [3]. This pattern may be due to supply factors; cocaine is sourced only from South America. Alternative synthetic stimulants such as amphetamines or synthetic cathinones ("bath salts") may be more readily available elsewhere [6]. (See "Stimulant use disorder: Treatment overview".)

  A United States population-based, nationally representative survey of community-dwelling individuals age 12 years or older (National Survey on Drug Use and Health [NSDUH]) estimated that 5.5 million individuals were current (past-year) cocaine users (2 percent of that age group), of whom 14 percent smoked cocaine ("crack") [4]. The survey estimated that the mean age of first cocaine use was 22.6 years.

- **Patterns of use** – The vast majority of individuals use cocaine infrequently and in small amounts. As an example, a nationally representative, population-based, cross-sectional survey of 36,309 noninstitutionalized United States adults (National Epidemiologic Survey on Alcohol and Related Conditions-III) identified 3543 respondents who reported lifetime cocaine use [7]. The following frequencies were identified:

  - 73 percent were low-frequency, low-quantity users, averaging use 0.4 days per week, 0.8 grams per day
  - 18 percent used daily (6.6 days per week) in moderate amounts (2.6 grams per day)
  - 8 percent used moderately: 3.5 days per week and 1.8 grams per day
  - 1 percent used frequently (5.6 days per week) and heavily (19 grams per day)

- **Risk factors** – In a population-based registry study of 1196 male-male monozygotic and dizygotic twin pairs, 56 percent of the variance in liability to lifetime cocaine use was due to genetic factors, 14 percent to shared environmental factors, and 29 percent to unique environmental factors [8].

  Familial, sociodemographic, and psychiatric factors have the strongest influence on initiation of cocaine use [9]. As examples:

  - Sex – Male versus female sex (adjusted hazard ratio 1.17, 95% CI 1.05-1.32).
  - Single marital status – Never married (adjusted hazard ratio 2.20, 95% CI 1.87-2.60) or previously married (adjusted hazard ratio 2.45, 95% CI 2-3) compared with married status.
  - Tobacco use (adjusted hazard ratio 1.36, 95% CI 1.19-1.55).
  - Alcohol use (adjusted hazard ratio 1.84, 95% CI 1.55-2.19).
  - Antisocial or borderline personality disorder (adjusted hazard ratio 1.48, 95% CI 1.29-1.70).
  - Cannabis use (adjusted odds ratio 4.22, 95% CI 2.40-7.44) [10].
  - Adolescent exposure to stimulants – Cocaine use or prescription stimulant misuse by age 18 years, but not a prior history of prescription stimulant use as prescribed for attention deficit hyperactivity disorder (ADHD), is associated with onset of cocaine or methamphetamine use during young adulthood (age 19 to 24 years) [10].

    A six-year prospective longitudinal survey including 5034 12^{th} grade students (55.3 percent retention rate) reported, use of cocaine or prescription stimulant misuse during adolescence was associated with increased odds, compared with adolescents who never misused prescription stimulants, of initiating or using cocaine during early adulthood (age 19 to 24 years). After controlling for personal and parental sociodemographic variables and cigarette, alcohol, cannabis, stimulant use, and prescription opioid misuse at baseline, adjusted odds ratio were 2.23 (95% CI 1.31-3.81) for cocaine use and 2.59 (1.51-4.46) for prescription stimulant misuse [10].

    Prescription stimulant use as treatment for ADHD, whether associated with prescription stimulant misuse, was not associated with increased odds. The greater the frequency of lifetime prescription stimulant misuse the greater the prevalence of cocaine or methamphetamine use, ranging from 17.7 percent (11.1 to 26.8 percent)

with one to two occurrences to 34.1 percent (24.7 to 44.8 percent) with 10 or more occurrences.

These findings suggest that screening and monitoring adolescents for prescription stimulant misuse is warranted to prevent future cocaine use.

Cocaine use disorder

- **Prevalence** – The Global Burden of Disease Project, using data from 195 countries, has previously estimated that 5.8 million individuals 15 to 64 years old had a cocaine use disorder. This represented an age-standardized prevalence of 77.6 (95% UI 70.7-85.9) per 100,000 people [11].

  The United States NSDUH estimated that 1 million community-dwelling individuals 12 years or older had a cocaine use disorder (approximate American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision [DSM-5-TR] criteria). This corresponds to 18 percent of the estimated current cocaine users [4].

- **Risk factors** – Individuals who use cocaine are at a high risk for developing a cocaine use disorder. In a national cross-sectional survey, 46 percent (95% CI 14.2-17.9) of respondents with lifetime cocaine use also had a lifetime cocaine use disorder [12], while 16 percent (95% CI 14.2-17.9) had lifetime moderate-severe cocaine use disorder [13].

  The following factors are associated with the development of cocaine use disorder:

  - **Frequency and quantity of use** – Higher quantity and frequency of cocaine use increase the risk of cocaine use disorder compared with low-intensity use.

    According to a national cross-sectional survey those who used cocaine more frequently had an increased odds of developing cocaine use disorder [7].

    - Three to 12 times per year (odds ratio 2.65, 95% CI 1.35-5.17)
    - Daily or near daily (odds ratio 12.09, 95% CI 6.33-23.07)

    The survey also found that the odds of developing cocaine use disorder increased in those who used more than 0.3 grams/day:

    - Up to 0.9 grams per day (odds ratio 1.97, 95% CI 1.10-3.53)
    - Up to 2 grams per day (odds ratio 2.69, 95% CI 1.5-4.83)
    - Over 2 grams per day (odds ratio 4.84, 95% CI 2.55-9.18)

Frequency and quantity of cocaine use had an additive influence on risk of cocaine use disorder. Among individuals with low quantity and frequency of cocaine use, 4 percent developed a cocaine use disorder; among those with high quantity and frequency of cocaine use, 43 percent developed a cocaine use disorder.

- **Route of administration** – Individuals smoking cocaine have significantly higher risk of developing a cocaine use disorder than those using cocaine intranasally or orally. In one cross-sectional survey, individuals smoking cocaine had a greater risk of developing cocaine use disorder than those using by injection, intranasally, or orally, after controlling for quantity and frequency of use (odds ratio 1.37, 95% CI 1.03-1.83) [7]. Individuals who smoke cocaine may also be at particularly high risk of a more severe cocaine use disorder [14].

  The greater abuse potential of smoked cocaine is attributed to the faster rate of drug delivery to the brain (within 10 seconds) and faster onset of psychological effects [15,16]. This is associated with a more intense pleasurable response (the so-called "rate hypothesis" of psychoactive drug action) [17].

  Oral use of the coca leaf is rarely associated with cocaine use disorder [18].

- **Childhood experience** – Adverse childhood experiences and childhood ADHD are associated with developing cocaine use disorder in later life.

  - **Adverse childhood experiences** – Individuals experiencing two to three adverse childhood experiences are more likely than those with no adverse childhood experiences to have lifetime cocaine use disorder (odds ratio 1.40, 95% CI 1.11-1.77). Individuals experiencing at least four different types of adverse childhood experiences are more likely than those with no adverse childhood experiences to have lifetime cocaine use disorder as adults (1.98, 95% CI 1.53-2.57) [19].

  - **ADHD** – Having ADHD as a child significantly increases the risk of developing cocaine use disorder in late adolescence or adulthood (odds ratio 2.05, 95% CI 1.38-3.04) [20].

- **Genetic influence** – Heritability of developing cocaine use disorder ranges from 65 to 79 percent [21]. There is no clear pattern of Mendelian transmission, suggesting that multiple genes are involved. While several promising candidate genes have been identified, no specific gene or allele has been clearly linked with cocaine use or use disorder [21].

In a population-based registry study of 1196 male-male monozygotic and dizygotic twin pairs the proportions for liability to lifetime cocaine use disorder were 63 percent due to genetic factors, 0 percent attributed to shared environmental factors, and 37 percent to unique environmental factors [8].

Morbidity and mortality — Cocaine use and use disorder represent a significant health burden. The Global Burden of Disease Project estimated that cocaine use disorder was associated with an estimated 3300 deaths, a rate of 0.8 per 100,000, and 2.6 million disability-adjusted life years in the United States and Canada [11].

A meta-analysis of 21 cohort studies including 170,019 individuals found that "regular" (variously defined) users of cocaine had significantly increased all-cause mortality compared with individuals who were not users of cocaine: standardized (for age, sex) mortality ratio 6.13 (95% CI 4.15-9.05) [22]. The leading causes of increased mortality were:

- AIDS-related (standardized mortality ratio 23.12, 95% CI 11.30-47.31)
- Homicide (standardized mortality ratio 9.38, 95% CI 3.45-25.48)
- Accidental injury (standardized mortality ratio 6.36, 95% CI 4.18-9.68)
- Suicide (standardized mortality ratio 6.26, 95% CI 2.84-13.80)

Cocaine overdose is a less common cause of mortality. Of the nearly 16,000 overdose deaths involving cocaine in the United States in 2019, two-thirds also involved synthetic opioids such as fentanyl [23,24]. Acute cocaine intoxication, including overdose, is discussed separately. (See "Cocaine: Acute intoxication".)

The contribution of cocaine itself to observed morbidity and mortality is often unclear. Recreational cocaine is illicitly produced, not diverted from regulated prescription sources. Analysis of both wholesale and retail cocaine samples shows that cocaine typically comprises only 40 to 60 percent of the sample indicating that consumers are not always ingesting what they assume they bought [25,26]. Common adulterants in cocaine samples include caffeine, lidocaine, benzocaine, phenacetin, and levamisole. These adulterants themselves can have toxic effects (see 'Other systemic effects' below). A retrospective survey of Chicago metropolitan area emergency departments from 2004 through 2010 found a significant positive association between the number of cocaine-associated visits and the purity of cocaine samples assayed by the United States Drug Enforcement Administration [27].

Psychiatric comorbidity — There is substantial bidirectional comorbidity between cocaine use and disorder and psychiatric disorders:

- **Anxiety and depression** – Individuals with generalized anxiety disorder or lifetime major depression appear to be at higher risk of developing cocaine use disorder. For example, in a cross-sectional survey [28]:

  - The risk of developing cocaine use disorder was higher in those with lifetime generalized anxiety disorder than in individuals without lifetime generalized anxiety disorder (odds ratio 1.95, 95% CI 1.38-2.76).

  - The risk of developing cocaine use disorder was higher in those with lifetime major depressive disorder than in those without lifetime major depressive disorder (1.47, 95% CI 1.17-1.83).

  Additionally, a meta-analysis of five published studies found a 5 percent (95% CI 3.7-6.6) prevalence of lifetime cocaine use disorder among individuals with lifetime major depressive disorder [29].

  A population-based, cross-sectional survey of 39,994 United States adults found that those who were current users of cocaine had a 16 percent prevalence of major depressive episode and 11 percent prevalence of any anxiety disorder, compared with prevalence of 6 and 5 percent, respectively, among those who never used cocaine [30]. The prevalences were higher among those with moderate-severe cocaine use disorder: 29 percent for major depressive episode and 20 percent for any anxiety disorder.

- **Bipolar disorder** – A meta-analysis of published general population surveys found a 7 to 12 percent lifetime prevalence of cocaine use disorder among individuals with bipolar disorder and an 11 to 28 percent lifetime prevalence of bipolar disorder among individuals with cocaine use disorder [31] compared with an estimated lifetime prevalence of bipolar disorders of 1 to 3 percent among adults worldwide [32]. (See "Bipolar disorder in adults: Epidemiology and pathogenesis".)

- **Psychotic disorders** – A meta-analysis of 21 published studies found 7.1 percent (95% CI 4.1-12.1) lifetime prevalence of cocaine use disorder among individuals with a lifetime schizophrenia spectrum disorder [33]. A cross-sectional survey found a 7 percent (95% CI 3.41-14.52) lifetime prevalence of schizophrenia and related psychotic disorders among those with current cocaine use and a 10 percent (95% CI 3.94-23.52) lifetime prevalence among those with current cocaine use disorder [34]. The estimated lifetime prevalence of schizophrenia in the United States is slightly less than 1 percent. (See "Brief psychotic disorder", section on 'Substance-induced psychoses' and "Psychosis in adults: Epidemiology, clinical manifestations, and diagnostic evaluation", section on 'Comorbid disorders'.)

A small number of cocaine users may be self-medicating an underlying neuropsychiatric disorder, such as ADHD [35], excessive daytime sleepiness [36], Parkinsonism [37], or cluster headaches [38].

The potential role of cocaine use and disorder as a risk factor or cause of psychiatric illness is discussed below. (See 'Psychiatric effects' below.)

Associated substance use — Cocaine use is highly associated with concurrent and simultaneous use of other legal and illegal substances [39,40].

A meta-analysis of 16 published studies found that 77 percent (95% CI 62-87) of individuals using cocaine reported concurrent use of alcohol and 64 percent (95% CI 47-79) reported use of cannabis [41]. Simultaneous use of cocaine with alcohol produces a new compound, cocaethylene, which is pharmacologically active and may enhance the subjective experience [41,42]. Heroin and other opioids are also sometimes used simultaneously with cocaine (so called “speedballing”) [43].

Other studies have also found that cocaine users are also likely to use other substances in addition to alcohol and cannabis, including amphetamine and opiates [44,45].

PHARMACOLOGY

Illegal cocaine comes in two forms: base (alkaloid, as in coca leaves) and salt [46]. Both forms consist of the same cocaine molecule and exert the same pharmacologic actions once they reach the brain or other target organ. They differ in physical properties, which allow different routes of administration and therefore different pharmacokinetic profiles (see below).

Cocaine base ("crack," "freebase") can be smoked because it has a relatively low melting point (98°C) and vaporizes before substantial pyrolytic destruction has occurred. Cocaine base is difficult to dissolve for injection because it is relatively insoluble in water.

Cocaine salt, in contrast, cannot be efficiently smoked because it melts at 195°C, with substantial breakdown of the cocaine molecule before vaporization. Cocaine salt is readily injected or insufflated ("snorted") through the nose; it is highly water soluble, making it easy to dissolve for injection purposes and facilitating absorption across mucus membranes.

Cocaine enhances monoamine neurotransmitter (ie, dopamine, norepinephrine, and serotonin) activity in the central and peripheral nervous systems [47]. The positive psychological effects and addiction liability are due to its enhancement of brain dopamine activity, particularly in the frontal cortex-mesolimbic dopamine reward circuit [48]. Cocaine also acts as a local anesthetic

by blocking membrane sodium channels [2]. Cocaine is rapidly absorbed through mucous membranes and taken up by most body organs [49]. Cocaine (and its hydrolytic metabolites, such as benzoylecgonine) appears in blood, urine, hair [50], sweat [51], oral fluid [52], and breast milk [53]. It crosses the placenta to appear in meconium [53].

Chronic cocaine use can result in either of two distinct pharmacologic adaptations: sensitization (increased drug response) or tolerance (decreased drug response) [54,55]. While sensitization has been demonstrated in laboratory studies only [56], tolerance to the psychological, cardiovascular, and neuroendocrine effects of cocaine develops after several doses [57,58]. Tolerance to the cardiovascular effects may develop more quickly and completely than does the tolerance to psychological effects. This rapid tolerance presumably allows binge users to take large cumulative doses of cocaine [47,48,59,60].

Route of administration has a significant influence on the pharmacokinetics of cocaine and thus on its addiction liability [61]. Intravenous and inhaled (smoked, vaporized) administration result in onset of action within seconds, higher peak blood cocaine concentrations, and effects lasting 15 to 30 minutes [62]. Intranasal (insufflation, “snorting”) and oromucosal (eg, chewing coca leaf) administration result in slower onsets of 20 to 30 minutes and up to 90 minutes, respectively, lower peak blood cocaine concentrations, and effects lasting approximately one and three hours, respectively [62]. Quicker onset of action and higher blood cocaine concentrations are associated with more intense, but shorter duration, pleasurable subjective effects, which drive addiction liability [61].

Cocaine can also be administered rectally (“plugging,” “booty bumping”) or vaginally, as these mucosa absorb cocaine (in the salt form), as does the nasal mucosa. Little is known about prevalence, as these routes of administration are not asked about in epidemiological surveys. Isolated cases of acute toxicity, including death, are reported in the literature [63,64]. An anonymous online survey of more than 76 department of psychiatry faculty and trainees at a North Carolina medical school found that 35 percent were aware of rectal administration of stimulants including cocaine [65].

The pharmacology, forms of cocaine, and mechanisms of action are discussed elsewhere. (See "Cocaine: Acute intoxication", section on 'Pharmacology' and "Cocaine: Acute intoxication", section on 'Kinetics'.)

CLINICAL MANIFESTATIONS

Acute intoxication — The intended effects of cocaine intake include increased energy, alertness, sociability, elation or euphoria, and decreased need for sleep.

Other acute effects of cocaine intake may include:

- **Physiological effects** – These effects include tachycardia, pupillary dilation, diaphoresis, nausea, tremor, dyskinesias, appetite suppression, and weight loss.
- **Behavioral effects** – These effects include restlessness, agitation, and repetitive stereotyped behaviors (eg, skin picking).
- **Psychiatric effects** – These effects include dysphoric mood, anxiety, panic attacks, suspiciousness, paranoia, grandiosity, and impaired judgment. (See 'Psychiatric effects' below.)

The presentation of acute cocaine intoxication is discussed in detail separately. (See "Cocaine: Acute intoxication", section on 'Clinical manifestations'.)

Withdrawal symptoms — Cessation of heavy chronic cocaine use results in a withdrawal syndrome that has prominent psychological features, but is rarely medically serious [66,67]. Symptoms include depression, anxiety, fatigue, difficulty concentrating, anhedonia, increased cocaine craving, increased appetite, and disturbed sleep, often with initial insomnia and subsequent hypersomnia), and increased and disturbing dreams [68]. Subjective sleep quality often improves after one to two weeks while objective sleep parameters (polysomnography) remain disturbed.

An initial period of intense symptoms (commonly termed the "crash") includes psychomotor retardation, and severe depression with suicidal ideation may occur. However, most users experience milder symptoms that resolve within one to two weeks without treatment.

Physical signs of cocaine withdrawal are usually minor and rarely require treatment. These include nonspecific musculoskeletal pain, tremors, chills, involuntary motor movement, and bradycardia [69]. The first week of stimulant withdrawal has been associated with myocardial ischemia [70], possibly due to coronary vasospasm.

Complications associated with chronic use

Central nervous system

- **Seizure** – Seizures may occur after large doses of cocaine in individuals without a seizure focus [71]. Additionally, cocaine can exacerbate a pre-existing seizure disorder or cause an

ischemic or hemorrhagic stroke that leads to a seizure. However, evidence supporting a causal relationship between cocaine use and a seizure disorder is mixed [72-75].

Seizures occurring in the setting of acute intoxication are discussed separately. (See "Cocaine: Acute intoxication", section on 'Central nervous system'.)

- **Stroke** – Cerebrovascular disease and hemorrhagic and ischemic stroke are increased in cocaine users, even in patients with no other risk factors [74,76-78]. Etiologic mechanisms include tachycardia and increased blood pressure from sympathetic activation, vasoconstriction, vasospasm, and intravascular thrombosis due to increased platelet aggregation [76].

  Cocaine use and stroke are discussed separately (See "Clinical manifestations, diagnosis, and management of the cardiovascular complications of cocaine abuse", section on 'Stroke'.)

- **Cognitive impairment** – Chronic cocaine use is associated with selective cognitive impairment affecting attention, working memory, episodic memory, prospective memory [79], and executive function [80,81]. Many studies are of low quality (eg, do not control for relevant confounding variables), thus the clinical significance of observed impairment remains unclear [80].

  Cocaine-associated cognitive impairment appears to be exposure dependent. For example, one study compared the cognitive performance of 68 adults who were stimulant-naïve with 68 adults with recreational cocaine use and 30 who were dependent cocaine users [82]. Compared with controls, dependent users had impaired performance on tests of attention, working memory, declarative memory, and executive function. The performance of recreational users was intermediate between controls and dependent users.

  Cocaine-associated cognitive impairment is reversible after several months to a year of abstinence and may partially recover with several months of reduced use [83]. The mechanism of cognitive impairment and recovery may be related to cocaine-associated changes in brain cortical thickness [84].

- **Movement disorders** – Up to three-quarters of cocaine users experience movement disorders, including repetitive stereotyped behaviors, acute dystonic reactions, choreoathetosis and akathisia (so-called "crack dancers"), buccolingual dyskinesias ("twisted mouth" or "boca torcida"), and exacerbation of Tourette syndrome and tardive dyskinesia [85,86]. Cocaine users are at increased risk of acute dystonic reactions from

neuroleptic (antipsychotic) medications [87]. These movement disorders may be related to cocaine-associated changes in brain dopamine function in the striatum [86].

- **Headache** – Headache occurs in up to 90 percent of chronic cocaine users [88]. Inhaled and intravenous users may experience an immediate headache, typically occipital or bilateral, lasting at least several hours. Intranasal users may get a throbbing frontal headache during binges. This may continue for several days into abstinence. Further discussion of cocaine-associated headache can be found elsewhere. (See "Cocaine: Acute intoxication", section on 'Central nervous system'.)

- **Brain structure** – Evidence linking cocaine use disorder to associated brain structure abnormalities is mixed:

  A large study mapping cortical and subcortical asymmetries in substance dependence found no association between moderate-severe cocaine use disorder and hemispheric asymmetry [89], brain gray matter volume, or cortical thickness (except in the right supramarginal gyrus) [90,91], after controlling for alcohol and tobacco use.

  - Moderate-severe cocaine use disorder is associated with lower fractional anisotropy of major white matter tracts throughout the brain, especially in the genu of the corpus callosum, suggesting impaired myelin integrity [92,93].

  - Chronic cocaine use is associated with decreased levels of neuromelanin in the ventral striatum [94,95]. Neuromelanin is a breakdown product of cytosolic dopamine; its depletion may suggest reduced dopamine activity.

  The clinical implications of these findings are unclear.

Psychiatric effects — Individuals who use cocaine have higher rates of psychiatric comorbidity than those who do not use cocaine. Unless there is a clear temporal order to the onset of cocaine use and of the psychiatric disorder, it is often uncertain whether cocaine use was a risk factor for developing the psychiatric disorder, the psychiatric disorder was a risk factor for developing cocaine use (or use disorder), or both (ie, a bidirectional relationship). (See 'Psychiatric comorbidity' above.)

Specific psychiatric symptoms associated with cocaine use and use disorder include:

- **Suicidal ideation and attempts** – Cocaine use is associated with suicidal ideation and suicide attempts in up to 20 percent of patients in clinical settings [96]. A meta-analysis of 10 published studies found that cocaine use disorder, compared with other substance use disorders, was associated with a higher rate of suicide attempt in the prior year (odds ratio

2.01, 95% CI 1.56-2.59) but not with a higher rate of suicidal ideation [97]. The extent to which suicide is a direct consequence of use, rather than an associated sociodemographic or psychological factor, remains unclear [98,99]. Factors associated with increased risk of suicidality among cocaine users include depression, severe cocaine withdrawal, comorbid alcohol or opioid dependence, history of childhood trauma, and family history of suicidality [100,101].

- **Cocaine-induced psychotic symptoms** – Cocaine-induced psychotic symptoms include paranoia, delusions or hallucinations and often resemble the positive symptoms of schizophrenia [102-104]. Such symptoms fall into two categories [105].

  - **Cocaine intoxication** – Cocaine intoxication presents with perceptual disturbances (hallucinations, illusions). There is no thought disorder, insight is usually retained that the symptoms are related to cocaine intake, and symptoms resolve usually within several hours [105]. (See "Cocaine: Acute intoxication".)

  - **Cocaine-induced psychosis** – In cocaine-induced psychosis, paranoia and/or delusions may persist after acute intoxication. Cocaine-induced psychotic symptoms usually resolve within several weeks after cessation of cocaine use.

    In the absence of a history of recent cocaine use or a positive drug test, the differentiation between cocaine-induced psychosis and a primary psychotic disorder such as schizophrenia can be challenging. Samples of adults in treatment or presenting to psychiatric emergency services suggest the following differences:

    - Individuals with cocaine-induced psychosis, compared with those with a primary psychosis, experience less disorganized thought disorder and bizarre delusions, less disorganized behavior or catatonia, and fewer negative symptoms such as alogia, anhedonia, and inattention [102-104].

    - Visual or tactile hallucinations are more common with cocaine-induced psychosis use than with primary psychosis [102-104]. Tactile hallucinations are especially typical of stimulant-associated psychosis and include the sensation of something (eg, insects) crawling under the skin (“formication,” “cocaine bugs”) [106]. (See "Cocaine: Acute intoxication", section on 'Central nervous system'.)

    - Persistence of symptoms beyond one month after cessation of cocaine use suggests a primary psychotic disorder, especially if there is a history of prior psychotic episodes in the absence of psychoactive substance use [105].

The frequency of this complication is uncertain. One meta-analysis of 13 published studies found the prevalence of cocaine-induced psychosis in individuals with lifetime cocaine use to be 68 percent (95% CI 62.8-73.6) [107]. In contrast, a meta-analysis of four published studies that used the more restrictive DSM-5-TR definition of cocaine-induced psychotic disorder found the prevalence to be 16 percent (95% CI 10.7-23.2) [107].

Risks factors for cocaine-induced psychosis, based on small, cross-sectional studies of clinical samples, include long duration and high intensity of cocaine use, moderate to severe cocaine use disorder, cannabis use, and high impulsivity [108,109].

An unknown proportion of patients will transition from cocaine-induced psychosis to a primary psychotic disorder such as schizophrenia. The proportion of such patients with amphetamine-induced psychosis (based on a meta-analysis of five published studies) is 22 percent (95% CI 14-34) [110].

Cardiovascular system — Cocaine acutely increases heart rate, blood pressure, and systemic vascular resistance. (See "Cocaine: Acute intoxication", section on 'Cardiovascular'.)

- **Hypertension** – While acute cocaine use causes hypertension, chronic cocaine use is not clearly associated with chronic hypertension. The national health and nutrition examination survey of 5861 United States adults age 20 to 59 years found no significant association between lifetime cocaine use (at least 50 times) and hypertension (blood pressure >140/90; adjusted odds ratio 1.41, 95% CI 0.91-2.19) or prehypertension (blood pressure >120/80; adjusted odds ratio 1.18, 95% CI 0.85-1.63) [111].

- **Other cardiovascular complications** – Cocaine use is associated with a variety of cardiovascular conditions, including coronary artery disease, acute heart failure, acute myocardial infarction, and arrhythmias, among others. These are discussed separately. (See "Clinical manifestations, diagnosis, and management of the cardiovascular complications of cocaine abuse".)

Pulmonary system — Both acute and chronic cocaine-induced pulmonary injury can occur. The effects of cocaine on the pulmonary system depend on the route of administration. Although smoking crack cocaine accounts for most cases of pulmonary toxicity, intravenous use, and snorting also result in lung damage [112-117].

Pulmonary complications of cocaine use are described separately. (See "Pulmonary complications of cocaine use".)

Other systemic effects

- **Gastrointestinal system** – Cocaine reduces gastric motility and delays gastric emptying [118]. Cocaine-induced vasoconstriction and ischemia may result in gastrointestinal ulceration, infarction, perforation, and ischemic colitis [118,119].

- **Liver** – Individuals who use cocaine may have mild, transient elevation in transaminases [120], but there is no direct evidence that cocaine is hepatotoxic in humans. Patients being treated for acute cocaine intoxication may have elevated transaminases due to rhabdomyolysis, but this rarely progresses to severe liver damage [121]. Concurrent alcohol intake may sensitize hepatocytes to damage by cocaine [122], as well as generating the hepatotoxic metabolite cocaethylene [42].

  While chronic cocaine use by any route of administration is associated with an increased risk of viral hepatitis, cocaine use, per se, does not appear to worsen the course of individuals infected with HIV or hepatitis viruses [123,124].

- **Kidneys** – Population-based studies do not find a significant association between cocaine use and reduced estimated glomerular filtration rate [111,125]. This is despite the fact that cocaine use can impair kidney function by a variety of mechanisms [126,127]. These include rhabdomyolysis, vasculitis, acute interstitial nephritis [128], and renal infarction, with rhabdomyolysis being the most common. (See "Drug-induced myopathies" and "Clinical features and diagnosis of heme pigment-induced acute kidney injury".)

  Cocaine use by hypertensive patients enhances their decline in kidney function [129] and the progression from hypertensive nephrosclerosis to end-stage kidney disease [130].

- **Endocrine/diabetes** – Cocaine use can exacerbate diabetes or sequalae of diabetes. In small samples of adults with acute diabetic ketoacidosis, up to one-quarter of cases are associated with cocaine use [131]. Cocaine use disorder has also be associated with a diagnosis of diabetic neuropathy but not diabetic nephropathy [132].

- **Skin** – Cocaine use is associated with a variety of skin lesions that mimic rheumatologic syndromes [133]. Chronic cocaine-induced tactile hallucinations or delusions of parasites under the skin may cause persistent itching and scratching, resulting in excoriation and pruritic skin nodules (prurigo) [134].

  Additionally, a common adulterant found in cocaine is levamisole, an anthelminthic agent withdrawn from human use in the United States in 2000 but still approved for veterinary use. Use of cocaine contaminated with levamisole has been associated with leucopenia,

agranulocytosis, cutaneous vasculitis, and necrotizing skin lesions (picture 1) [135]. (See "Evaluation of adults with cutaneous lesions of vasculitis", section on 'Types of cutaneous vasculitis' and "Approach to the patient with retiform (angulated) purpura", section on 'Other' and "Cocaine: Acute intoxication", section on 'Adulterants and their effects'.)

- **Sexual dysfunction** – Although cocaine is often considered an aphrodisiac, it actually may impair sexual function, especially with chronic use, and may cause delayed or inhibited ejaculation in men [136].

- **Reproductive, fetal, and neonatal health**

  - **Effects in pregnancy** – The pregnancy risk summary within the US Food and Drug Administration labeling for topical cocaine notes that human studies are lacking however risks cannot be ruled out. Maternal cocaine use during pregnancy has been associated with vaginal bleeding, abruptio placenta, placenta previa, premature rupture of membranes, premature birth, decreased head circumference, low birth weight, and autonomic instability [137,138]. (See "Substance use during pregnancy: Overview of selected drugs", section on 'Cocaine'.)

  - **Breastfeeding** – Cocaine appears in breast milk and meconium when used by mother during breast feeding and pregnancy, respectively [53]. (See "Prenatal substance exposure and neonatal abstinence syndrome (NAS): Clinical features and diagnosis", section on 'Cocaine' and "Prenatal substance exposure and neonatal abstinence syndrome (NAS): Management and outcomes", section on 'Effects of specific substances'.)

  - **Spermatogenesis and sperm motility** – Cocaine use may decrease male sperm count and sperm motility, based on cross-sectional studies of small convenience samples with high risk of bias [139].

  - **Others** – Chronic cocaine use by any route of administration is associated with increased risk of HIV infection [140], sexually transmitted infections [118], and of risky sexual behavior (such as unprotected sex) [141].

- **Nasal septal perforation** – Cocaine inhalation can cause nasal septal perforation. This can lead to the need for further medical treatment (ie, humidifying sprays, vitamin emollient drops to lessen discomfort, infectious complications) and, in some cases, surgical repair [142].

SCREENING AND ASSESSMENT

Screening — Screening for cocaine use can be performed with brief self-report instruments or by drug testing. These are typically done in high volume clinical settings such as a primary care practice or emergency department. (See "Screening for unhealthy use of alcohol and other drugs in primary care", section on 'Unhealthy use of other drugs'.)

Patient self-report — Patient self-report via questions or screening instruments provide an economical and efficient means of screening for cocaine use. Several studies suggest that self-reports of cocaine and other illegal substance use can be fairly accurate, as long as there are no adverse consequences (such as criminal charges) for acknowledging use [143].

A systematic review identified several cocaine-use screening instruments, comprised of one to three questions, with good (though varying) sensitivity and reliability [144]. Based on simplicity of use and favorable test performance characteristics, we favor the use of the three-question Tobacco, Alcohol, Prescription Medication, and Other Substance Use screening instrument [145]:

- “In the past three months, did you use cocaine, crack, or methamphetamine (crystal meth)?” If yes,
- “Did you use at least once a week or more often?” If yes,
- “Has anyone expressed concern about your use?”

In a study of 2000 adult patients consecutively recruited from the waiting areas of five primary care clinics, a “yes” answer to the first question had a sensitivity of 0.68 (95% CI 0.59-0.77) and specificity of 0.99 (95% CI 0.98-0.99) for identifying problem stimulant use. Two “yes” answers had a sensitivity of 0.57 (95% CI 0.47-0.67) and specificity of 0.99 (95% CI 0.99-1.00) for identifying stimulant use disorder.

Individuals screening positive for cocaine use should have further assessment.

Drug testing — Drug testing has a limited role in screening or evaluation of patients with cocaine use disorder. Drug testing detects cocaine use but is not diagnostic of a cocaine use disorder, which implies adverse consequences from use. Conversely, a negative drug screen may only indicate lack of recent use. Drug testing is typically reserved for screening in patient populations likely enriched in individuals with a substance use disorder, to further evaluate someone suspected of giving a false-negative response to a self-report screening instrument or to monitor the course of someone with a cocaine use disorder.

Cocaine and its major metabolite, benzoylecgonine, can be measured in urine, blood, oral fluid, sweat, and hair [146]. Urine and oral fluid are typically used for screening because of their noninvasive and inexpensive collection, which makes on-site testing practical. The window of detection varies with the biological matrix being tested and the cut-off value used to define a positive screening test. The windows of detection for benzoylecgonine with commonly used commercial assays and cut-off values are two to four days in urine, one-half to three days in oral fluid, and one-half to two days in blood.

A variety of relatively inexpensive commercial assays are available for testing of urine and oral fluid, including disposable kits that allow on-site testing with results available within minutes. Since results from these screening tests can very rarely show false positive for benzoylecgonine, positive results that are disputed or that occur in legal or workplace settings should be confirmed with a definitive, standard laboratory assay.

Initial medical and neuropsychiatric examination — Patients who screen positive for cocaine use or who are otherwise suspected of cocaine use disorder (eg, because of collateral information from family or law enforcement) should undergo an initial evaluation directed towards evaluating medical and psychiatric sequelae of cocaine use or cocaine use disorder, assessing psychosocial functioning and level of support, and level of motivation for treatment. In addition, this evaluation can identify important comorbidities that may require independent treatment. (See 'Clinical manifestations' above.)

Initial evaluation for an individual who has tested positive by screening for cocaine use should include:

- Current and past history of substance use (including other substances and alcohol).
- Medical history with particular attention to cardiac history (history of myocardial infarction, arrhythmia, cardiomyopathy, or hypertension), and neurologic history (ie, history of stroke seizure or cognitive decline).
- Psychiatric history with particular attention to:
  - Psychiatric hospitalizations
  - Psychiatric diagnosis
  - Psychiatric medications
  - History of suicidal ideation or attempt
- Social history, family history, and developmental history:
  - Review of support system, education and work history

- Review of legal history
- Review of social skills including interpersonal skills and coping mechanisms

- Mental status examination, including review of cognitive functioning, mood instability (eg, depression, dysphoria, mania), insight and judgment, and motivation for treatment.
- General physical examination, including assessing for evidence of stigmata of cocaine use (eg, skin lesions from injection, perforated nasal septum from insufflation ["snorting"]).
- Laboratory tests, including electrocardiogram, complete blood count, chemistry.

DIAGNOSIS

Cocaine use disorders are found under the broader category of stimulant use disorder in the DSM-5-TR. The diagnosis of cocaine use disorder is made on the basis of history, obtained primarily from the patient and from collateral sources (eg, family, friends, and medical records) when available.

The DSM-5-TR considers cocaine use disorder as a unitary diagnosis varying in severity from mild to severe [105]. The DSM-5-TR diagnostic criteria encompass the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) psychiatric diagnoses of cocaine abuse and cocaine dependence. Cocaine dependence is approximately comparable to cocaine use disorder, moderate to severe subtype, while cocaine abuse is similar to the mild subtype [13].

DSM-5-TR criteria — A problematic pattern of amphetamine type substance, cocaine or other stimulant use leading to clinically significant impairment or distress, as manifested by two or more of the following within a 12-month period:

- Cocaine is often taken in larger amounts or over a longer period than was intended
- There is a persistent desire or unsuccessful efforts to cut down or control cocaine use
- A great deal of time is spent in activities necessary to obtain cocaine, use cocaine, or recover from its effects
- Craving, or a strong desire or urge to use cocaine
- Recurrent cocaine use resulting in a failure to fulfill major role obligations at work, school, or home

- Continued cocaine use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cocaine
- Important social, occupational, or recreational activities are given up or reduced because of cocaine use
- Recurrent cocaine use in situations in which it is physically hazardous
- Continued cocaine use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by cocaine
- Tolerance
- Withdrawal

Specifiers for the diagnosis include:

- In early remission – After full criteria for cocaine use disorder were previously met, none of the criteria for cocaine use disorder have been met (with the exception of craving) for at least three months but less than 12 months.
- In sustained remission – After full criteria for cocaine use disorder were previously met, none of the criteria for cocaine use disorder have been met (with the exception of craving) during a period of 12 months or longer.
- In a controlled environment – If the individual is in an environment where access to cocaine is restricted.

The severity of cocaine use disorder at the time of diagnosis can be specified as a subtype based on the number of symptoms present:

- Mild: Two to three symptoms
- Moderate: Four to five symptoms
- Severe: Six or more symptoms

TREATMENT

The treatment of cocaine use disorder is discussed separately. (See "Stimulant use disorder: Psychosocial management" and "Stimulant use disorder: Treatment overview".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Cocaine use and cocaine use disorder" and "Society guideline links: Stimulant use disorder and withdrawal".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topic (see "Patient education: Cocaine use disorder (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Epidemiology** – Cocaine is used by an estimated 20 million people worldwide, approximately 0.4 percent of the global population age 15 to 64 years. Approximately one-fifth of these individuals have a cocaine use disorder. (See 'Epidemiology' above.)
    - **Risk factors** – The risk of cocaine use disorder is increased by the frequency and quantity of cocaine use and the route of administration. Individuals smoking cocaine have a higher risk of developing cocaine use disorder than individuals who use cocaine intranasally or orally. Adverse childhood experiences and attention deficit hyperactivity disorder are significant risk factors for developing cocaine use disorder. Genetic factors play a role, but no specific gene or allele has been clearly linked to cocaine use disorder. (See 'Epidemiology' above.)
    - **Mortality and comorbidities**

- Users of cocaine have a significantly increased all-cause mortality compared with individuals who do not use cocaine. The leading causes of increased mortality are AIDS-related deaths, homicide, accidental injury and suicide. (See 'Morbidity and mortality' above.)

- Cocaine use is highly associated with concurrent and simultaneous use of other legal and illegal substance including amphetamines, alcohol, cannabis, opioids, and cigarettes. (See 'Associated substance use' above.)

- There is substantial bidirectional comorbidity between cocaine use and disorder and psychiatric disorders including mood disorders, anxiety disorders, and psychotic disorders. (See 'Psychiatric comorbidity' above.)

- **Clinical manifestations**

  - The intended acute effects include increased energy, alertness, sociability, elation or euphoria and decreased need for sleep. Other acute effects may include physiological effects such as tachycardia, nausea, and behavioral and psychiatric effects such as restlessness, anxiety, and agitation. (See 'Acute intoxication' above.)

  - Cessation of heavy chronic cocaine use results in a withdrawal syndrome that has prominent symptoms including depression, fatigue, anhedonia, and craving, but is rarely medically serious. Most users experience mild symptoms that resolve within one to two weeks without treatment. (See 'Withdrawal symptoms' above.)

- **Complications** – Complications of cocaine use include its effects on the central nervous system, cardiovascular effects, psychiatric effects, and effects to other systems such as pulmonary, gastrointestinal, endocrine system, sexual functioning. (See 'Complications associated with chronic use' above.)

  - Central nervous system effects include seizure, stroke, cognitive impairment, movement disorders, headache, and brain structure changes.

  - Psychiatric effects include suicidal ideation and attempts, anxiety, mood disorders, and psychosis.

  - Cardiovascular effects include coronary artery disease, acute left heart failure, myocardial infarct, supraventricular and ventricular arrythmias, left ventricular hypertrophy, cardiomyopathy, myocarditis, and sudden cardiac death.

- **Screening and assessment**

- Screening for cocaine use can be performed with brief self-report instruments or by drug testing. These are typically done in high volume clinical setting such as a primary care practice or emergency department. (See 'Screening and assessment' above.)

- For patients who screen positive for cocaine use or those otherwise suspected of cocaine use disorder, the initial evaluation should be directed towards evaluating medical and psychiatric sequelae of cocaine use disorder, as well as the severity of the addiction, concurrent substance use, and evaluating motivation for treatment and treatment planning. (See 'Initial medical and neuropsychiatric examination' above.)

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