Cocaine Use Disorder

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Faculty

Mark Rose, BS, MA, LP, is a licensed psychologist in the State of Minnesota with a private consulting practice and a medical research analyst with a biomedical communications firm. Earlier healthcare technology assessment work led to medical device and pharmaceutical sector experience in new product development involving cancer ablative devices and pain therapeutics. Along with substantial experience in addiction research, Mr. Rose has contributed to the authorship of numerous papers on CNS, oncology, and other medical disorders. He is the lead author of papers published in peer-reviewed addiction, psychiatry, and pain medicine journals and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to law firms that represent disability claimants or criminal defendants on cases related to chronic pain, psychiatric/substance use disorders, and acute pharmacologic/toxicologic effects. Mr. Rose is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine and is a member of several professional organizations.

Faculty Disclosure

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

Division Planner

Margaret Donohue, PhD

Senior Director of Development and Academic Affairs

Sarah Campbell

Division Planner/Director Disclosure

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

Audience

This intermediate course is designed for psychologists who are involved in the evaluation or treatment of persons who use cocaine.

Accreditations & Approvals

American Psychological Association

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Course Objective

The purpose of this course is to provide a current, evidence-based overview of cocaine use disorder and its treatment, in order to allow healthcare professionals to more effectively identify, treat, or refer patients who abuse cocaine.

Learning Objectives

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

1. Describe the history and background of cocaine use, including the development of different forms of the drug.
2. Discuss the epidemiology of cocaine use.
3. Describe the pharmacodynamics and pharmacokinetics of cocaine.
4. Review the acute and chronic effects of cocaine use, including effects on fetal development.
5. Select possible treatment modalities for cocaine use disorder, including psychosocial therapy, pharmacotherapy, immunotherapy options,alternative/complementary approaches, and interventions for non-English-proficient patients.
6. Recognize the withdrawal syndrome associated with cessation of cocaine use.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

DEFINITION OF COCAINE ABUSE AND DEPENDENCE

Stimulant drugs are substances that activate the central nervous system (CNS) and peripheral nervous system. There are two main categories of commonly used illicit stimulants: cocaine and amphetamine and its derivatives and analogs, such as methamphetamine. Prescription stimulants (e.g., methylphenidate [Ritalin], mixed salts of amphetamine [Adderall]) used to treat attention deficit hyperactivity disorder (ADHD), narcolepsy, and other disorders, may also be used illicitly. Cocaine and nonprescription amphetamines have the highest potential for abuse and dependence and constitute a serious public health, medical, and criminal justice concern due to the number of individuals addicted to these agents. Repeated use in escalating doses over time can lead to the development of addiction [1; 2].

The syndrome of substance abuse and dependence is highly similar regardless of the particular substance and is best conceptualized as a brain disorder, with a chronically waxing and waning course of relapse and remission. It is associated with neurobiologic changes that result in craving for the substance [3; 4; 5; 6]. The etiology of dependence in any one person is multifactorial, representing the convergence of a multitude of biologic, psychologic, social, and interpersonal factors [1; 5].

Cocaine addiction is best described as a chronic relapsing disease. It is characterized by the compulsive seeking and use of cocaine accompanied by functional and molecular changes to the brain [4; 5]. The single most defining aspect of cocaine use disorder is the salience of the relationship with the drug. The stronger the relationship, the more likely the patient is to continue problematic use despite internal and external consequences. Psychologic dependence, whereby the patient believes the drug is necessary to complete daily activities, alleviate stress, and cope with problems, is a symptom of stimulant dependence. Physiologic adaptation, evidenced by tolerance and withdrawal, is often present but is not sufficient for a diagnosis of cocaine use disorder. Cocaine use disorder is diagnosed behaviorally and is evidenced by at least two of the following within a 12-month period [7; 8]:

- Persistent desire or unsuccessful attempts to cut down or control use
- Great deal of time spent in activities necessary to obtain the drug
- Craving
- Failure to fulfill obligations at work, home, or school as a result of cocaine use
- Continued use despite persistent or recurrent social or interpersonal problems caused by cocaine use
- Important activities abandoned or reduced
- Recurrent cocaine use in physically hazardous situations
- Continued use despite knowledge of a problem likely to have been caused by or exacerbated by cocaine use
- Tolerance
- Withdrawal

Cocaine abuse is a condition of frequent, binge-type use and continued use despite negative consequences, but with less severity and fewer behavioral symptoms than a use disorder [7; 8; 9]. In this course, the term cocaine use disorder will be used interchangeably with cocaine addiction.

HISTORY AND BACKGROUND OF COCAINE USE

FIRST WAVE

Cocaine, a tropane alkaloid, is extracted from the leaves of *Erythroxylumcoca* bush, which contain 0.6% to 1.8% of the alkaloid [3; 5; 10]. Archeologic evidence indicates that use of these leaves for their stimulant and anesthetic properties by South American natives dates back to 2000 B.C.E. [11]. Although Spanish explorers discovered the mild stimulant effects of the leaves and returned to Europe with them in the 16th century, their use did not become widespread for more than 300 years, partially because the leaves lost much of their potency on the journey back to Europe [12].

Cocaine was first isolated and synthesized in 1859 in Germany, and its medicinal effects were first documented in the 1880s [13; 14]. Among the proponents of cocaine during this period was Sigmund Freud, who initially lauded the use of cocaine to treat a variety of conditions (most of which he retracted in 1887), including depression, alcoholism, and morphine addiction, in an 1884 paper titled *On Cocaine*. The surgeon William Halstead also utilized the drug for its local anesthetic effects [13; 14]. Both men developed documented cocaine addictions. In 1886, the soft drink Coca-Cola, which contained cocaine and caffeine, was introduced. The ability of cocaine to reduce hunger, fatigue, and the need for sleep was highly valued during the industrial revolution in the late 19th century, and its use was encouraged to promote worker productivity [13; 15]. The demand for cocaine skyrocketed during this period; the pharmaceutical company Merck produced 0.75 pounds of cocaine in 1883 and 158,352 pounds in 1884 [9; 12]. Cocaine was widely available during this period in cigarettes, inhalers, candy, elixirs, solutions, and over-the-counter products, as well as in wine and soft drinks [13; 15]. Use of cocaine eventually reached epidemic proportions. In 1910, President Taft declared cocaine to be a public enemy, and strict controls were enacted at the state level [9; 15]. Cocaine was removed from the Coca-Cola formulation in 1903, and the passage of the Harrison Narcotic Act in 1914 severely restricted the manufacture, distribution, and sale of cocaine in the United States. Cocaine use plummeted and remained very low for the next six decades [9; 15].

SECOND WAVE

Cocaine use did not experience a resurgence until the late 1960s, coinciding with the tighter regulatory control and decreased use of amphetamines [12; 16]. The seriousness of cocaine abuse and dependence was discounted in the 1960s and 1970s, and little effort was made to understand the mechanism of cocaine addiction and its treatment, partially because heroin addiction was seen as the most significant drug-related public health concern [17]. The introduction, widespread use, and substantial morbidity and mortality of freebase and crack cocaine in the early 1980s alerted scientists and clinicians of the urgency in understanding the nature of cocaine addiction and in developing effective treatments.

The increase in cocaine use in the 1980s correlated with the introduction of new forms of the drug. When cocaine is treated with hydrochloric acid (HCl), it becomes cocaine HCl, which is highly soluble in water and highly lipophilic. Until the late 1970s, this was the predominant illicit form [9]. Cocaine HCl may be administered intranasally, mixed with water and used intravenously, or combined with heroin and injected, which is referred to as a "speedball" [5; 9]. Freebase cocaine is a highly pure form created by removing the hydrochloride base and is not water soluble. Unlike cocaine in the powdered hydrochloride form, which is destroyed by heat, freebase is smokable. Crack cocaine is made by dissolving cocaine HCl in water, mixing in baking soda, and heating the mixture to create a hard substance that is cut into "rocks" [12]. In the early 1980s, cheap and readily available crack cocaine was introduced, resulting in a rapidly escalating number of regular users and addicts [9].

EPIDEMIOLOGY AND DEMOGRAPHICS OF COCAINE ABUSE AND DEPENDENCE

In 2021, 4.8 million Americans (1.7%) had used cocaine within the past year, with 1.4 million individuals 12 years of age or older classified as dependent on or abusing cocaine [18]. Every day, 1,310 people use a cocaine product for the first time, with 60% of initiates 18 to 25 years of age and 39% of initiates 26 years of age or older [18]. Between 2002 and 2021, the number of annual initiates of cocaine declined from 1,032,000 to 478,000 [18]. Older estimates in the United States have shown that cocaine is used primarily by young men, who outnumber female users by approximately 2 to 1 [19]. Past-year cocaine use rates do not differ significantly by race/ethnicity, except among multiracial (defined as more than one race, but not Hispanic or Latino) individuals, of whom 3.2% reportedly used cocaine in the past year [18]. Overall, environmental and social factors (e.g., approached by someone selling cocaine, parental involvement, religious beliefs, scholastic environment) account for risk of cocaine use considerably more than race or ethnicity [19].

Based on the Substance Abuse and Mental Health Services Administration (SAMHSA) Treatment Episode Data Set (TEDS), primary cocaine treatment admissions decreased from 60 per 100,000 in 2010 to 26 per 100,000 in 2020, with the highest rates of admissions in the Middle Atlantic and New England regions [20]. The primary reported substances used at admission in 2020 were: alcohol (31.2%), opioids (26.9%), stimulants (12.7%), marijuana/hashish (9.8%), and cocaine (5.1%) [20]. In 2010, cocaine treatment admissions for persons 12 years of age or older represented 8.3% of all treatment admissions, compared with 5.1% in 2020 [20]. Data in the 2020 SAMHSA publication represented 49 states, Puerto Rico, and the District of Columbia, and of the 1,416,357 reported treatment admissions for all substances, approximately 71,725 were for primary cocaine use [20]. Approximately 60% of these admissions were for smoked (crack) cocaine.

Cocaine, in general, was the fifth most common illicit drug among treatment admissions in 2020, accounting for 5.1% of TEDS admissions, with smoked cocaine accounting for 3% of total admissions. Cocaine users who ingest cocaine by routes other than smoking were more likely to be White and male than those who smoke cocaine [20]. Of those admitted for smoked cocaine, approximately 51% were Black and 40% were White [20]. Women comprised 36.8% of cocaine treatment admissions in 2020, with 63.8% of women being treated for smoked cocaine and 3.2% of women being pregnant. Hispanic/Latino individuals accounted for 13.3% of treatment admissions in 2020 [20].

Certain populations are more vulnerable to cocaine-induced toxicity, primarily due to their inefficient capacity for metabolism and clearance of the drug and its breakdown products. These include the elderly, infants, fetuses, pregnant women, and patients with liver disease [13]. Other factors that influence individual variation in susceptibility to cocaine-induced toxicity include age, sex, body mass, hepatic and renal function, drug-drug interactions, and genetic variability [21]. Black American users are more likely than non-black users to experience rhabdomyolysis, excited delirium, and changes in cardiac rhythm [13].

Gender differences in the effects of cocaine have also been observed. Men who use cocaine experience higher blood concentration levels and greater drug effect than women, and women are more sensitive to the cardiovascular effects than men [12; 22]. Women presenting for treatment of cocaine dependence are more likely than males to be severely dependent, to abuse other drugs, to have a briefer period of abstinence, and to have childhood histories of physical or sexual abuse [17]. Gender differences in comorbidity have also been found, with female cocaine abusers more likely to have major depression and male cocaine abusers more likely to have antisocial personality disorder [17].

COCAINE USE

PHARMACODYNAMICS

Cocaine's specific mechanism of action involves increasing the synaptic transmission of dopamine, serotonin, and norepinephrine by interaction with plasma membrane transporters to block presynaptic reuptake. Action involving the dopamine transporter is the most important in producing the reinforcing effects, which lead to dependence [23]. The increased postsynaptic dopamine activity following its blocked presynaptic reuptake forms the basis of cocaine action [17].

Dopamine receptors are grouped into two families: dopamine D1-like (D1 and D5) and dopamine D2-like (D2, D3, and D4). Both D1-like and D2-like receptors are believed to mediate the acute and chronic effects of cocaine [24; 25]. A study employing multiple regression analysis to identify the biochemical receptor mechanism most associated with the reinforcing properties of cocaine examined dopamine, serotonin, choline, and norepinephrine receptors and their transporters [26]. Researchers found that cocaine binding to the dopamine transporter or cocaine inhibition of dopamine uptake accounted for most of the variability [27].

The basal ganglia, the brain region with the highest density of dopamine receptors, is the site with the highest concentration of cocaine binding [28]. In addition to affinity for mesocorticolimbic dopamine receptors, cocaine also inhibits activity in the locus coeruleus and the pons, providing an anxiolytic effect [12].

PHARMACOKINETICS

Cocaine can be absorbed through any mucous membrane. Different routes of cocaine delivery into the body produce different patterns and levels of blood cocaine concentration. Intranasally administered cocaine is absorbed and distributed into the body gradually, while the onset of effect is rapid when smoked or injected. The effect of cocaine is experienced most rapidly and intensely when smoked, with an onset of effects typically occurring within 8 to 10 seconds; thus, cocaine is most addictive when smoked [23]. Injected cocaine takes twice as long to enter the brain (i.e., 16 to 20 seconds), and snorted cocaine begins to act in three to five minutes [12]. The lungs are the most rapid and efficient cocaine delivery modality because of the large surface area of absorption and rapidity of arterial circulation to the brain [9; 29].

Peak plasma levels of cocaine occur 20 to 40 minutes following intranasal ingestion, with a typical concentration of 100–500 mcg/L. Toxicity is rarely seen at this dose level. Plasma half-life ranges from 31 to 82 minutes, with a mean of 38 minutes [13].

Cocaine has long been used medicinally as a local anesthetic agent and is believed to be the only naturally occurring agent with this specific property [30]. Cocaine interferes with sodium channel activity, leading to diminished or blocked nerve conductivity. By entering the sodium channel and binding to the membrane interior, the drug further inhibits membrane sodium activity in electrically active cells, such as myocardium and nerve cells [29; 30].

The majority of cocaine (i.e., 75% to 90%) is hydrolyzed by plasma and hepatic esterases to ecgonine methyl ester and benzoylecgonine, while a smaller proportion undergoes hepatic demethylation to produce the CNS-active norcocaine [29; 30; 31]. Hepatic metabolism occurs with cytochrome P450-2C9, 2C19, 3A4, and 2D6 [21]. Decreased hepatic perfusion results in prolonged elevation of cocaine levels [29]. Concurrent alcohol use produces the metabolite cocaethylene, which has a longer plasma half-life than cocaine [21; 29]. The rapid metabolism of cocaine in the liver accounts for its short half-life, which also influences the duration of the subjective "high" from a single dose. It is believed that both the intensity of the high and its brief duration contribute to the addictive properties of the drug [23; 29].

EFFECTS OF COCAINE USE		
Type of Use	**Psychologic Symptoms**	**Physiologic Signs**
Acute ingestion	Euphoria Heightened self-confidence, well-being, energy, and alertness Restlessness Reduced need for food Insomnia	Elevated arterial pressure Increased heart rate and respiration Coronary vasoconstriction Increased myocardial oxygen demand Hyperthermia secondary to cutaneous vasoconstriction Increased locomotor activity
Chronic ingestion	Dysphoria Agitation Anxiety and panic Loss of concentration Diminished libido Paranoia Visual or auditory hallucinations Delusions	Pacing Restlessness Hyperactivity Grinding of teeth Mood lability Insomnia

Source: [2; 9; 17] *Table 1*

USE CHARACTERISTICS OF COCAINE ABUSE

Cocaine users often begin in the evening and use the drug continuously over several hours [32]. Over a longer period of time, cocaine use appears to follow what has been described as an "up-top-down" trajectory [33; 34]. This means that use generally increases to a peak, then decreases. However, this may be more true of certain delivery routes than of others.

EFFECTS OF COCAINE USE

ACUTE EFFECTS

The intensity and quality of CNS effects of cocaine are influenced by the quantity and route of ingestion, as well as past drug use. One hundred milligrams is considered a fairly modest dose, with a high dose being several hundred milligrams [12]. Tolerance to the desired effects of cocaine can result from as little as one week of regular use, although the rapidity of the onset of tolerance varies by the route of administration, dose, and frequency of ingestion [12]. Subjective and behavioral effects from single- and multiple-dose acute ingestion of cocaine include euphoria, increased heart rate, restlessness, anxiety and panic, delusions, heightened alertness, and insomnia (***Table 1).***

CHRONIC EFFECTS

The effects of chronic cocaine use on brain neuronal pathways are influenced by the duration and intensity of cocaine use, length of abstinence, and vulnerability to the effects of cocaine [35]. Long-term use of the drug induces a partial depletion of presynaptic dopamine reserves in the targeted brain regions, which is compensated by an increase in the number of dopamine receptors in the striatal region of the brain [12]. This results in the symptoms of dysphoria, anxiety, restlessness, and paranoia.

Cocaine obtained illicitly is always adulterated, or "cut," resulting in wide variations in concentration and purity. Consequently, users may underestimate the purity of the drug and overdose, which can result in toxicity or even death. Certain adulterants can produce harmful effects, as evidenced by the exaggerated sympathetic stimulation caused by ephedrine, Parkinson-type symptoms caused by manganese salts, and the increased likelihood of seizures with the addition of lidocaine [13]. Cocaine use is responsible for more hospital admissions than any other recreational or illicit drug, and the actual incidence of cocaine-induced toxicity is likely to be under-reported [29; 30].

CNS Effects

The sympathomimetic and vasoconstrictive effects of cocaine can induce migraine-like headaches. Cocaine use is also associated with the development of cerebrovascular pathology, including [29]:

- Ischemic strokes
- Hemorrhagic strokes
- Thromboembolic strokes
- Primary and secondary seizures
- Cocaine-induced excited delirium
- Hyperthermia

Cocaine-induced dopamine accumulation in the basal ganglia may result in movement disorders that can present as Tourette syndrome, dystonic reactions, tardive dyskinesia, and akathisia [12; 30].

Neurocognitive Effects

Chronic and heavy cocaine use can lead to the development of diverse neuropsychologic sequelae [36]. Many studies have been performed utilizing a variety of brain imaging techniques, including brain blood flow studies employing transcranial Doppler; single photon emission computed tomography (SPECT); magnetic resonance angiography (MRA); computed tomography (CT); magnetic resonance imaging (MRI); diffusion tensor imaging (DTI); and positron emission tomography (PET) [36]. Evidence obtained from these brain-imaging studies of patients with cocaine use disorder indicates that cocaine use leads to functional, structural, and molecular changes, including dysfunction in the prefrontal cortex, anterior cingulated gyrus, and basal ganglia. This corresponds with functional impairment in abilities related to executive functioning; error detection and performance monitoring and adjustment; and cognition and movement [36]. However, studies attempting to elucidate the durable structural and functional changes to the brain from cocaine use are not longitudinal, and thus cannot rule out the possibility that structural and functional deficits predispose or contribute to cocaine-induced pathology [35; 37; 38].

Cardiovascular Effects

Drugs that increase brain monoamine concentration also have the potential to elevate peripheral monoamine activity [28]. Cocaine stimulates dopamine and alpha- and beta-adrenergic receptors in the CNS and in the peripheral nervous system, which is the underlying basis of the adverse systemic effects of this drug [12; 29]. The cerebrovascular complications caused by cocaine are the result of its effect on noradrenergic neurotransmission and include vasoconstriction and resultant decrease in blood flow, inflammation of blood vessel walls, and hyperpyrexia [23; 29].

Cocaine produces cardiovascular pathology in susceptible users by altering the myocardium and vasculature in a manner that may eventually manifest as cardiac disease, hypertension, or atherosclerosis [30]. The cocaine molecule has a high affinity for cardiac tissue, and both acute and chronic cocaine use can induce a variety of cardiac complications in persons with a negative history of such conditions, primarily from the powerful sympathomimetic properties of the drug [28; 39]. Specific cocaine-induced cardiac conditions include myocardial infarction, ischemia, arterial thrombosis, ventricular tachycardia, ventricular fibrillation, and sudden death. Other cardiac conditions attributable to cocaine use include dilated cardiomyopathy, hypertension, myocarditis, and coronary artery occlusion [12; 29].

Cigarette smoking acts synergistically with the adrenergic effects of cocaine to further increase vasoconstriction [29; 31]. Other risk factors predisposing users to cocaine-induced cardiovascular disease or events include [29; 30]:

- Myocarditis
- Hypercoagulability
- Early-onset atherosclerosis
- Heavy or chronic alcohol use
- Hyperadrenergic syndrome
- Previous history of excited delirium
- Aneurysm or stroke
- High-risk behaviors for sepsis, such as injecting drug use or unsafe sex practices

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American Heart Association, the neuropsychiatric symptoms and cardiovascular complications of cocaine use are interrelated; therefore, management of neuropsychiatric manifestations favorably impacts the systemic manifestations of cocaine toxicity. Benzodiazepines are indicated for this use.

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Level of Evidence: IB (Evidence derived from a single randomized trial or nonrandomized studies for and/or general agreement that the procedure or treatment is beneficial, useful, and effective)

Pulmonary Effects

Most of the pulmonary complications from cocaine use involve smoked cocaine in the form of crack or freebase. These effects usually develop shortly after inhalation. The more common symptoms include productive cough, chest pain, shortness of breath, and worsening of pre-existing asthma. Other pulmonary conditions include thermal injury to the airway, asthma severe enough to necessitate mechanical ventilation, interstitial pneumonitis, pneumothorax, pulmonary edema, pulmonary hemorrhage, and degraded pulmonary function [12; 29].

Gastrointestinal Effects

Malnutrition is the most common gastrointestinal (GI) complication from cocaine use. This is influenced by the adverse effect of cocaine on food and beverage consumption, taste, and nutrient absorption. Other GI complications from cocaine use are less common and include gastroduodenal ulceration, acute bowel perforation, liver toxicity, and pancreatic and endocrine disease [12].

Sexually Transmitted Infections

Cocaine abuse is associated with increased transmission of sexually transmitted infections (STIs), primarily as the result of unsafe and/or high-risk sexual practices. The transmission of human immunodeficiency virus (HIV) has been a particular concern and may stem from exchanging sex for money or cocaine and high numbers of homosexual unprotected sexual encounters, particularly anal receptive sex [9; 40; 41].

NEONATAL EFFECTS

Because a number of people in the United States are believed to use cocaine during pregnancy (estimated at up to 10,000 each year), serious concern has been raised regarding the effects of cocaine on fetal development [19]. There were approximately 800 admissions with positive pregnancy status to treatment centers for primary cocaine use in 2020, compared with 1,300 in 2013 [20; 42].

The adverse effects of cocaine on fetal development stem from its diffusion across the placental barrier, where its vasoconstrictive effect diminishes the flow of blood and oxygen. The resultant hypoxia can retard fetal somatic and CNS development. Damage to the developing fetus can occur in both early and later pregnancy. Although ascertaining the impact of prenatal cocaine exposure is complicated by the influence of other factors (e.g., maternal nutrition, exposure to STIs/STI treatments, amount and route of ingestion of cocaine, use of alcohol, use of tobacco/nicotine, other illicit drug use, the postnatal environment), it is believed that the cocaine-induced effects originate in systems mediated by dopamine function, encompassing the cognitive, motor, emotional, and reward development of the infant [2; 12; 43; 44]. However, some of these effects may be minor in severity and transient in nature, and there is no specific syndrome or condition associated with prenatal cocaine exposure [44; 45]. Other adverse effects from maternal cocaine ingestion include spontaneous abortion, stillbirth, prematurity, and low birth weight [2; 12; 46].

A 2013 systematic review found that the effects of prenatal cocaine exposure may not be as clearly clinically significant as once thought [44]. Although there are obvious early effects (e.g., prematurity, low birth weight) and possible effects on childhood development (e.g., reduced cognition/school performance), test scores and developmental measures were within normal limits in nearly all studies. It is difficult to accurately assess the role of prenatal cocaine exposure on adolescent outcomes due to a host of environmental factors in the prenatal period and during childhood (e.g., violence exposure, secondhand smoke, malnutrition, toxic exposures). One study demonstrated that prenatal cocaine exposure had direct effects on young adult emotion regulation problems, arrest history, and conduct disorder not explained by earlier adolescent behavior [47]. It is safe to say that cocaine exposure can cause premature birth or low birth weight, which are known risk factors for hyperactivity disorders [48].

DIFFERENTIAL DIAGNOSIS

Repeated heavy cocaine use can lead to the development of symptoms that resemble distinct psychiatric and neurologic conditions; therefore, a thorough differential diagnosis is vital. Careful history, observation, and monitoring are useful in performing an accurate differential diagnosis [48]. Some conditions to consider in the differential diagnosis process include mood and psychotic disorders.

The affect and behavior of patients intoxicated with cocaine can mimic a broad spectrum of mood disorders, including the elevated and expansive mood, hypertalkativeness, euphoria, irritability, and sleep and appetite reduction of mania; the volatile cycling of euphoria and dysphoria of bipolar disorder; and the dysphoria, anergia, anhedonia, and suicidal ideation that characterizes acute withdrawal resembling major depression [48]. Cocaine use can also induce the paranoia and delusional thinking that resemble a psychotic disorder [49]. The most frequent delusion types observed in cocaine abusers are the persecutory, jealous, and somatic types [48].

COMORBID ALCOHOL USE DISORDER

Cocaine has a profound liability of abuse and dependency associated with its use [50]. Perhaps the most serious condition associated with repeated use of cocaine is the development of addiction, which may extend to other substances.

Alcohol is a frequently abused substance among patients who use stimulants. Many patients are dependent on both cocaine and alcohol, presenting a challenge for researchers and clinicians in optimizing treatment outcomes [28; 29; 42].

Cocaine abusers consume alcohol for several reasons, including the enhancement and prolongation of euphoria and minimization of the undesired effects. The rewarding effects of both substances are mediated through the mesocorticolimbic dopamine pathway. As noted, the combined effects of cocaine and alcohol can also be explained by the formation of cocaethylene, a metabolic byproduct of ingestion of both substances. Cocaethylene is speculated to be less anxiogenic than cocaine and thus may counteract or mask the dysphoria that can accompany cocaine use. Cocaethylene shares many neurochemical and pharmacologic properties with cocaine and is also an indirect dopamine agonist. Alcohol enhancement of cocaine toxicity is partially explained by the presence of cocaethylene, which increases heart rate and systolic blood pressure. As the result of the substance's cardiotoxic effects, it contributes to the increase in ischemia, infarction, and arrhythmia seen in patients abusing both cocaine and alcohol. Additionally, cocaethylene may elevate the potential of violent ideation, threatening behavior, and violent behavior [51; 52].

Differences in the patterns of combined cocaine and alcohol use have been observed between persons who smoke cocaine compared with those who use intranasally. Users of intranasally administered cocaine typically use alcohol both concurrently and in alternating doses. They also tend to use alcohol excessively. These users usually increase the quantity of both substances when using them together. Crack

cocaine users, however, are more likely to ingest alcohol at the end of an episode of use and to drink less alcohol when using cocaine [52]. Co-abusers are also more likely to use alcohol to alleviate the unpleasant after-effects of cocaine use.

TREATMENT OF COCAINE USE DISORDER

Cocaine use disorder shares many characteristics with general substance dependence. However, it also includes specific identifying symptoms. According to the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5-TR), an early sign of cocaine use disorder is difficulty resisting using cocaine whenever it is available [7]. Physiologic dependence is associated with a higher risk for cocaine-related problems. Because frequent dosing is necessary to maintain the desired effects, patients with cocaine use disorder must often deal with the effects of spending large amounts of money on the drug.

Although cocaine has been a drug of abuse for decades, research on the treatment of cocaine use disorder was delayed until the later part of the 20th century. The introduction and widespread use of crack cocaine in the 1980s, severity of the addiction, and comorbid problems finally prompted the scientific community to investigate treatment options [17].

Regardless of therapeutic modality, the goals of treatment for cocaine abuse or dependence are to retain the patient in treatment, disrupt the binge cycle, and prevent relapse [17; 53; 54; 55]. Inpatient treatment is perhaps the most desirable option. It allows the patient to be shielded from the environmental cues that are associated with cocaine use and the resultant euphoria and craving that are triggered by these cues [17].

After the patient has detoxified and acute withdrawal is over, rehabilitation is implemented, typically in three stages. The initial emphasis is on motivating the patient to remain abstinent. This is accomplished by educational lectures, family outreach, and group therapy. Treatment personnel who are themselves recovering can serve as positive role models, and self-disclosure in this context is appropriate and even therapeutic. During this phase, the patient is also introduced to self-help groups such as Alcoholics Anonymous (AA), Cocaine Anonymous (CA), and Narcotics Anonymous (NA) [1; 56].

The second stage of rehabilitation focuses on helping patients rebuild their lives without substances. Patients are given the strategies and tools needed to acquire a sober social network, appropriately cope with stress, and use free time constructively without using cocaine. The third stage of rehabilitation focuses on relapse prevention, which can be addressed in group therapy or individual counseling. Orientation and encouragement of 12-step program involvement occurs during all three stages of treatment. The three-stage treatment modality for stimulant abuse incorporates behavioral, cognitive, and psychologic elements and provides the basis of psychosocial treatment [1]. The use of pharmacotherapy may also be necessary in each stage.

PSYCHOSOCIAL THERAPY

Treatment of substance use and dependence with psychosocial or behavioral therapy is based on the assumption that addictive behavior is developed and maintained by specific mechanisms [55]:

- Expectancies and modeling
- Reinforcing properties of the drug
- Secondary social reinforcement

The goal of these types of treatments is to modify drug-seeking and other behavioral aspects of drug dependency [53]. Psychosocial therapy and pharmacotherapy are not mutually exclusive; in fact, some drug therapies for substance abuse are considered useless without a psychosocial/behavioral component [53; 55].

Psychosocial therapies for stimulant abuse disorders can be divided into two broad categories. The first category consists of therapies that were originally developed for patients with anxiety and depression and modified for use with patients with addictive disorders. This group of therapeutic approaches includes cognitive-behavioral therapy (CBT), the behavioral therapies, and interpersonal therapy. The second group of psychosocial therapies was developed explicitly for substance-abusing patients and includes motivational interviewing and motivation enhancement therapy [53; 57]. All psychotherapies are intended to be delivered in a supportive, empathic manner that minimizes confrontation.

Drug counseling is a widely used therapy approach with cocaine and other substance abusers. It consists of a focus on abstinence, problem solving, and 12-step orientation and involvement. Drug counseling is usually provided by counselors who have a certificate in addiction counseling. A fair number of addiction counselors are themselves recovering from alcohol and/or substance abuse disorders [57].

Contingency Management

There is considerable evidence that cocaine use is sensitive to the application of contingencies. Contingencies occur on a spectrum from contrived to naturalistic. Contingency management (CM) and vouchers are examples of contrived interventions, while 12-step programs are examples of naturalistic interventions [56]. Contrived contingencies may be effective in initially engaging patients in abstinence, but relapse to drug use may occur following removal of the reinforcer. In contrast, naturalistic contingencies are more likely to maintain the initial gains made by the patient and to facilitate the sustained change of behavior over time [58].

The goal of CM interventions is to increase the opportunity cost of stimulant use by arranging an environment where drug use results in the forfeiture of a predetermined item or privilege, referred to as an alternate reinforcer [59]. Treatment with a CM component was first used with cocaine-abusing methadone patients, a highly suitable population for two reasons: cocaine abuse is prevalent among patients with opioid use disorder receiving methadone maintenance, and methadone patients are required to report to the clinic daily to receive their medication under staff supervision. Daily clinic appointments are often considered a significant constraint on employment, travel, and other activities. Patients who are able to abstain from drugs of abuse, as measured by a urine drug screen, may be allowed several days of take-home methadone doses, which can act as a behavioral contingent [60]. Several studies have shown that this contingent condition has led to greater treatment retention and reductions in cocaine use than those found in comparison treatment conditions, although this effect dissipates with longer-term follow-up [58; 61; 62; 63].

Community Reinforcement

Community reinforcement approaches (CRAs) are biopsychosocial interventions designed to engage and change the lifestyle of the drug abuser by addressing the role of environmental cues and alternative reinforcers in influencing behavior. The theoretical basis of the CRA is that substance abuse is maintained by substance-related reinforcers as well as by the absence of competing alternative reinforcers. The primary goal of the CRA is to build and strengthen relationships, recognize appropriate leisure activities, and identify vocational interests of the patient to provide competing reinforcement with cocaine use and the drug-using lifestyle [64]. CRA aims to increase abstinence by increasing or highlighting the opportunity cost of relationships and social support the patient stands to lose through drug use [58]. In addition to integrating cognitive-behavioral and, in some cases, pharmacologic approaches, CRA may also include the use of vouchers, whereby tokens are given to the patient for producing substance-free urine samples, which are then used to purchase goods and services desired by the patient.

A review of four studies utilizing CRA with patients with cocaine use disorder found evidence that CRA employing abstinence-contingent incentives in the form of vouchers was more effective in promoting abstinence than CRA using noncontingent incentives and usual care. Patients assigned to CRA incorporating abstinence-contingent incentives experienced a greater reduction in disease severity as measured by the Addiction Severity Index than comparison groups [64]. Despite early, promising reports of CRA with patients with alcohol use disorder and evidence that patients receiving CRA have demonstrated more favorable drug use outcomes than patients receiving standard outpatient counseling, CRA is seldom used because of the relatively high cost and labor intensity [53; 65].

Motivational Interventions

Motivational interventions for substance abuse stem from the theory that targeting and enhancing motivation to quit drugs will increase positive outcome; positive outcome is increased when motivation comes internally rather than when it is externally imposed. Specifically, motivational-enhancement therapies (MET) are based on the Transtheoretical Stages of Change Theory, which postulates that patients pass through a series of stages of thought, planning, and action in the process of behavior change [66]. MET is intended to enhance motivation and commitment to change, activate patient resources, and facilitate movement along the readiness-to-change spectrum [67]. MET helps patients build internal motivation through the resolution of issues related to ambivalence. The therapeutic approach is characterized by nonconfrontive, nonjudgmental interviewing that helps the patient consider the pros and cons of change. MET also strives to enhance patient self-efficacy [66]. MET seems to be more effective in patients with low initial levels of motivation when used for patients with cocaine use disorder. It tends to result in less relapse to cocaine use and fewer total days of cocaine use [68].

Coping and Social Skill Training

Coping and social skill training (CSST) evolved from social learning theory and is used to improve the inadequate coping skills found in many addicted persons, including deficits in regulation of emotion and in effectively coping with social situations. CSST addresses four primary areas [69]:

- Interpersonal skills
- Cognitive and affective regulation
- Coping skills to manage stressful life events
- Coping skills when substances or substance-related cues are encountered

An added emphasis on drug-related cues is used when CSST is employed with patients with cocaine use disorder [69].

An inventory of high-risk situations for recovering cocaine abusers was developed and validated with a sample of 179 cocaine abusers. The Cocaine High-Risk Situations Questionnaire identified the following situations as the most evocative of urges to use cocaine [70]:

- Negative emotional states, such as depression, fear, or anger
- Peer or other external pressure to use
- Spontaneous urges to use
- Desire to augment positive or elevated mood
- Direct using cues, such as receiving a paycheck or cash

CSST has incorporated these findings into the treatment approach used with cocaine users. Preliminary results indicate some benefit of cocaine-specific CSST in reducing frequency of cocaine use and increasing duration of abstinence from cocaine, although these results have not been replicated in subsequent research [68; 69].

Drug Counseling

A large treatment study performed by the National Institute on Drug Abuse randomized 487 cocaine-dependent outpatients to four treatment conditions [71]. All patients received group drug counseling once a week for six months. In addition, the four groups received individual drug counseling, CBT, supportive-expressive therapy twice a week for three months, or no additional therapy. All drug counseling was 12-step oriented. At six-month follow-up, the entire sample exhibited an overall decline in cocaine use, from an average of 10 times per month at baseline to once per month, with corresponding reductions in psychiatric symptoms. Reductions in cocaine use and in the Addiction Severity Index-Drug Use Composite scores were significantly greater in the group that received individual plus group drug counseling than in either of the psychotherapy groups [57; 71]. Further analysis found that patients assigned to individual drug counseling who were regular participants in 12-step programs achieved the best outcomes of any treatment subgroup [72].

PHARMACOTHERAPY

Because dropout and relapse rates are high among patients in treatment for stimulant abuse, pharmacologic therapy has been used to augment standard psychosocial therapy, with the goal of increasing retention in treatment, reducing relapse rate, and treating coexisting psychiatric disorders that may contribute to poorer prognoses. Pharmacotherapy is based on the classic medical model that addresses any given disorder as the manifestation of neurochemical or biologic imbalance and dysregulation. This imbalance is viewed either as a precursor for addictive behavior or the consequence of repeated exposure to alcohol or drugs [53].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Department of Veterans Affairs, there is insufficient evidence to recommend for or against the use of any pharmacotherapy for the treatment of cocaine use disorder.

(https://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPG.pdf. Last accessed March 30, 2023.)

Strength of Recommendation: Neither for nor against

Pharmacotherapy for cocaine use disorder follows the model used in the treatment of alcoholism and heroin addiction, which targets the neurobiologic and behavioral components of addiction [23]. Agonist therapy is a component of several different pharmacotherapy strategies for stimulant abuse and dependence; it partially replaces the effects of the abused drug to stabilize the patient. Antagonist therapy, which blocks the abused drug effect, may be utilized to preclude use, alleviate symptoms of use or withdrawal, or treat comorbid conditions. A combination of these approaches may also be utilized [73].

Although a large number of medications have been used in patients with cocaine use disorder, all are either U.S. Food and Drug Administration (FDA)-approved drugs used off label or investigational drugs [2; 5]. The following overview is comprised mainly of review papers that summarize the efficacy in individual therapeutic classes of drugs.

Antidepressants

The theoretical basis for antidepressant treatment of cocaine addiction is to enhance synaptic monoamine transmission by blocking the presynaptic reuptake of brain catecholamines. The goal of this therapy is the alleviation of cravings for cocaine and reduction of withdrawal symptoms, including dysphoria, depressed mood, and cognitive dysfunction [23; 74]. Three types of antidepressants have been studied: tricyclics, such as desipramine and imipramine; selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine and sertraline; and atypical antidepressants, such as bupropion.

A Cochrane review of 31 randomized, double-blind, placebo-controlled studies found only five trials that reported significant differences between the study drug and placebo [74]. Among the reviewed studies, desipramine showed a trend in reducing the frequency of cocaine-positive urine samples; however, the effect was not statistically significant. There were no significant differences between antidepressants and placebo on measures of percentage of abstinent days or total abstinence. There was some evidence that fluoxetine reduced the intensity of craving for cocaine and increased treatment retention, although these findings were inconsistent. Overall, the reviewers' findings did not support the clinical use of antidepressants in the treatment of cocaine use disorder [74].

Psychostimulants

Selegiline is a monoamine oxidase-B (MAO-B) inhibitor used in the treatment of Parkinson disease. However, it has been found to reduce the subjective sensation of "high" and to alter the cerebral metabolism of cocaine. Though promising, more research is needed to confirm the possible efficacy of selegiline and other psychostimulant agents (e.g., bupropion, dexamphetamine, lisdexamfetamine, methylphenidate, modafinil, mazindol, methamphetamine, mixed amphetamine salts) in the treatment of cocaine use disorder [24; 75]. A Cochrane review noted that sustained abstinence was most pronounced with bupropion and dexamphetamine; however, there was high attrition in all included studies, which complicated interpretation of the results [75].

Modafinil is a novel stimulant used to treat narcolepsy and excessive daytime sleepiness, with a pharmacologic mechanism opposite the effects of cocaine-induced neuroadaptation on brain reward systems. This action serves as the basis for its use in cocaine use disorder [76; 77; 78]. Preliminary evidence has suggested that this agent may play an important role in blocking cocaine-induced euphoria, enhancing periods of cocaine abstinence, and reducing total cocaine use, although replication is needed in larger trials for greater study periods [63; 75; 79; 80; 81; 82; 83; 84].

Dopamine Agonists

The difficulties many cocaine addicts encounter in early abstinence, with intense drug craving, fatigue, dysphoria, depression, and difficulties with concentration, are believed to originate from dopamine depletion in key brain systems following chronic enhancement of dopamine transmission. This is the theoretical basis for dopamine agonist treatment [85]. The three most studied dopamine agonists in the treatment of cocaine addiction are amantadine, bromocriptine, and pergolide. A Cochrane review of 24 randomized controlled trials and controlled clinical trials concluded that there were significant forms of bias, including selection bias, performance bias, and detection bias, in all of the studies. The findings did not support the clinical use of dopamine agonists in the treatment of cocaine use disorder [85]. Also, the side effects common with this class of drugs further limit their therapeutic appeal [23]. There is evidence that amantadine may be effective in more severe cases of cocaine withdrawal, but confirmation is needed from additional research [24].

Methylphenidate, a drug used to treat ADHD, shares many of the pharmacologic properties of cocaine, including the inhibition of dopamine, serotonin, and norepinephrine reuptake. On this basis, it has been proposed as an agonist therapy strategy for cocaine use disorder. Evaluation of controlled trials employing methylphenidate have suggested better treatment retention, but no differences have been observed between active drug and placebo groups, indicating a lack of efficacy in the treatment of cocaine use disorder [24; 75]. Methylphenidate has been found to induce craving for cocaine only when administered concomitantly with cocaine cues (e.g., video scenes of subjects self-administering cocaine) [86].

Overall, results from dopamine agonist trials have been disappointing, with neither direct agents, such as bromocriptine and pergolide, or indirect dopaminergic agonists, such as methylphenidate or amantadine, demonstrating consistent efficacy in reduction of withdrawal symptoms [39; 87; 88].

Dopamine Antagonists

Dopamine antagonists, typically D2 antagonists, have been used primarily to block the euphoric or reinforcing drug effect of cocaine. Antipsychotic drugs, such as risperidone, ecopipam, and olanzapine, are usually employed for this use. Studies of these drugs have been typified by high subject attrition, frequent side effects, and poor compliance, resulting in this class being largely discounted as having therapeutic potential [63; 73; 88]. An unfortunate side effect observed during trials of the D1 antagonist ecopipam was that cocaine self-administration increased [89].

Disulfiram

Disulfiram is an oral medication used for decades as aversive therapy for alcohol dependence. It acts by inhibiting aldehyde dehydrogenase, thereby increasing the amount of the toxic alcohol metabolite acetaldehyde. Disulfiram also inhibits the enzyme that converts dopamine to norepinephrine. This increase in dopamine has been hypothesized to make disulfiram a helpful drug for cocaine use disorder. Several studies have been performed with patients with cocaine use disorder, and researchers have found that, relative to placebo, use of disulfiram results in decreased craving for cocaine, increased dysphoria in patients who have ingested cocaine concurrently, decreased quantity and frequency of cocaine use, and reduced number of cocaine-positive urine samples. These results are encouraging. However, additional trials are needed to determine the optimal dose and duration of treatment [24; 80; 90]. A small 2016 trial sought to determine if supplementing CBT with disulfiram would enhance abstinence outcomes but found no benefit with addition of the drug [91].

Gamma-Amino Butyric Acid Agents

Gamma-amino butyric acid (GABA) is the primary inhibitory neurotransmitter in the brain, and evidence suggests that GABA modulates both dopamine brain pathways and the subjective effects of cocaine. There are two primary subtypes of GABA receptors: GABAa and GABAb. GABAa is involved in mediating the effects of antiepileptics, benzodiazepines, barbiturates, and neurosteroids such as progesterone. GABAb is distinct from GABAa in that it mediates the slow inhibitory response to GABA; the antispasm drug baclofen is a GABAb receptor agonist [24].

A rationale for treating cocaine addiction with antiepileptic drugs is the observation of the "kindling" effect of cocaine, whereby repeated administration of subthreshold electrical impulses to specific brain structures increases seizure activity [9]. Randomized, placebo-controlled trials of several GABAergic antiepileptic drugs have produced encouraging results. The antiepileptic and mood stabilizer valproic acid has led to reductions in the frequency and severity of cocaine cravings, self-reported cocaine use, and total number of days of cocaine use in a dose-dependent manner [92]. Topiramate, also an antiepileptic, was found to decrease the total number of cocaine-positive urine screens, although these results require replication [79; 83; 93].

Tiagabine is another antiepileptic drug that increases synaptic GABA levels. Studies with cocaine abusers on methadone maintenance found that patients randomized to tiagabine exhibited less cocaine use than subjects receiving gabapentin or placebo. Baclofen also demonstrated superior ability to reduce cocaine use than placebo, with some evidence of greater efficacy among more severe cocaine addicts [92]. Its use in the treatment of alcohol/cocaine codependence has also been supported [94].

Gabapentin is a GABA analog used as an antiseizure drug and mood stabilizer. Gabapentin has been found to block some of the reinforcing effects of smoked cocaine, although other trials have found no differences between gabapentin and placebo in reducing cocaine use among cocaine-abusing methadone patients [95].

One systematic review of 20 studies and 2,068 patients compared the anticonvulsants carbamazepine, gabapentin, lamotrigine, phenytoin, tiagabine, topiramate, and vigabatrin with placebo. The authors found no evidence supporting the use of anticonvulsants in the treatment of cocaine dependence [96].

Progesterone possesses GABA agonist, glutamate antagonist, and alpha-adrenergic antagonist properties. Laboratory studies have found that progesterone attenuates some of the reinforcing effects of smoked cocaine among women in the early follicular stage of the menstrual cycle and attenuates some of the subjective and physiologic effects of cocaine. However, it did not alter cocaine self-administration in a mixed-gender sample [24; 92].

Alpha-Adrenergic Antagonists

Cocaine is a powerful stimulator of central and peripheral adrenergic activity. Adrenergic systems mediate several of cocaine's effects, such as increased heart rate, heightened blood pressure, and increased arousal. Adrenergic blockers have been utilized in clinical trials with patients with cocaine use disorder. Labetalol, an alpha- and beta-adrenergic blocker, attenuates some of the physiologic effects of cocaine but has not been shown to alter the subjective drug effect [97]. On the other hand, carvedilol, which has similar pharmacology as labetalol but greater CNS potency, blocked not only some of the cardiovascular effects of acute cocaine ingestion but also some of the subjective effects when given in a lower dose. Use of the beta1- and beta2-adrenergic antagonist propranolol results in greater treatment retention and more frequent drug-free urine samples than placebo among patients with more severe withdrawal symptoms, an effect not observed among subjects with milder withdrawal symptoms [24; 79]. Propranolol administered at a dose of 100 mg/day has been found to be effective in reducing withdrawal symptoms and improving treatment retention among patients with greater cocaine addiction severity [98; 99]. In a separate randomized, placebo-controlled study, a 40-mg dose of propranolol was found to reduce subjective cocaine craving and objective cue reactivity (e.g., heart rate, blood pressure) in response to a video of people using cocaine and in vivo cues (e.g., forms of preferred simulated cocaine/drug paraphernalia) [100]. Overall, adrenergic receptor antagonists seem to be effective in reducing or blocking the physiologic effects of acute cocaine ingestion and may be helpful in symptom reduction in a subset of patients with greater withdrawal severity. However, the American Heart Association has recommended that these agents be avoided for the treatment of cocaine toxicity in the acute setting [101].

IMMUNIZATION AND VACCINE THERAPY

Pharmacotherapy for cocaine use disorder targets brain neuronal pathways, whereas immunotherapy for cocaine use disorder acts peripherally to inhibit the effects of cocaine by blocking or delaying entry of the cocaine molecule into the brain [24]. The impetus for the development and evaluation of biologic therapies for cocaine use disorder stems, in part, from the potential side effects and disappointing results of pharmacotherapy trials targeting reward pathways that mediate the addictive effects of cocaine [23].

The two biologic-based therapies for cocaine use disorder that have been subjected to empirical evaluation are immunization and vaccination. Both are variants of the concept of antagonist therapy to block drug effect [73]. In passive immunization, the catalytic antibodies that bind with and convert circulating cocaine molecules to an inactive molecule through hydrolysis are injected into the patient. The action of the antibody breaks down cocaine into ecgonine methyl ester and benzoic acid, resulting in a lack of desired effects. Active immunization employs vaccination, which triggers the production of antibodies against cocaine through the administration of a cocaine-protein conjugate. Both inactive and active immunization prevent induction of the positive effects of cocaine ingestion. Several drawbacks to vaccine therapy for cocaine use disorder have been identified. These include the lack of protection against drugs that are structurally distinct from cocaine, but that produce the same effect; lack of effect on craving; wide variation in antibody formation across individuals; and patient motivational factors [102; 103].

WITHDRAWAL FROM COCAINE

Physiologic adaptation and psychologic dependence may result from regular, long-term use of cocaine. Withdrawal symptoms are a result of the increased receptor density and receptor supersensitivity to neurotransmitters that characterize the adaptation to chronic cocaine use. Craving may occur either spontaneously or in response to environmental cues. Craving diminishes gradually in most users, but in severe users, it may never become fully extinguished [13; 104].

A triphasic abstinence syndrome from heavy cocaine use has been identified [17]. Phase one is acute withdrawal, or the "crash." Immediately upon cessation of use, a withdrawal syndrome can manifest, consisting initially of a rapidly declining mood and energy level, agitation, and retarded major depression. Depression and dysphoria are observed and reported, as well as agitation, sweating, tachycardia, and unstable blood pressure. Symptoms of paranoia peak and then decline during this period. Patients experience overwhelming cravings to use cocaine at this point, partially to terminate the extreme discomfort of the withdrawal symptoms. However, many patients will attempt to use sedatives, opioids, alcohol, or cannabis to terminate anxiety and agitation and to induce sleep. Phase one can last up to four days [12; 17].

Phase two can last one to ten weeks, during which time patients are likely to experience prolonged anhedonia, impaired motivation, dysphoria, and craving. It is during this period that patients are at highest risk of relapse. Outpatients are especially vulnerable to environmental cue-induced triggers for cocaine use. Persons, places, and things associated with cocaine use stimulate vivid recollection and cocaine-induced euphoria that, when contrasted with the ongoing dysphoria, can make resumption of use irresistible. If relapse occurs during this phase, it can activate the vicious cycle of heavy use, attempts to quit, and relapse [17].

Phase three consists of episodic craving that is gradually diminished if the cocaine user is able to remain abstinent [17]. The severity and duration of the symptoms of cocaine abstinence syndrome may be considerably less in the inpatient setting, where the patient is removed from the ubiquity of triggers encountered in the using environment [17; 104; 105].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The World Health Organization asserts that there is no evidence that medication-assisted withdrawal would benefit pregnant women with these respective disorders.

(https://www.who.int/substance_abuse/publications/pregnancy_guidelines/en/. Last accessed March 30, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

TREATMENT OF CONDITIONS ASSOCIATED WITH COCAINE USE

POLYSUBSTANCE DEPENDENCE

As noted, patients with cocaine use disorder are often found to be addicted to or abuse other substances, such as alcohol, opioids, and benzodiazepines. These patients should be treated with therapies with established efficacy to manage the coexisting substance dependence, such as methadone or buprenorphine for patients with opioid use disorder, or naltrexone, acamprosate, or disulfiram for alcohol dependence [39].

Treatment Issues for Patients with Opioid Use Disorder Who Use Cocaine

Stimulant abuse and dependence is a significant problem among heroin addicts being treated with methadone maintenance therapy and one of the most treatment-resistant behaviors among this population. Numerous studies have evaluated the efficacy of pharmacotherapeutic agents in reducing cocaine use in this patient population [60]. A review of several randomized, double-blind, placebo-controlled studies failed to find superior efficacy on measures of cocaine use and dropout rate among patients receiving any antidepressant for cocaine use disorder [74]. A review of 17 studies involving amantadine, bromocriptine, and pergolide failed to show significant differences in rates of cocaine-positive urine samples [85]. Pergolide has since been withdrawn for human use [106].

The efficacy of voucher-based incentive programs for reducing cocaine use among patients with cocaine use disorder on methadone maintenance is well established and has been extended to the treatment of alcohol, cannabis, nicotine, and opioid dependence [107]. One study demonstrated a 50% abstinence rate at 12 weeks for patients receiving vouchers contingent on abstinence, compared with only 15% abstinence among patients receiving vouchers with no contingency [108]. Another multisite study included patients receiving methadone maintenance for opioid use disorder who exhibited intractable stimulant abuse. These patients were randomized to either usual care or usual care plus voucher-contingent incentive delivered on an intermittent-reinforcement schedule [60]. Results showed that intermittently providing incentives essentially doubled the likelihood of stimulant- and alcohol-free urine samples on any given clinic visit. Patients in the incentive groups were 11 times more likely to achieve 12 or more weeks of continuous abstinence than patients receiving usual care only.

ADHD

As discussed, methylphenidate has not been shown to be effective in reducing cocaine use in patients with cocaine use disorder and comorbid ADHD. However, it does substantially reduce ADHD symptoms [109]. The FDA warns that priapism may occur in men taking methylphenidate products, particularly after a dosage increase or following drug abstinence or an unusually long length of time between doses [110].

MAJOR DEPRESSION

Mood disorders are associated with substance abuse in general, and cocaine abuse and dependence are specifically associated with depression. Lifetime rates of major depression range from 25% to 61% among cocaine-dependent inpatients [111]. Managing both disorders is essential because the presence of one of these disorders decreases the likelihood of remission from the other [111]. With many depressive symptoms resolving in early abstinence, the traditional approach has been to monitor depressive symptoms during the first four weeks of treatment and withhold antidepressant treatment until the end of the four weeks. However, this approach often is not practical, as many cocaine-addicted patients cannot abstain during the initial four weeks. This problem is compounded by the increasing scarceness of resources for inpatient treatment, which underscores the importance of treating both conditions simultaneously [112].

Results from numerous clinical trials support the use of antidepressants in patients with comorbid depression and cocaine abuse. Research has suggested that the more activating antidepressants, such as bupropion and the tricyclics, are more effective than SSRIs, supporting the observation that substance-abusing patients respond preferentially to medications whose direct or side effect profiles resemble the effects of their drug of choice [111]. Unfortunately, tricyclics have worse side effects, tolerability, and safety profiles than SSRIs and should be used with extreme caution in depressed patients [112]. As previously noted, there is no empirical support for antidepressant treatment to reduce cocaine usage in these patients. Although limited, research on behavioral therapy treatment of comorbid depression and cocaine abuse suggests that CBT can promote greater treatment retention and longer periods of abstinence, and patients receiving motivational interviewing remain engaged in aftercare longer and have fewer depression-related hospitalizations following treatment [63; 111].

ALTERNATIVE/COMPLEMENTARY TREATMENT OF COCAINE USE DISORDER

ACUPUNCTURE

Auricular (ear) acupuncture has become a widely used treatment for cocaine use disorder and is employed by hundreds of treatment centers and clinics in the United States. The procedure, which was developed at Lincoln Hospital in New York City in the 1970s, entails the placement of needles in five ear locations that represent the lung, kidney, liver, sympathetic, and shen men (a universal enhancer) points. This specific methodology has become a standardized treatment for substance abuse and is not specific to cocaine use disorder or abuse [113].

Gates et al. performed a review of seven randomized, controlled trials enrolling 1,433 subjects of auricular acupuncture with cocaine use disorder [113]. Overall, there was little evidence of significant improvement among acupuncture recipients compared to groups receiving either nonaccupoint acupuncture or no acupuncture on measures of severity of dependence, cocaine use self-report, cocaine use assessed by urine toxicology screen, and cocaine craving. As is the case with many studies of addiction, high rates of subject attrition limited the quality of evidence. With any alternative therapy, it is difficult to separate the therapeutic effect of the intervention from the nonspecific effects of interaction with the practitioner and the heightened expectancy of therapeutic benefit. These limitations result in unreliable evidence.

SELF-HELP AND 12-STEP THERAPY

Twelve-step programs for stimulant and other drug abuse and dependence, such as NA and CA, are modeled after AA, an abstinence-based support and self-improvement program that is based on the 12-step model of recovery [114; 115]. AA is widely considered the most successful treatment program for alcoholism and has helped hundreds of thousands of alcoholics achieve sobriety. The 12-step model emphasizes acceptance of addiction as a chronic progressive disease that can be arrested through abstinence but not cured. Additional elements of the AA model include spiritual growth, personal responsibility, and helping other addicted individuals. By inducing a shift in the consciousness of the addict, 12-step programs offer a holistic solution and a resource for emotional support [116; 117].

The understanding of drug addiction as a chronic and relapsing disorder has helped professionals gain a better understanding of the vital role played by 12-step programs. All patients attempting to recover from a substance use disorder will encounter a time when they face urges to use without having access to the resources or assistance of addiction professionals. Twelve-step programs are not considered substitutes for treatment. Instead, they provide ongoing and indefinite support in the achievement and maintenance of abstinence and in personal growth and character development [117; 118].

Part of the effectiveness of AA, NA, and CA is rooted in their ability to provide a competing and alternative reinforcer to drug use. Involvement in a 12-step program can enhance the quality of social support and the social network of the member, which is a potentially highly reinforcing aspect that would be forfeited if drug use was resumed [72].

Other reinforcing elements of 12-step involvement include recognition for increasingly durable periods of abstinence and frequent awareness of the consequences of drug and alcohol use through attendance at meetings [58]. Research has shown that establishing a pattern of 12-step program attendance early in treatment predicts the level of ongoing involvement. Thus, healthcare providers should emphasize and facilitate early engagement in a 12-step program [119].

Although research on efficacy and patient outcome in NA and CA is limited, many prominent addiction researchers have emphasized the important role that ongoing involvement in a 12-step program plays in recovery from substance abuse [118]. An important finding related to 12-step program efficacy was observed by Weiss et al., who found that 12-step attendance was not associated with decreased drug use, but that 12-step involvement (i.e., speaking or performing service work at a meeting, working with a sponsor outside of the meeting, reading 12-step literature, or working on a step) was [72; 119]. In particular, active involvement in a given month predicted a significant reduction in cocaine use the following month. An interesting finding was that patients who involved themselves in 12-step program activities but whose attendance at meetings was inconsistent achieved rates of drug use reduction that were comparable to those who regularly attended and were involved in the 12-step meetings and program.

One study found that the majority of cocaine-dependent outpatients who attended 12-step programs actually attended AA more often than CA. The authors speculated that in addition to AA being more established and available than CA, some patients might have urges for cocaine triggered by the explicit cocaine-related discussion content found in CA [72].

Narcotics Anonymous (NA)

NA was founded in California in 1952 and has grown to include 67,000 weekly meetings in 139 countries. The following demographic information was obtained in a survey returned by almost half of the 22,803 attendees at the 2015 NA World Convention held in Rio de Janeiro, Brazil [115]:

- Gender: 59% male, 41% female
- Ethnicity: 74% white, 11% African American, 6% Hispanic, 4% multiracial, 3% Asian, and 1% Native American/ Alaska Native
- Average abstinence/recovery period: 8.3 years
- Substance(s) used by members:
  - Alcohol: 79%
  - Cannabis: 68%
  - Cocaine: 55%

The NA website provides additional information regarding sponsors and meetings.

INTERVENTIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

For patients who are not proficient in English, it is important that information regarding the risks associated with the use of cocaine and available resources be provided in their native language, if possible. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. Interpreters can be a valuable resource to help bridge the communication and cultural gap between patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers who ultimately enhance the clinical encounter. In any case in which information regarding treatment options and medication/treatment measures are being provided, the use of an interpreter should be considered. Print materials are also available in many languages, and these should be offered whenever necessary.

PROGNOSIS

Despite numerous interventions that have demonstrated a degree of efficacy in clinical trials, patients in outpatient treatment for cocaine use disorder exhibit very high rates of dropout and relapse, with an average of approximately 50% of patients enrolled in 90-day outpatient programs terminating prematurely [120]. Among outpatients, abstinence upon treatment entry and in the initial weeks of treatment has been associated with abstinence during post-treatment follow-up, with severity of cocaine abstinence symptoms negatively correlated with outcome [61; 120]. Environmental factors that increase the risk of resumption of cocaine use include contact with drug users or a drinking environment [17]. Craving often precedes relapse to cocaine use. One study that measured the effect of extinguishing the reinstating or priming effect of cocaine found it to be an unreliable approach to relapse prevention [121]. Patients addicted to crack cocaine are believed to have a higher relapse rate because of the greater intensity of drug craving, which can be triggered by aspects of the using environment [17; 122].

Factors associated with poor prognosis include a dual diagnosis of psychiatric illness, including comorbid major depression [123]. Antidepressants seem to be less effective in managing the depression in these patients and are not generally effective in reducing cocaine use. Such patients have a poorer prognosis than nondepressed cocaine abusers, possibly due to a unique feature that lowers the response rate to antidepressants. The higher rates of character pathology, higher psychiatric distress, and lower psychosocial functioning found in these patients also are believed to affect outcomes [112].

Patients who abuse both cocaine and alcohol constitute a large proportion of those seeking treatment for cocaine abuse and dependence. Addressing dependence to both substances is important, as polysubstance abusers are more likely than monosubstance cocaine abusers to relapse back to cocaine abuse as the result of alcohol consumption [51]. The severity of cocaine use disorder, initial urine drug screen

results, and frequency of recent cocaine use also have been shown to significantly impact treatment outcomes in patients with comorbid alcoholism [124].

A study of situational, interpersonal, and intrapersonal factors associated with cocaine relapse was performed in a sample of 132 cocaine-dependent outpatients [125]. At two years following treatment, single variable analysis found that abstinence commitment, self-efficacy, positive mood, family support, employment, attendance at aftercare, and participation in a 12-step program predicted less cocaine use. However, multivariate analysis found that the degree of participation in a 12-step program was the single most robust predictor of reduced cocaine use. The authors of the study concluded that these results further validated the important role that 12-step program involvement plays in abstinence; increasing the emphasis to patients on the importance of 12-step program participation could increase positive outcomes [125].

Another study sought to identify the ways in which different social networks foster substance use change in individuals with cocaine dependence [126]. The authors used data from two studies of 489 adults with cocaine use disorder enrolled in intensive outpatient programs between 2004 and 2009. A greater degree of perceived social support from friends was associated with a greater readiness to change, whereas a greater degree of perceived social support from family was associated with a change in substance use goal. A greater degree of social support from both friends and family were associated with less substance use [126].

Short-term outpatient treatment of stimulant abuse and dependence seldom results in abstinence for any sustained period. The traditional view that program failure is a patient problem is being replaced by the view that program failure is reflective of program shortcoming [120; 127].

CONCLUSION

Until the 1980s, cocaine was considered a relatively innocuous recreational drug, and research on the pathophysiology and treatment of cocaine addiction was limited. The introduction and widespread use of crack cocaine, with the associated serious morbidity and profound addiction liability associated with its use, introduced a new emphasis on stemming and treating cocaine use and dependency. The development of pharmacologic interventions and psychosocial therapies for cocaine use disorder has been the focus of much research. It is the goal of this course to provide the knowledge necessary to identify, treat, and provide an appropriate referral to patients with cocaine use or dependence disorders.

RESOURCES

Cocaine Anonymous World Services
https://www.ca.org

Narcotics Anonymous World Services
https://www.na.org

National Institute on Drug Abuse
https://www.drugabuse.gov

Substance Abuse and Mental Health Services Administration
https://www.samhsa.gov

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Evidence-Based Practice Recommendations Citations

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