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REVIEW

# Cocaine Use Disorder (CUD): Current Clinical Perspectives

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**Abstract:** Cocaine use disorder (CUD) is a devastating disorder, impacting both individuals and society. Individuals with CUD face many barriers in accessing treatment for CUD, and most individuals with CUD never receive treatment. In this review, we provide an overview of CUD, including risk factors for CUD, common co-occurring disorders, acute and chronic effects of cocaine use, and currently available pharmacological and behavioral treatments. There are no FDA-approved pharmacological treatments for CUD. Future studies with larger sample sizes and testing treatment combinations are warranted. However, individuals with CUD and co-occurring disorders (eg, a mood or anxiety disorder) may benefit from medication treatments. There are behavioral interventions that have demonstrated efficacy in treating CUD – contingency management (CM) and cognitive-behavioral therapy for substance use disorders (CBT-SUD) in particular – however many barriers remain in delivering these treatments to patients. Following the discussion of current treatments, we highlight some promising emerging treatments, as well as offer a framework that can be used in building a treatment plan for individuals with CUD.

**Keywords:** cocaine, cocaine use disorder, treatment, pharmacotherapy, behavioral interventions

## Introduction

Cocaine use disorder (CUD) – the compulsive use of cocaine despite its medical, psychological, and behavioral consequences – is a severe public health problem, affecting millions of people globally. In the United States (US) alone, approximately 2.2 million people use cocaine regularly (compared to 600,000 methamphetamine users), 1.5 million of whom meet the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) criteria for CUD.[1,2]

Recent nationwide epidemiological data show that both cocaine use and cocaine-related problems, including CUD, are increasing in adults as well as in adolescents.[3–5] In the US, the percentage of overdose deaths involving cocaine is increasing, doubling in one year alone between 2015 and 2016 – in 2017, among the 70,237 drug overdose deaths in the US, about 20% involved cocaine.[6] Currently, the rate of cocaine overdose deaths is higher than opioid overdose deaths in Black men and women.[7] In 2011, cocaine use contributed to more than 500,000 emergency room visits in the US[8] due to overdose, medical disorders, accidents, and violence. In addition to contributing to medical emergencies, cocaine use causes many disabling and costly health problems, including heart attack, stroke, neuropsychiatric complications, and increases the risk of contracting HIV and hepatitis C.[9,10] Cocaine use is also associated with frequent encounters with the criminal justice system, including crime, arrests, and imprisonment – and thus altered family structures, which disproportionately affects minorities in part due to racial disparities in crack-cocaine sentencing.[11–14] More than one-third of homeless adults report lifetime cocaine use problems.[15] The availability of effective and widely accessible treatments for CUD remains an urgent challenge.

The development of novel and efficacious treatments for CUD has been an area of intense research over the past 3 decades. The results of these studies have been the subject of several excellent systematic reviews and meta-analyses.[16–19] In this review article, we provide a clinically relevant overview of the current literature on CUD. We

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first summarize the clinical epidemiology of CUD and then follow with an overview of the neurobehavioral consequences of short- and long-term cocaine use. We then summarize the current pharmacological and behavioral treatment approaches for CUD, and discuss emerging treatment approaches.

## Diagnostic Criteria

The DSM-5 defines CUD as clinically significant impairment or distress caused by at least 2 of 11 criteria in the preceding 12 months.[20] The 11 criteria can be organized into the following 4 groups: 1) physiologic, including craving, tolerance, and withdrawal, 2) loss of control of cocaine use, 3) cocaine use taking precedence over other activities (including responsibilities at home, work, or school), and 4) other negative consequences from cocaine use. According to the DSM, the presence of two or three symptoms indicates mild CUD, the presence of four or five symptoms indicates moderate CUD, and the presence of six or more symptoms indicates severe CUD.

The DSM-5 also provides definitions for different levels of remission. Early remission is defined as the absence of symptoms, except for cravings, for more than 3 months and less than 12 months, and sustained remission is defined as 12 months without symptoms, except for cravings. CUD, like all substance use disorders, tends to be chronic and relapsing in nature, and, similar to other chronic diseases, many patients require multiple episodes and modalities of treatment, which can together over time contribute to sustained recovery.[21]

The DSM-5 does not offer a definition of recovery, and there is no standardized definition of the term. While recovery has many meanings, most extend beyond cessation of substance use, emphasizing improved health and broader changes in behavior and sometimes even identity.[22]

## Clinical Epidemiology

### Overview

According to the 2019 National Survey on Drug Use and Health, which included people aged 12 and older, 5.5 million people reported past year cocaine use.[23] Among cocaine users, about 20% will meet the criteria for CUD at some point in their lifetime.[24,25] Among individuals who report cocaine use (including even just once), approximately 15% are estimated to progress to CUD within the following 10 years[26] – a rate of progression higher than those found for cannabis (8%) and alcohol (12–13%). Additionally, the speed of progression from first cocaine use to CUD is much faster than the speed of progression from first use of alcohol to alcohol use disorder or from the first use of cannabis to cannabis use disorder, with one in 16 to 20 cocaine users becoming dependent within the first year of cocaine use.[26] The National Epidemiological Survey of Alcohol and Related Conditions study, utilizing a large-scale community-based sample, found that the probability estimate of transitioning from first substance use to dependence was 7.1% for people who use cocaine, compared to 2.0% for those who use nicotine, alcohol, or cannabis.[24] Although over time ongoing cocaine use continues to carry a high risk of progressing to CUD, given that the peak risk for initiation of cocaine use occurs at around age 20, much of the burden of CUD is carried by a younger population who often then struggle to quit for many years. For example, Simpson et al found that one year after completion of treatment (which in the study ranged from outpatient to residential), 21% of individuals initially diagnosed with CUD continued to use cocaine weekly, and the proportion of weekly cocaine users rose to 25% at 5 years.[11] Moreover, 5 years after treatment, 18% reported having been arrested, emphasizing the high rates of the psychosocial impact, including legal stigma, of CUD.

### Risk Factors

Many risk factors for CUD have been identified, including genetic, environmental, and other demographic and individual-level factors. Progression from experimentation with cocaine to the development of addiction has a significant genetic component.[27] While heritability estimates vary, CUD is thought to be one of the most heritable mental health disorders[28] – the risk for developing CUD is estimated to be up to 65% hereditary in women and up to 79% heredity in men.[29,30] In comparison, the heritability for both alcohol and opioid use disorders is estimated to be 50% for both men and women.[31,32] However, unlike tobacco and alcohol use disorders, specific genes directly linked to CUD remain to be identified. Environmental factors increase the risk of substance use disorders in general; however, CUD,

similar to stimulant use disorders, is largely influenced by shared environment.[33] Environmental factors can disproportionately affect minority populations. For example, black individuals have reported increased use of cocaine in the more addictive form of crack,[34] which, in one study, was shown to be accounted for by increased availability and shared social conditions in some communities.[35] Black individuals also experience longer gaps between problematic use and treatment entry.[36] Other risk factors for developing CUD include impulsivity,[37] childhood ADHD diagnosis,[38] childhood adverse experiences,[39] fewer years of education,[40] lower parental level of education,[41] polysubstance abuse,[42,43] and presence of co-occurring mental health disorders.[24] Using cocaine in more addictive forms such as crack-cocaine or via IV compared to intranasal routes,[44] and using cocaine more frequently and in higher amounts, all increase the risk for CUD.[25] Frequency of cocaine use seems to increase the risk of CUD more strongly than the amount of use; however, frequency and amount of use synergistically combine to increase the risk of progressing to CUD.[25]

## Co-Occurring Mental Health Disorders

Co-occurrence between CUD and other mental health disorders is frequently observed in both treatment samples and large epidemiological studies. Two studies of treatment-seeking cocaine users found similar rates – 73.5% and 65% – of co-occurring lifetime mental health diagnoses, not including a co-occurring substance use disorder.[45,46] Among responders in the US National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), 45% of cocaine users reported a lifetime mood disorder, and 31% reported a lifetime anxiety disorder.[47] Compared to those who have never used cocaine, current cocaine use is associated with an almost tripled risk for depression (6% vs 16%) and a more than doubled risk for anxiety disorders (11% vs 5%).[48] A meta-analysis estimated an 11 to 28% lifetime prevalence of bipolar disorder among individuals with CUD, compared to 1 to 3% for those in the general population.[49]

CUD is associated with high rates of both polysubstance use and co-occurring substance use disorders. In a study investigating mono vs polydrug use abuse, 77.8% of individuals who used cocaine reported polysubstance use (n = 21,970) – in terms of using substances simultaneously, the most common combination reported was cocaine and alcohol.[50] In a separate study, in a sample of 227 individuals with CUD, the prevalence of lifetime heroin, alcohol, and benzodiazepine dependence were 46%, 29% and 25%, respectively.[46] Concurrent use of cocaine and other drugs has multiple health risks. For example, co-use of cocaine and opioids contributes to cocaine overdose deaths,[51] and co-use of alcohol and cocaine increases blood cocaine levels by 30% and increases cardiotoxicity by forming cocaethylene, a potentially lethal byproduct.[52] About 75–84% of cocaine users also smoke cigarettes (the leading cause of preventable death in the US),[53,54] and the quit rate for smoking among cocaine users is much lower than for those who do not use other illicit substances (13% vs 56%).[54]

In general, co-occurring substance use disorders and other mental health disorders negatively impact the treatment outcome of each other.[55,56] This is true for CUD as well. The presence of mental health and substance use co-occurrence has a strong impact on the development and maintenance of CUD – contributing to the severity of CUD and to poorer treatment retention and outcomes.[57–59] For example, the presence of co-occurring depression is associated with greater euphoria from cocaine use,[60,61] more intense cravings, and more severe withdrawal symptoms during early abstinence from cocaine.[62,63] Co-occurring depression also predicts a higher likelihood of relapse.[64] Similar to depression, cocaine use is a well-known risk factor for suicidal ideation and suicide attempt,[65–67] emphasizing the risks associated with the co-occurrence of CUD and depression.

There are many theories as to why such high rates of co-occurrence exist between substance use disorders and other mental health disorders. Mental health disorders and SUDs may have shared genetic vulnerabilities. According to the self-medication hypothesis, individuals try to relieve symptoms of a psychiatric disorder (such as depression) or side effects of medications (such as sedation).[68,69] Features of anxiety and depression (such as negative internal mood states, including stress) may trigger substance use.

Another popular idea to explain high rates of co-occurrence is the shared vulnerability underlying substance use disorders and other mental health disorders (depression, bipolar disorder, and anxiety disorder). Genetic studies that found overlapping shared vulnerability across substance use and other psychiatric disorders support this hypothesis. For example, rather than being only driven by genetic variations in underlying biological processes directly linked to drug actions or drug metabolism, it is likely that addiction is driven by genetic variants that also mediate activity in brain circuits and regions involved in domains such as personality traits, reward, and mental health conditions.[70]

Clinically, it can often be difficult to distinguish an independent (or primary) mood disorder from a mood disorder secondary to (or caused by) a substance. This distinction often relies on determining the temporal sequences of mood symptoms and substance use, which is aided by following a patient longitudinally. Primary mood disorders are diagnosed when symptoms precede substance use or exist during periods of at least several weeks of abstinence. For individuals with long histories of overlapping mood symptoms and substance use, making the distinction between an independent and secondary mood disorder can be challenging, particularly as mood and substance use disorders tend to recur in nature, and patients with an SUD may have a difficult time achieving long periods of abstinence. For example, for individuals with co-occurring CUD and depression, it may be difficult to determine if depression is primary or caused by cocaine withdrawal. Given the high rates of co-occurring mental health disorders seen in SUDs and the overlapping symptomatology across these disorders, new paradigms may be needed for how we think about these conditions that we often try to diagnostically separate and treat individually. Ultimately, both substance-induced and "primary" mood disorders need clinical attention and treatment, even when making this distinction is challenging or not possible.

### Sex Differences

CUD is associated with critical sex-based differences. Rates of lifetime CUD are higher among men – 3% for men vs 1.8% for women.[71] Women, however, progress faster than men from first cocaine use to addiction. This rapid progression is termed a "telescoped course", and it may be related to women being more likely to use crack cocaine, which is highly addictive.[72] The profile of co-occurring mental health disorders among men and women with CUD also differ. Among individuals with CUD, men are more likely to have co-occurring SUDs and ADHD, while women are more likely to have co-occurring anxiety disorders, eating disorders, and post-traumatic stress disorder.[72–75] Among individuals who enter treatment for CUD, men and women report equal rates of homelessness; however, women are more likely than men to report past trauma and receive pharmacotherapies for psychiatric conditions, suggestive of a higher level of complexity and a higher disease burden.[75,76] Women who use cocaine also typically present to treatment reporting more socio-economic problems than men.[74] They are more likely than men to be unemployed and receive public aid,[76] and they report greater interpersonal problems.[74] They are also more likely than men to live with children,[76] and thus must balance treatment with childcare. Following treatment, women are more likely than men to return to cocaine use in the context of distressing emotional states and interpersonal conflict.[77] Collectively, these findings underscore the need for more sex-specific and tailored treatment approaches, as discussed below.

## Acute and Chronic Neurobehavioral Effects of Cocaine

### Acute Effects

There are several acute effects of cocaine that may drive typical patterns of use. As a psychostimulant, cocaine activates the sympathetic nervous system, causing increased arousal, vigor, activity, wakefulness, and elevated mood, as well as reduced appetite and sleep. Cocaine's acute effects last for approximately 20–30 minutes; during this time users report feeling an intense euphoria or "high." Acutely, and like other drugs of abuse, cocaine increases dopamine release in the brain's mesolimbic reward systems, and this effect is believed to underlie the euphoric and addictive potential of cocaine. At higher doses and with more rapid routes of administration (eg, smoked or intravenous vs intranasal), cocaine tends to induce more robust euphoria, thereby increasing the likelihood of developing addiction.[78]

In a study of 36,309 adults in the US, 73% of cocaine users reported using an average of 0.8 grams on 0.4 days per week, compared to the remaining 27% who reported using between 2.6 and 19 grams of cocaine daily, at least 3 or more days per week.[25] During cocaine binges, cocaine is used in large quantities during a discrete period until resources to do so have run out or the user is unable to continue use. These periods are associated with a higher risk of participating in criminal behavior, contracting sexually transmitted diseases such as HIV, and engaging in other impulsive behaviors with dire consequences for the individual and society.[79,80]

## Neurobehavioral Features of Individuals with Chronic Cocaine Use

Key neurobehavioral changes occur with continued regular use of cocaine. These changes include the emergence of withdrawal following cessation of cocaine use and reduced euphoria from a given dose of cocaine (ie, tolerance), which can drive dose escalation. Symptoms of cocaine withdrawal include fatigue, psychomotor slowing, anxiety, depression, sleep disturbance, increased appetite, and intense craving for cocaine use. Although milder than withdrawal symptoms that accompany alcohol or opioid use, cocaine withdrawal symptoms can drive further cocaine use due to physical and psychological distress. Approximately 82–86% of cocaine users experience cocaine withdrawal – these estimates are based on two recent studies, one of which included individuals using cocaine at least twice a week for 6 months, and one of which included individuals who met criteria for CUD.[81,82] Those who experience cocaine withdrawal are more likely to use cocaine in larger amounts, report stronger euphoria, and have more severe medical, psychiatric, and psychosocial problems.[81]

According to the incentive-sensitization theory, addiction develops due to an increased sensitivity to drug-related cues, even while the drug's euphoric effects are diminished. This phenomenon is driven by learned associations and neuroplastic brain changes, leading to a drastic increase of "wanting" or "desiring" of the substance (eg, craving) which is often decoupled from a corresponding "liking" of that substance.[83] One way to assess such hypersensitivity to drug-related cues is by measuring an automatic cognitive process called attentional bias for that drug.[84] Once an increased attentional bias to cocaine develops, one more quickly notices cocaine-related cues and also has difficulty switching attention to more neutral stimuli.[85,86] It has been suggested that increased attentional bias for cocaine cues may serve as a cognitive marker for CUD (reviewed in Sofuoglu et al 2014).[87] The incentive-sensitization model is particularly relevant to CUD, as its core features are intense cravings (or "wanting" the substance), and high responsiveness to drug cues – as opposed to prominent withdrawal symptoms, which tend to accompany alcohol or opioid use.[81]

Chronic cocaine use is associated with several chronic neurocognitive deficits. People who chronically use cocaine display deficits in attention (particularly sustained attention), visual and working memory, verbal fluency, sensory-perceptual functions, response inhibition, and impulsivity (reviewed in Potvin).[85,88,89] Notably, many of these deficits persist after several months of abstinence,[85] indicating that they are not caused by immediate drug effects or acute phases of withdrawal. In a meta-analysis of 15 studies comparing cocaine users to healthy controls, cocaine use caused the greatest deficits in visual and working memory and attention.[88] Furthermore, neuro-imaging studies, commonly utilizing functional magnetic resonance imaging (fMRI), conducted on cocaine users show decreases in activation or abnormal blood flow in brain regions that underlie executive and attentional function, such as anterior cingulate,[90] lateral prefrontal,[90] prefrontal,[91] and orbitofrontal cortices.[92] It is unclear if these cognitive deficits precede or follow cocaine use. Individuals with pre-existing cognitive deficits are more likely to use substances and develop SUDs.[93] Alternatively, chronic use of cocaine and other drugs (eg, alcohol, tobacco) may contribute to cognitive deficits in a dose-dependent manner.[94] Regardless of their cause, cognitive deficits observed in individuals with CUD have clinical relevance. For example, among cocaine users, treatment non-completers tend to perform worse in cognitive measures;[95] consistent with this, better executive function predicts longer retention in treatment.[96] Deficits in executive functioning can lead to decreased "top-down" processes important in recovery. For example, executive functions such as sustained attention and response inhibition are likely needed to help regulate drug use behavior,[97,98] and it follows that breakdown in these processes enhances vulnerability to substance use and relapse. These types of cognitive deficits may also serve as a treatment target for both pharmacologic and behavioral interventions, as we outline below (see Treatments Targeting Cognitive Deficits).

Finally, neuroimaging studies have revealed differences in underlying neural networks in individuals with CUD compared to healthy controls who do not use substances. As with other drugs of abuse, chronic exposure to cocaine causes neuroplastic changes that ultimately dysregulate neural circuitry. While different brain regions are affected by different stages of addiction, the mesocorticolimbic[99] circuit is the core circuit affected. While acute exposure to cocaine increases synaptic dopamine release in the mesolimbic circuit, chronic repeated exposure is associated with reduced dopamine function,[100] underlying the anhedonia that accompanies substance use disorders. Attempting to correct

imbalances in brain circuitry is the aim of emerging treatments such as transcranial magnetic stimulation (see Non-Invasive Brain Stimulation Methods, below).

# Overview of Current Treatment Approaches

## Pharmacotherapies

Over the past few decades, numerous studies have investigated pharmacologic treatments for CUD. However, thus far, no medication has met the Food and Drug Administration's (FDA) criteria for approval, which consists of treatment efficacy demonstrated in at least two adequately powered (typically n > 200) randomized, placebo-controlled trials (RCT). While no drug class has proven to be effective,[17] individual compounds with therapeutic promise have been used off-label. In this section, we discuss some of the most relevant findings per drug class.

### Antidepressants

Results from a Cochrane review,[101] a systematic review and meta-analysis,[17] and an umbrella review[102] suggest that, as a class, antidepressants have no consistent effect on any clinically relevant measure of CUD studied thus far (including cocaine use, sustained abstinence, retention, and harm outcomes). Instead, antidepressants have been associated with higher drop-out rates, possibly by causing adverse events – although the quality of the evidence for this finding has been deemed low.[17,101]

Among the studies that have found therapeutic effects of antidepressants for CUD is a double-blind placebo-controlled trial administering citalopram, a selective serotonin reuptake inhibitor (SSRI) antidepressant. In this study, citalopram was superior to placebo in reducing cocaine use, when combined with a behavioral intervention (either cognitive-behavioral therapy or contingency management).[103] Likewise, in a 12-week double-blind RCT, sertraline, another SSRI, delayed time to returning to using cocaine among 86 cocaine-dependent individuals with depressive symptoms who had already been abstinent for two weeks when the trial began.[104] Finally, in another trial, bupropion, with a mechanism of action that differs from SSRIs, enhanced the efficacy of contingency management in promoting abstinence from cocaine.[105,106]

### Psychostimulants

By mimicking some actions of cocaine through increased dopaminergic activity but with key differences in pharmacokinetic properties – such as slower onset of effects and a longer half-life, and thus less abuse risk – psychostimulants have been used off-label to promote abstinence from cocaine. While a Cochrane review that included 26 trials (N = 2366) found low strength evidence that psychostimulants may promote abstinence in 14 trials (defined by 3 weeks of non-use in 13 of the studies and 2 weeks of non-use in 1 study), no differences in cocaine use, study retention, or harm outcomes were found.[105] In another study, a high-dose (60 mg) but not low dose (30 mg) of sustained-release preparation of dextroamphetamine reduced cocaine use.[107] Finally, another RCT administering 60 mg sustained-release dextroamphetamine in heroin- and cocaine-dependent individuals also being treated with methadone and diacetylmorphine found that dextroamphetamine was well tolerated and decreased days of cocaine use.[108]

### Dopamine Agonists

A Cochrane review of 17 studies found no difference between dopamine agonists (bromocriptine, amantadine, and pergolide) in any clinically relevant outcome – including positive urine samples for cocaine metabolites and study retention.[109] Another Cochrane review of 24 trials found no difference between dopamine agonists (including bromocriptine, amantadine, and pramipexole) compared to placebo in treatment retention or abstinence from cocaine use among people with CUD.[110] The authors also found no evidence that combining a dopamine agonist with a psychosocial intervention improved treatment outcomes.[110] A study investigating amantadine to reduce cocaine use and cravings found it was no more effective than placebo, in a group of cocaine-dependent individuals who were receiving methadone for co-occurring opioid use disorder.[111] A separate study examining amantadine's efficacy in reducing cocaine withdrawal symptoms and improving CUD outcomes found that amantadine decreased cocaine use, measured by urine samples and self-reports, in a group of cocaine-dependent people who were experiencing severe withdrawal symptoms at the start of the study.[112] In this study, amantadine did not promote abstinence in the individuals who experienced less

severe cocaine withdrawal at the start of the study, consistent with the authors' speculation that amantadine reduces cocaine withdrawal symptoms.

Modafinil is another well-known cognitive enhancer with the potential to treat CUD. Modafinil affects multiple neurotransmitter systems, and increases dopamine by blocking dopamine transporters.[113] In an inpatient setting, modafinil improved working memory and sustained attention in cocaine-dependent individuals (N= 16), compared to individuals randomized to escitalopram, escitalopram plus modafinil, or placebo.[114] In a separate study, modafinil treatment was associated with more days of abstinence from cocaine, when combined with weekly one-hour psychotherapy sessions.[115] In another study, modafinil increased the likelihood of negative urine samples and chances of achieving cocaine abstinence for more than 3 weeks after treatment.[116] However, in a follow-up study, the authors were unable to replicate this effect.[117] A meta-analysis including 11 studies found that overall, modafinil was not superior to placebo in improving measures of CUD, yet the authors noted that in a subgroup analysis of 6 studies conducted in the US, modafinil increased cocaine abstinence rates.[118] The authors concluded that, based on modafinil's tolerability and good safety profile, it deserves further investigation.

### Antipsychotics/Dopamine Blockers

A recent Cochrane review of 14 studies (N = 719) investigating the efficacy of antipsychotic pharmacotherapy for the treatment of CUD (via actions on dopaminergic and serotonergic systems) found that antipsychotics reduced treatment drop-out rates but had no significant effect on any other outcomes related to CUD.[119] Similarly, a systematic review and meta-analysis including 8 RCTs investigating antipsychotics for the treatment of CUD concluded that antipsychotics may improve treatment retention.[17] Clozaril, however, has shown some promise in reducing substance use, including cocaine use, in patients who are receiving this medication for a co-occurring psychotic disorder.[120,121]

### Anticonvulsants and Muscle Relaxants

Stimulation of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) decreases activation of the dopamine reward circuitry. Thus, anticonvulsants, which increase GABA activity, may decrease cocaine-induced dopamine release and reinforcing effects. A systematic review of 20 RCTs (N = 2068) found no significant difference between anticonvulsants and placebo in cocaine use, craving, rates of anxiety and depression, and treatment retention.[122] Studies investigating topiramate, an anticonvulsant that stimulates GABA and inhibits glutamate, have found conflicting results. A meta-analysis of five RCTs (N = 518) examining topiramate for CUD found that, compared to placebo, topiramate increased abstinence (low strength of evidence) but did not affect study retention (moderate strength of evidence).[17] A recent RCT, completed after the above meta-analysis was published, found that, compared to placebo, topiramate decreased the amount and frequency of cocaine use for the first 4 weeks of the study, but by week 12 there was no difference between treatment with topiramate and placebo.[123]

### Repurposing of Medications Approved to Treat Other SUDs

With the exception of disulfiram – which has mixed evidence to treat CUD – no significant differences in outcomes have been found for medications approved to treat other SUDs. Disulfiram inhibits the enzyme dopamine-beta-hydroxylase, which converts dopamine to norepinephrine, thus increasing synaptic dopamine levels. Some clinical trials show that disulfiram may decrease cocaine use in those with co-occurring opioid use disorder,[124] and also in those with co-occurring alcohol use disorder with and without co-administration of naltrexone.[125] In a different study, disulfiram reduced cocaine use in individuals with CUD who were not alcohol dependent or who did not drink alcohol during treatment, compared to those who were using alcohol or who were alcohol dependent.[126] A meta-analysis of 12 RCTs found low strength evidence that disulfiram does not increase abstinence and instead decreases retention; however, the authors noted that the evidence was insufficient for drawing conclusions due to the heterogeneity of effects measured.[17]

### Ketamine

Finally, ketamine has shown some promise as a novel treatment for SUDs including CUD. NMDA receptors are believed to be the main glutamate receptor involved in learned behavior, and ketamine, through NMDA receptor antagonism, modulates glutamate signaling. A recent RCT found that one single subanesthetic ketamine infusion, compared to an

infusion of midazolam, improved several treatment outcomes of CUD – including lowering the likelihood of using cocaine and decreasing cravings and relapse risk – in a group of 55 cocaine-dependent individuals who also initiated mindfulness-based relapse prevention therapy (MBRPT) as part of the study.[127] MBRPT was combined with ketamine because the authors speculated that the two treatments would activate similar brain networks and therefore enhance each other. Impressively, the group who received ketamine and therapy had higher rates of abstinence even at a 6-month follow-up. These promising findings warrant future studies with larger samples.

There are many reasons why, despite numerous studies, no medications have been approved for CUD. These include methodological issues, small sample sizes leading to underpowered studies, high drop-out rates, and heterogeneity of both study design and sample population. Additionally, as observed recently by Brandt et al, a great many pharmacological treatments for CUD have been explored; however, only a few studies have been carried out for each individual medication.[18] Thus, they argue that medications that have demonstrated positive signals in early studies should be given further investigation. Exploring combination therapies is another promising area.

## Psychosocial Treatments for Cocaine Use Disorder

Psychosocial treatments for CUD are limited in variety but nonetheless are the current standard of practice for this disorder, representing the culmination of nearly four decades of clinical research.[128–131] Here, we discuss two approaches that have received the greatest degree of empirical support: Contingency Management (CM)[130,132] and Cognitive-Behavioral Therapy for Substance Use Disorders (CBT-SUD).[133,134] We begin by providing a brief history of each treatment's development before describing its structure, application, and empirical support. Lastly, we note treatment limitations and discuss ongoing efforts to refine these psychosocial interventions for CUD.

### Contingency Management

CM was first implemented in the US within opioid treatment clinics, in which the possibility of frequent objective drug-use monitoring (eg, via urine toxicology screens) and related, salient natural rewards (eg, take-home methadone doses) allowed researchers to demonstrate the value of positive contingencies in reducing substance use.[131,135–137] CM was later applied to CUD during the 1980s, prompted in large part by the lack of effective pharmacotherapies for this condition.[129,136,138] These initial efforts were crucial for establishing CM as a formal treatment and in the culmination of the treatment practiced today.

Application of CM draws heavily from operant conditioning principles, focusing on systematically adjusting reinforcers and punishers in a patient's environment to increase behavior in alignment with treatment goals.[139] Abstinence, assessed via urine toxicology screens 2–3 times per week, is frequently indicated as the main treatment goal and reward for negative (drug-free) toxicology screens serve as the primary reinforcer in CM. That is, patients who provide negative screens receive monetary-based vouchers[130,140] or opportunities for prizes[141,142] redeemable for retail goods or services. Voucher/prize-value is systematically increased following consecutive negative screens to incentivize sustained abstinence; conversely, positive screens or failure to submit urine screens at scheduled times results in resetting of reward values to their initial levels. CM for CUD is typically offered in an outpatient setting over 12-weeks[132,143] and has been provided in both individual and group formats.[144]

Within this common framework, reinforcement is organized around several principles including rapidly and accurately detecting cocaine use, positively reinforcing abstinence close-in-time to detection, loss of positive reinforcement upon drug use, and incorporation of reinforcers to compete with drug use.[129] As the evidence base supporting CM has grown, its refinements in its practice have similarly developed, with, for example, better outcomes resulting in more immediate provision of reinforcement following objective verification of abstinence or provision of higher-magnitude reinforcers.[145,146] Additionally, individuals who demonstrate greater within-treatment abstinence tend to show better long-term outcomes after treatment ends.[147]

CM has routinely demonstrated a high level of efficacy in treating CUD, with multiple studies and RCTs showing effectiveness of CM over standard care and in patients who have co-occurring SUDs or mental health disorders.[148–154] Studies have also indicated that CM is effective across several different clinical groups, including community[155] and veteran populations.[150] For example, Bentzley et al conducted a meta-analysis comparing several different treatments for

CUD including psychotherapies, various medications (eg, antidepressants, psychostimulants, opioids), and placebo groups; collectively, results suggested only CM was associated with greater likelihood of negative urine toxicology screens for cocaine.[148]

Despite CM's extensive empirical support, several ongoing barriers impede its widespread adoption including societal and provider stigma, concerns about the durability of treatment effects, and pragmatic concerns such as implementation costs and personnel availability.[156] Additionally, there is some concern with how CM can be implemented alongside other treatment approaches such as 12-step facilitation. Approximately two-thirds of substance use clinics report that the 12-step method is the predominant treatment approach.[157,158] Clinic staff that use a 12-step approach may hesitate to implement CM due to philosophical or practical concerns.[159] However, CM is a remarkably effective intervention generally and in some meta-analyses has outperformed other active treatments for CUD.[148,149,160,161] Furthermore, the emphasis on abstinence is consistent with 12-step treatment perspectives. While reductions from peak treatment abstinence levels can occur, multiple studies show lasting effects of CM up to 1-year post-treatment completion.[162–164] Finally, while CM can be an expensive treatment to implement (eg, patients in trials conducted by Higgins et al could earn nearly $1000)[140], a large body of research illustrates that CM can be implemented at costs as low as $240/per patient and conducted in cost-effective formats, such as in therapy groups. [155,165]

## Cognitive-Behavioral Therapy for Substance Use Disorders (CBT-SUD)

CBT-SUD for CUD grew from broader efforts to apply cognitive-behavioral principles to the treatment of addictive behaviors. Drawing from applications of CBT in depression and anxiety, initial applications of CBT in addictive behaviors were validated by Marlatt et al in patients seeking treatment for alcohol use.[136,166,167] Following its initial validation, CBT-SUD was then applied to treat CUD, largely through the work of Carroll et al. These efforts culminated in the publication of Carroll's seminal manual, A Cognitive-Behavioral Approach: Treating Cocaine Addiction.[128,133,134] CBT-SUD has since become a widely familiar model amongst practitioners with a strong evidence base.

CBT-SUD focuses on helping patients understand their cocaine use and teaching them new skills to help manage it. A core aspect of this approach is the integration of "functional analysis", which aids patients in understanding the antecedents and consequences prompting/maintaining cocaine use. From this foundation, patients receive skills training on how to understand, recognize, and intervene during cravings/urges, identify and challenge unhelpful cognitions related to cocaine use, effectively problem-solve, implement assertive communication to refuse drug offers, reduce drug-related cues in their environment, and recognize and intervene on seemingly minor decisions that can increase risk of cocaine use.[134] Within this framework, sessions are often structured to ensure time is allocated for psychoeducation, skill/home practice review, and introduction of novel skills. Several "core" skill modules (eg, functional analysis, coping with cravings, drug refusal skills)[134] are integral components of this manualized protocol, though later iterations have expanded these topics to include numerous "adjunctive" modules (eg, mood management, listening skills, social and recreational counseling)[168]. In CBT-SUD, patients are asked to complete regular home-practice between each session that, as indicated above, is then reviewed by providers in subsequent meetings. CBT-SUD is typically conducted in 1-hour weekly, individual sessions occurring over 12 to 16 weeks; however, this treatment has commonly been applied in group formats.[169]

There is a large body of evidence supporting the efficacy of CBT in treating CUD. Several RCTs have shown CBT-SUD is effective in reducing cocaine use.[126,170,171] Notably, some evidence has indicated "sleeper effects" of CBT-SUD for CUD, in which improvements in cocaine use continue after treatment completion.[133] Rawson et al, for example, conducted an RCT in which methadone-maintained participants with CUD were randomly assigned to either CBT, CM, CBT+CM, or treatment as usual (TAU).[163] Their results indicated reductions in cocaine use after the treatment period (16 weeks) for both CM and CBT, though CM demonstrated slightly larger effects immediately post-treatment; however, at 26- and 52-week follow-ups, CBT participants continued demonstrating improvements, resulting in equivalent improvements between CBT and CM at these timepoints. Thus, CBT-SUD is not only effective but its effects may persist beyond the completion of treatment.

Despite CBT-SUD's empirical support, several treatment considerations and implementation barriers are important to note. First, with respect to treatment considerations, CBT-SUD's efficacy is in part dependent on patient skill and

generalization.[172,173] This is exemplified in work by Decker et al that showed patients who completed less than half of assigned home practice demonstrated greater cocaine use than patients completing more than half of assigned home practice; these effects remained significant even after statistically controlling for baseline cocaine use frequency and session attendance.[174] Second, fidelity has remained an ongoing challenge to effectively implementing CBT-SUD,[171,175] with research suggesting higher levels of didactic training and supervision are necessary to maintain adequate model-adherence in practice.[176] Even among individuals who have been thoroughly trained to use evidence-based treatments, like CBT-SUD, clinicians are not as adherent to treatment protocols even though they believe themselves to be competent.[177] Collectively, these issues present significant practical demands from practitioners and administrations to ensure adequate delivery of CBT-SUD for patients with CUD.

These barriers prompted adaptations in the delivery of CBT-SUD, with the most notable example being a computer-assisted program known as "CBT4CBT".[178–181] CBT4CBT utilizes multimedia (eg, video, text, games, cartoons) features to help coach patients through learning CBT-SUD coping skills. The platform provides a standardized method of delivering clinician-adjunctive services to help treat cocaine and other substance use disorders. Evidence for CBT-SUD demonstrates comparable efficacy and effect duration with its traditional modality generally for substance use disorders,[178,182] as well as specifically for CUD .[183–185] In Carroll et al's RCT of CBT4CBT, methadone-maintained patients with CUD who completed an 8-week course of the program reported high acceptability of CBT4CBT, alongside greater odds of obtaining ≥3 consecutive weeks of cocaine abstinence and negative urine screens for all drugs; further, these effects were retained at a 6-month follow-up.[183] Finally, cost-effectiveness research has suggested stark superiority of CBT4CBT versus traditional implementations of CBT-SUD.[186]

### Summary of Psychosocial Treatments for CUD

In summary, psychosocial treatments represent the current gold-standard for CUD treatment. Within this broader category, CM and CBT-SUD currently have the greatest empirical support in positive treatment outcomes (eg, reduced cocaine use), collectively garnered over approximately 3 decades of research and application. Nonetheless, ongoing barriers remain including implementation barriers such as stigma towards these practices, pragmatic limitations (eg, cost, staff availability), and model adherence. Though ongoing research efforts are refining the extent and application of these modalities (eg, computer-assisted methods like CBT4CBT),[179] there remains a need for greater dissemination and implementation of both CM and CBT-SUD for CUD.

## Integrated Care and Combined Treatments

Integrated treatment refers to when treatment of both the SUD and the co-occurring mental health disorder are delivered by the same clinician or clinical team. This approach has been considered the ideal treatment for individuals with co-occurring mental health disorders and SUDs at all levels of treatment (inpatient, outpatient, etc.).[187–189] Although integrated treatment approaches are supported in the literature, a recent Cochrane review found low-quality evidence of no difference between integrated models of care and standard models of care for multiple outcomes including substance use and global functioning.[190] There are several reasons that could explain this finding, including the difficulty in standardizing integrated dual diagnosis treatment.[191] Aside from the difficulties in ensuring standardization of integrated treatment, there are other barriers to this type of care in both research and clinical practice. Most treatment centers are still not even designed to offer this type of care. For example, a survey of 180 community addiction programs spanning residential treatment programs, outpatient programs, and intensive outpatient programs found that only 20% offered integrated or dual diagnosis services,[192] and a separate study which sampled 256 programs across the US found that only 18% of addiction treatment programs and 9% of mental health programs offered integrated treatment approaches.[193]

Multimodal care typically includes combining psychosocial interventions (such as CM or CBT) with medications, and this approach often has better outcomes than treatment with a single intervention. For example, in a study investigating the efficacy of desipramine combined with CM for the treatment of opioid and cocaine dependence, while both CM and desipramine were individually effective in increasing opioid and cocaine-negative urines, the combined treatment was more effective in improving these outcomes than either treatment alone.[194] Similarly, individuals treated with 40mg

fluoxetine and the environmental contingency of decreased clinic visit requirements for fewer cocaine-positive urine samples had fewer cocaine-positive urine samples than those treated with only 20 mg fluoxetine or placebo.[195] Another study of 106 opioid-dependent cocaine users found evidence that combining CM with bupropion reduced cocaine use more than bupropion alone, and for a longer period than for CM alone.[106] Taken together, these studies underscore the potential synergism between behavioral and pharmacological treatments for CUD.

# Emerging Treatments

## Treatments Targeting Cognitive Deficits

As discussed above, there are neurocognitive deficits associated with regular cocaine use. Many of these overlap with changes seen in the mental health disorders that are commonly co-occurring among people with CUD. As this overlap in symptomatology exists, cognitive domains hold promise as treatment targets for both pharmacologic and behavioral interventions.[196,197]

### Behavioral Treatments

Changes in attentional bias, seen in both CUD and anxiety and depressive disorders, are a promising treatment target (reviewed in).[87] Attentional bias modification (ABM) is a relatively new approach in which participants learn how to shift attention away from drug cues and towards neutral cues.[198] Authors of a recent study investigated ABM's potential to reduce drug use behaviors in individuals with CUD – they found no differences between the group receiving ABM and the group receiving control therapy, although both groups report decreased use and cravings.[199] Another study found that intensity of attentional bias may be a predictor of imminent relapse to cocaine use, as measured and tracked by a hand-held portable device.[200] Building on these findings, portable and user-friendly interventions may help people identify the need to adjust the intensity and frequency of treatment or gain a better understanding of their own unique triggers to use cocaine, in real-time.

### Pharmacological Approaches

N-acetylcysteine, by balancing glutamate function, may help reduce attentional bias to cocaine-related cues. This was supported by results of a study of 14 individuals who, during n-acetylcysteine treatment, had reduced attentional bias to cocaine cues.[201] They also had reduced cocaine choices, as measured by the Drug Choice Procedure in which participants were asked to choose between cocaine and a monetary reinforcer.

The cholinergic system plays a role in many cognitive processes including attention, memory, mood, motivation, reward, and stress response. Findings from multiple lines of evidence indicate that the cholinergic system is another promising potential target for the treatment of CUD.[202] Cholinesterase inhibitors, such as galantamine and rivastigmine, increase synaptic acetylcholine levels and have been used to enhance cognitive function in neuropsychiatric disorders such as Alzheimer's disease. Recently, among abstinent cocaine users (N = 28), galantamine improved sustained attention and working memory functions after only 10 days.[203] In another study conducted among cocaine-dependent individuals (N = 41), rivastigmine improved performance on a measure of working memory after 7 days of treatment.[204] Another study found a trend for galantamine to decrease cocaine use in methadone-maintained patients with opiate use disorder and CUD (N = 14);[205] and in a larger trial (N = 120) galantamine significantly reduced cocaine use in methadone-maintained patients.[184] Notably, post-hoc analyses of data from this trial showed that galantamine also reduced opioid use.[206] Conversely, a recent randomized placebo-controlled trial of galantamine in patients with only CUD showed no reduction in cocaine use with galantamine treatment at either 8 mg/day (N = 31) or 16 mg/day (N = 30).[207] Taken together, and combined with galantamine's safety and tolerability, results from these studies indicate that galantamine holds promise as a novel pharmacotherapy for CUD.

Although the psychostimulant methylphenidate has shown promise in improving response inhibition in cocaine-dependent individuals,[208,209] clinical trials investigating methylphenidate's ability to improve symptoms of CUD have yielded mixed results.[210] Methylphenidate, however, was shown to decrease cocaine use in individuals with co-occurring

ADHD and CUD, when compared with controls,[211] thereby supporting its use for patients with CUD and co-occurring ADHD.

## Sex-Specific Treatments

Studies investigating sex and gender differences in cravings, relapse, stress response, and other features of addiction (see Sex Differences) support the need for tailored treatment approaches to address sex and gender-specific needs. This includes the possibility of providing different medications to men and women. The female sex hormone progesterone, produced during the second half of the menstrual cycle, has been found to decrease cravings and euphoria produced by substances of abuse including cocaine, as well as improve cognitive function.[212–214] Progesterone may also reduce stress responses,[215] which are more prominent in cocaine-dependent women compared to men.[216] A stronger stress response is a known risk factor for substance use and relapse, particularly in women drug users. A narrative review looking at 16 studies, nine of which included patients with CUD, found cumulative evidence supporting progesterone in its ability to decrease cravings and subjective positive effects of cocaine.[215] Oxytocin may also play a role in modulating stress response. In a recent study of 112 adults with CUD, women reported greater stress provoked by a social stress test than men, but had decreased cortisol response when the hormone oxytocin was administered intranasally 40 minutes prior to the test.[217] A logical next step would be to examine if intranasal oxytocin reduces cocaine use triggered by stress in women.

Non-pharmacological interventions aimed at stress reduction may also hold promise to reduce cocaine use, particularly for women. Authors of a study investigating the relationship of sex and cocaine dependence on cravings found that cocaine-dependent woman had increased corticostriatal-limbic activity – which correlated with craving – in response to stress, compared to cocaine-dependent men, who had activation of these areas in response to drug cues.[218] The authors reported that these findings emphasize the importance of therapies targeting stress reduction, such as mindfulness skills,[219] for women. Another example is offering services that help with caretaker responsibilities.

## Non-Invasive Brain Stimulation Methods

Compared to individuals who do not use substances, individuals with CUD exhibit dysfunctional circuitry (see Neurobehavioral Features of Individuals with Chronic Cocaine Use), which can be modulated by brain stimulation methods. In transcranial magnetic stimulation (TMS), which is non-invasive and generally well tolerated, magnetic pulses are applied to modulate activity in specific cortical regions, thus alleviating certain symptoms by regulating underlying brain networks. TMS has been FDA approved to treat major depressive disorder and obsessive-compulsive disorder, and it is being explored for a variety of other conditions including substance use disorders. Most studies target the dorsolateral prefrontal cortex (DLPFC) with the aim of both increasing prefrontal cortex functioning and strengthening the modulation by the DLPFC of the dopaminergic mesolimbic circuitry (reviewed by Diana et al, 2017).[220] In transcranial direct current stimulation (tDCS), a weak electrical current is passed between two electrodes placed on the scalp, which then modulates cortical excitability. tDCS also most commonly targets the DLPFC, due to the reasoning mentioned above. There have been several studies examining these neurostimulation techniques as potential treatments for CUD (recently reviewed by Bolloni et al, 2018, Rachid, 2018, and Lupi et al, 2017).[221–223] In summary, several studies found that TMS and tDCS have efficacy in reducing cravings[224–228] or reducing risky behaviors[229] found in CUD. However, several methodological issues deserve attention. These include small sample sizes, in some cases lack of a sham control group, differences in stimulation protocols used, and an unclear understanding of the mechanisms of the treatments. Several authors emphasize the potential efficacy of these novel approaches in treating CUD and suggest ways to standardize these treatments, as well as point to the strength of combining these techniques with neuroimaging to better understand and target relevant neural circuits.[220,223,230]

### Immunotherapies

Since the early 90s, researchers have attempted to produce an anti-cocaine vaccine, which would block cocaine's effects (reviewed by Kinsey et al in).[231] While cocaine by itself does not provoke an immune response, it can stimulate the production of antibodies when bound to a larger carrier protein. As a result, in the presence of cocaine, these antibodies bind to cocaine, preventing it from reaching the brain and therefore blocking its euphoric and reinforcing effects. One cocaine vaccine – termed TA-CD – that was investigated through Phase III trials was synthesized by linking succinylnorcocaine – a chemical derivative of cocaine – to a carrier protein derived from the cholera B toxin (rCTB).[232] In a double-blind, placebo-controlled randomized trial, cocaine-users who developed high antibody titers following vaccination reduced cocaine use; however, only 38% of vaccinated individuals had sufficient antibody levels, and the antibodies remained elevated for only 2 months.[233] Notably, the favorable retention rate in this study was attributed to the fact that the participants were in methadone maintenance treatment, which required frequent clinical visits. In a follow-up clinical trial with cocaine users who were not on methadone, no significant treatment differences were found. In fact, those who had developed higher vaccine-induced antibody levels actually had more positive-cocaine urines, indicating increased cocaine use. The authors speculated that the individuals with greater antibody levels and more positive-cocaine urines may have increased cocaine use to overcome a blockade of euphoria caused by the vaccine.[234] Other cocaine vaccines are being explored in pre-clinical studies.

### Personalized Treatments

Given the heterogeneity of the patient population involved – each individual with CUD has varying illness severity, personal characteristics, backgrounds, and social support – personalized, multi-dimensional treatment approaches are needed. Identifying risk factors for SUDs, including genetic,[235] behavioral, and environmental, may help to predict treatment course and thus assist in treatment selection. For example, it has been suggested that those with higher impulsivity may respond better to behavioral interventions targeting this symptom cluster,[236] and, as mentioned above, that female substance users may especially benefit from a multidisciplinary team that can provide treatment for interpersonal stress such as mindfulness-based therapies.

## Identifying Treatments and Supporting Recovery

Only 19% of individuals with CUD receive much-needed treatment.[237] Referral to evidence-based substance use treatment and other needed services is critical, and any time individuals with CUD interface with a health care team (in the emergency department, in primary care, etc.) is an important opportunity to link individuals to appropriate care. Treating CUD directly is just one aspect of care that should be considered. In fact, each individual can benefit from a comprehensive care plan that targets multiple domains (see Figure 1). After ruling out or managing mental health and medical emergencies – including ones related to intoxication, overdose, or withdrawal – it is important to address several critical domains of the patient's experience. These include addressing CUD and other co-occurring substance use disorders, mental health and emotional needs, medical and physical needs, and social and environmental needs. Each individual's motivational status and goals should also be assessed. These domains should be continuously considered to help guide an individual's treatment plan, including the appropriate level of care (outpatient, inpatient, residential, etc.) which may be affected by the presence of co-occurring medical conditions or other critical needs including homelessness, or lack of adequate social support. The American Society of Addiction Medicine (ASAM) criteria can be used to help make this type of assessment and guide treatment.[238]

The Substance Abuse and Mental Health Services Administration (SAMHSA) offers a working definition of recovery as "a process of change through which individuals improve their health and wellness, live a self-directed life, and strive to reach their full potential".[239] This highlights recovery as a multi-step, evolving process that encompasses many domains.

In summary, in this review, we have highlighted many challenges that exist in the field of CUD therapeutics, outlined evidence-based treatments, and underscored promising novel therapies. It is our hope that we have also highlighted the

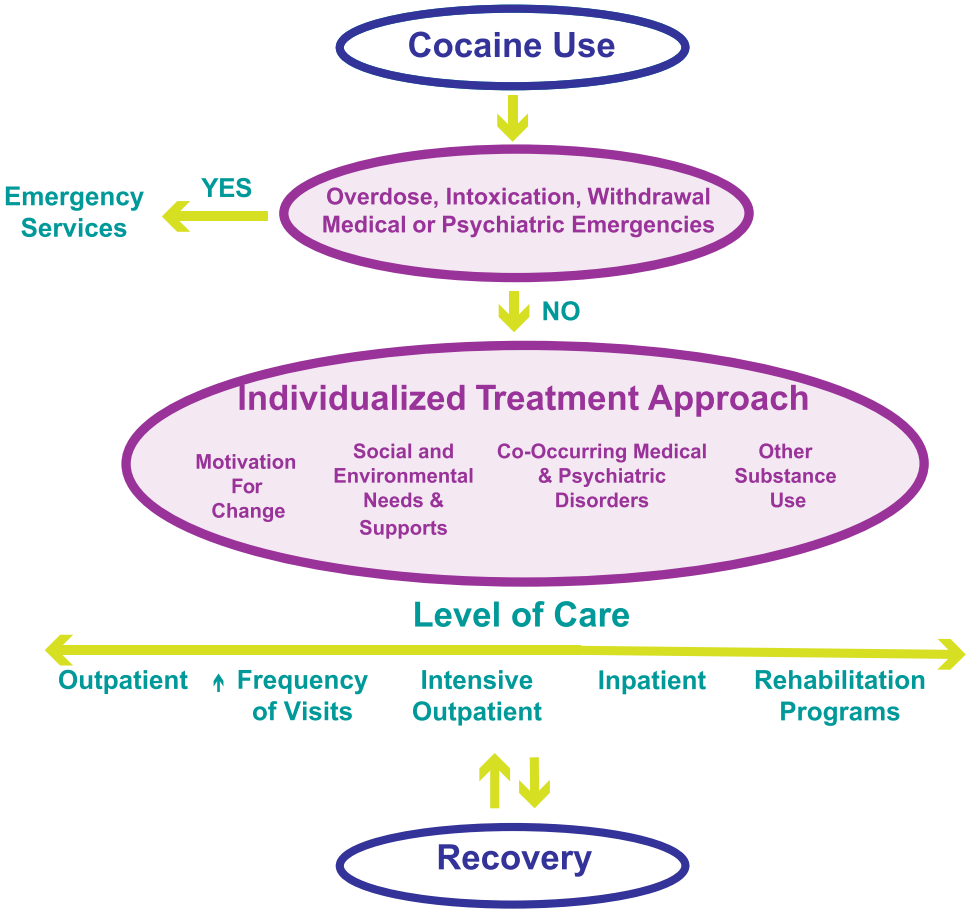


**Figure 1** CUD: **A Comprehensive Treatment Approach**: After ruling out the need for acute medical or psychiatric care, a dynamic comprehensive treatment plan should be formulated for each patient based on an ongoing assessment of several critical domains. This assessment can also help to determine the appropriate level of care which may be lower or higher, depending on several different factors (such as the presence or severity of co-occurring disorders or co-occurring substance use, presence of immediate stressors, or different levels of social support).

many existing opportunities to support individuals with CUD in their recovery process. These opportunities must be seized by professionals from multiple disciplines – from medicine to psychology and from social work to occupational therapy. While it may take time for each individual with CUD to find their own unique combination of treatments that will work best, it is critical to keep individuals engaged in care until their own most effective path toward recovery can be discovered.

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The authors report no conflicts of interest in this work.

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