

Abuse and addiction: crack

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CONFLICT OF INTEREST

None.

DESCRIPTION OF THE EVIDENCE COLLECTION METHOD

Articles found in MEDLINE databases (PubMed) and other research sources, with no time limit, were reviewed. The search strategy used was based on structured questions in the PICO format (Patient, Intervention, Comparison, and Outcome). The following descriptors were used: *crack cocaine, cocaine, cocaine-related disorders, substance-related disorders, behavior, addictive; incidence, prevalence, risk, signs and symptoms, chronic disease, acute disease, cocaine/poisoning, cocaine/toxicity, emergency service, hospital; nervous system diseases/chemically induced, psychoses, substance-induced; abnormalities, drug-induced; adverse effects, complications, substance withdrawal syndrome; rehabilitation, ambulatory care, comorbidity, mental disorders, diagnosis, urine, analysis, hair/chemistry, crack cocaine/pharmacology, cocaine/analysis, substance abuse detection, forensic toxicology, brain, brain mapping, brain/radionuclide imaging, tomography, emission-computed; positron-emission tomography, fetus, infant, newborn; infant premature, neonatal screening, infant, child, preschool; child, adolescent, prenatal exposure delayed effects, neonatal abstinence syndrome, child development/drug effects, child behavior/drug effects, intelligence, growth, developmental disabilities/chemically induced, language development, neuropsychological tests, cognition, psychomotor performance, pregnancy, pregnancy complications, pregnancy outcome, genetics*. These descriptors were used to cross-check each topic of PICO questions according to the theme. After examining the retrieved material, the articles concerning the questions that provided the evidence supporting this guideline were selected.

DEGREE OF RECOMMENDATION AND STRENGTH OF EVIDENCE

A: Experimental or observational studies of higher consistency.

B: Experimental or observational studies of lower consistency.

C: Case reports (non-controlled studies).

D: Opinions without critical evaluation, based on consensus, physiological studies, or animal models.

INTRODUCTION

Cocaine reemerged in Brazil in the last twenty years¹ (**B**). Since then, new patterns of drug consumption and presentations have been introduced² (**B**). Currently, cocaine consumption affects all social strata³ (**B**). Cocaine and crack are consumed by 0.3% of the world's population⁴ (**D**). Most users are concentrated in the Americas (70%), and the number of users has increased in the last decade⁵ (**D**). Among the emerging countries, Brazil is the largest market in South America in absolute numbers, with more than 900,000 cocaine users —nearly triple the number of previous surveys⁶ (**D**).

Before 1989, none of the national epidemiological surveys detected the presence of crack. However, lifetime use was 36% in 1993 and reached 46% in 1997⁷ (**A**). About 2% of the Brazilian students have used cocaine at least once in their lifetime, and 0.2% used crack⁸ (**A**). Among the largest cities in the state of São Paulo, the lifetime use of cocaine reaches 2.1% of the population, becoming the third most widely used illicit substance after solvents (2.7%), and marijuana (6.6%), and the lifetime use of crack reaches 0.4%⁹ (**A**). The use of crack is starting at ever-earlier ages, spreading across the country and across all social classes, with easy access and almost always preceded by alcohol and/or tobacco consumption¹⁰⁻¹² (**A**)^{13,14} (**B**).

The two national household surveys (2001 and 2005), conducted in 24 cities with over 200,000 inhabitants by the Brazilian Information Center on Psychotropic Drugs (Centro Brasileiro de Informações sobre Drogas Psicotrópicas – CEBRID) showed that crack consumption has doubled, and the south region was the most affected, the lifetime use increasing from 0.5% to 1.1%, followed by the southeast region with 0.8%. In the north region, the highest lifetime use of merla (1.0%), another form of smoked cocaine, was found¹¹ (**A**). The combination of crack use

with other behaviors was instrumental in the development of complications, such as the association with HIV infection, violence, and crime^{15,16} (B).

Specialized outpatient services for addiction treatment began to experience the impact of consumption growth from the early 1990s, when the proportion of crack users in some centers increased from 17% (1990) to 64% (1994)¹⁷ (B). In emergency rooms, cocaine is responsible for 30% to 40% of admissions related to illicit drugs, 10% of hospital admissions among all kinds of drugs, and 0.5% of total admissions¹⁸ (B). Cocaine consumption complications requiring medical attention are usually acute and individual¹⁹ (B). Cocaine and crack users have great difficulty in seeking specialized treatment because they do not recognize the problem, are faced with prejudice due to the illegality of the drug and its relation with crime, and find that access to treatment is difficult and that specialized services do not offer interventions tailored to their needs.

Because there is an increase of cocaine seizures in Brazil, as well as in the number of users, an increase in users seeking treatment is also expected. Given the barriers encountered, such as access to treatment, current therapeutic model, and lack of team training prior to the new wave of patients and their complications, the purpose of this guideline may reduce the distance between the users' needs and the currently available resources.

1. WHAT IS THE INCIDENCE AND PREVALENCE OF CRACK ADDICTION?

The use of crack is a recent phenomenon that emerged around 25 years ago in the United States²⁰ (B) and 20 years ago in Brazil²¹ (C). In some European countries, this issue has become relevant just over five years ago²² (D).

Qualitative studies of crack users began to be published in the early 1990s in Brazil²¹ (C). Follow-up studies of addicts have only been completed and released from the second half of the 2000s onward^{23,24} (B).

CEBRID conducted two national surveys on drug use in Brazil in 2001 and 2005 and found that the lifetime use of crack increased from 0.4% to 0.7% during this period. The largest increase occurred in the south (0.5% to 1.1%) and in the southeast (0.4% to 0.8%). In the northeast, there was an increased perception among respondents about the ease to obtain crack (19.9% in 2001 and 30.5% in 2005)²⁵ (B).

In the five surveys among students, and in the survey among street children and adolescents also conducted by CEBRID between 1987 and 2004, a trend towards increased consumption was also found^{10,11} (A). Among street children, the first increase occurred in São Paulo and Porto Alegre in the first half of the 1990s, and in Rio de Janeiro, in the second half of the decade. Crack and cocaine arrived in the northeast region only in 2000¹⁰ (A).

Most crack users (62.8%) present positive criteria for addiction during their drug-use careers²⁶ (A). The interval between the onset of consumption and occurrence of related problems was shorter for crack users (3.4 years) than for intranasal cocaine users (5.3 years)²⁷ (C). When compared to intranasal cocaine users, crack users are more exposed to the risk of dependency because they use the drug more frequently, in larger quantities, and are more sensitive to the effects of the substance²⁸ (B). Novice crack users seem to have twice the risk of dependency than users of inhaled cocaine, regardless of gender, ethnicity, association with alcohol, or time of drug use²⁹ (B). The risk of dependence is more "explosive" with cocaine use, compared to marijuana and alcohol³⁰ (B).

According to the United Nations (UN), the demand for cocaine has declined in traditional markets, such as the United States, and gained ground in others, especially in Europe and developing countries like Brazil⁶ (D).

There was a significant increase (7.4% to 42.6%) of crack users in Canada over ten years, with injectable cocaine and crystal methamphetamine use, living in a city, and involvement with the sex trade as independent predisposing risk factors³¹ (B).

The Brazilian National Confederation of Municipalities interviewed the health secretaries of all Brazilian municipalities, and observed that 98% of the municipalities surveyed had problems related to crack, even those with less than 20,000 inhabitants³² (B).

RECOMMENDATION

Crack users are exposed to a greater risk of addiction²⁸ (B), with twice the risk of dependence than inhaled cocaine users²⁹ (B), and even greater risk when there is an association with cocaine, marijuana, and alcohol³⁰ (B). The prevalence of crack use in Canada is 42.6%³¹ (B), there is still no national data. There was an increase in crack consumption in Brazil, with the largest increase in the south region²⁵ (B); however, 98% of the municipalities surveyed (most with more than 20,000 inhabitants) reported problems related to crack³² (B).

2. WHAT ARE THE RISK FACTORS FOR CONSUMPTION INITIATION AND DEVELOPMENT OF CRACK ADDICTION?

Risk factors are conditions or behaviors that increase the likelihood of negative outcomes for health, welfare, and social performance. Protective factors are those that promote healthy growth and prevent the risk of dependency and worsening of social problems³³ (D).

A follow-up study of injectable drug users found that almost half of the participants had already been consuming crack for nine years, and that the previous use of intravenous cocaine, greater availability of drugs, and trading sex for drugs were directly related to increased risk of

starting its use³¹(B). Another study of street youth with HIV and/or hepatitis C found that the multiuse of substances increased the risk of starting crack use. The incidence rate for crack use in patients without previous use of cocaine was 136/1000 person-years (95% CI; 104-175), increasing to 205/1000 person-years (95% CI; 150-275) for those who have used cocaine³⁴(B). However, studies that include users of various substances appear to corroborate the multi-causal model of dependence as resulting from the interaction of protective and risk factors^{33,35}(D) – Box 1.

Family is one of the main agents capable of influencing the individual vulnerability to initiate and establish problematic patterns of consumption, both directly by genetic transmission or exposure to consumption within the family environment; and indirectly through violence, abuse, and continued stress, often due to rigid or chaotic family structures, poor communication among family members, and attachment relationships marked by insecurity and/or abandonment³⁶⁻³⁸(B). On the other hand, positive relationships within the family are always protective and structuring, reducing the vulnerability of individuals to drug use, and tending to prevent consumption from becoming an addiction^{36,39}(B). Therefore, family and other parts of substance abusers' lives should be continuously investigated for strengths and vulnerabilities in order to better plan and succeed in preventive and therapeutic actions⁴⁰(D).

An increasing prevalence of early crack consumption is observed, especially in situations of parties attended by young people, marginalized social groups, homeless, prostitutes, and patients dependent on opiates and/or cocaine⁴¹(B).

RECOMMENDATION

Both risk and protective factors for early consumption of crack must be known. Risk factors are: a) individual, such as the use of various substances (alcohol, cigarettes, cocaine, opiates^{31,34}(B)), and being part of a marginalized group⁴¹(B); b) family and friends^{37,38}(B); c) environmental, such as community and school³⁵(D). Protective factors are those that reduce the vulnerability of individuals and may prevent addiction^{36,39}(B).

3. WHAT ARE THE SIGNS AND SYMPTOMS FOUND IN CASES OF CRACK ACUTE INTOXICATION/ABUSE AND HOW SHOULD THEY BE MANAGED?

Crack consumption is often associated with severe patterns of dependence, varying along a continuum of severity⁴²(B). Studies have demonstrated occasional users⁴³(B).

The acute complications related to cocaine use requiring medical attention are individual⁴⁴(D). Psychiatric complications are frequent, occurring in 35.8% of cases²⁰(B), particularly panic attacks, depression, and psychosis⁴⁵(B)⁴⁶(C). Psychotic symptoms (paranoid delusions,

hallucinations) can spontaneously disappear after a few hours (end of cocaine action), but extreme agitation may require intramuscular sedation with benzodiazepines (midazolam 15 mg). Haloperidol 5 mg may be used for this condition, but phenothiazine neuroleptics, such as chlorpromazine and levomepromazine, should be avoided due to the significant reduction in seizure threshold.

If an individual has a mental disorder associated with the use of drugs of abuse, the picture is more severe and increases the likelihood of seeking treatment. Even when psychiatric symptoms emerge, there is always the possibility of relation to clinical abnormalities, such as hypoglycemia and metabolic disorders, and confusional states triggered by infections²⁰(B). Clinical complications and mental disorders are the most common presentations (57.5%), followed by cardiopulmonary complications (56.2%). Regarding neurological complications, 39.1% of the most common symptoms are seizures, focal neurological symptoms, headaches, and transient loss of consciousness²⁰(B). Therefore, the psychiatric diagnosis in a medical emergency should be syndromic or symptomatic, as the approach is focused on the psychiatric symptoms and there is a shortage of time and incomplete patient history¹⁸(B).

There is no consensus on the dose of cocaine, much less that of crack, needed to trigger serious health problems or even threaten the user's life, but it is believed that consumption of about 2 to 4 mg/kg produces a slight reduction of coronary blood flow and an increase of equal magnitude in heart rate and blood pressure⁴⁷(D). In addition to the inherent toxicity of the substance, the presence of concomitant diseases in the organs most affected by the sympathomimetic action of cocaine makes these patients even more susceptible to complications, such as coronary artery disease, arterial hypertension, aneurysms, epilepsy, and chronic obstructive pulmonary disease⁴⁸(D).

Among the acute complications associated with cocaine use, overdose is the most known and is considered a medical emergency. It can be defined as the failure of one or more organs caused by acute substance use and consequent increase in central and sympathetic stimulation⁴⁹(C). The clinical signs of cocaine overdose are: palpitations, sweating, headache, tremor, anxiety, hyperventilation, muscular spasm; and signs of adrenergic overstimulation, such as mydriasis, tachycardia, hypertension, arrhythmia, and hyperthermia. It can progress to seizures, angina pectoris with or without infarction, intracranial hemorrhage, and rhabdomyolysis, leading to death, often due to heart failure and/or respiratory failure.

Cardiovascular complications resulting from cocaine consumption are the most common among non-psychiatric disorders, with angina pectoris reaching the highest rate, present in 10% of users⁵⁰⁻⁵²(A). Acute myocardial infarction (AMI) is not so frequent³⁹(A). About one-third of

Box 1

Risk and protective factors in different aspects of life ³⁵ (D)	
Risk factors	Protective factors
Individual	Individual
<ul style="list-style-type: none"> *Genetic predisposition *Low self-esteem, feelings of hopelessness about life *Perceived approval of drug use by friends *Problems with social bonding; rebellious, defiant, and resistant to authority personality *Sensation-seeking behavior pattern, curiosity, impulse control problems *Deficits in skills for coping with situations 	<ul style="list-style-type: none"> *Beliefs, moral and religious values *Positive orientation towards health and perception of risks of drug use *Perception of social sanctions and controls, intolerance to deviant behavior, and good relationships with adults *Competent and assertive social skills, such as empathy, pragmatism, and good self-control
Friends	Friends
<ul style="list-style-type: none"> *Psychoactive substance users and/or those with deviant behavior *Favorable attitudes towards drug use 	<ul style="list-style-type: none"> *Followers of conventional models of behavior and social norms *Intolerant to deviant behavior
Family	Family
<ul style="list-style-type: none"> *Chaotic and conflictive home environment *Low bonding, poor relationship among members *Consumption or attitudes that favor substance use by parents or other members *Inconsistent and low supportive parenting, lack of monitoring *High and unrealistic expectations by family members 	<ul style="list-style-type: none"> *Supportive, harmonic, stable, and safe family environment, with clear rules of conduct and parental involvement in their children's lives *Strong, safe, and stable family bonding and relationships *Stronger norms and moral values
School	School
<ul style="list-style-type: none"> *Academic failure *Poor school involvement and adjustment *Peer rejection, bullying *Unrealistic expectations and lack of institutional support 	<ul style="list-style-type: none"> *Social integration among students policies, and school performance monitoring *School norms that discourage violence and psychoactive substance use *Positive school climate, targeted towards bonding
Community	Community
<ul style="list-style-type: none"> *Availability of substances, consumption encouragement, and lack of legislation and law enforcement for illicit drugs *Violence, poverty, and lack of social support *Social disorganization and absence of the State 	<ul style="list-style-type: none"> *Access to health and social welfare services *Safety, organization, and community norms against violence and drug use *Leisure activities, community ties, and religious practices *Cultural identity and ethnic pride

strokes in young adults are associated with drug use, and, among adults aged 20-30 years, this rate reaches 90%⁵³ (A). Seizures, the most common neurological complication, affect a small proportion of cocaine users who seek emergency rooms⁵⁴ (B).

Regarding pulmonary complications caused by acute use of crack, the most common symptoms, developing within hours after use, are: chest pain, dyspnea, dry cough or elimination of blood and/or dark material (combustion waste), and fever⁵⁵ (D). Thermal injury, inhalation

of impurities, local anesthetic effect, and vasoconstriction causing inflammation and necrosis are primarily responsible for airway lesions⁵⁵ (D). Hemoptysis occurs in 6% to 26% of users. Pleural effusion may also be present⁵⁵ (D). There are still few studies that directly relate the risk of tuberculosis and other infections in crack and cocaine users⁵⁶ (C).

Detoxification is a short-term approach (two to four weeks) performed either in an outpatient/home or hospital setting⁵⁷ (D). This approach is being increasingly valued in the treatment process of users, as it seems to increase adherence to subsequent treatments^{58,59} (B).

RECOMMENDATION

Crack users who seek medical care immediately after consuming crack frequently present with psychiatric symptoms⁴⁴ (D).

However, changes related to clinical symptoms, such as hypoglycemia, metabolic disorders, and confusional states triggered by infections, should always be investigated²⁰ (B). Overdose is the best known clinical complication, although unusual⁴⁹ (C). Crack users need specific pulmonary assessments⁵⁵ (D). Referral to short detoxification treatment may increase the adherence to subsequent treatments^{58,59} (B).

4. WHAT ARE THE SIGNS AND SYMPTOMS OF CRACK DEPENDENCE AND ABSTINENCE SYNDROME AND HOW TO START TREATMENT?

Dependence on alcohol, tobacco, and other drugs – including crack – is considered a syndrome characterized by the presence of a compulsive use pattern, generally aiming towards the relief or avoidance of withdrawal symptoms; this pattern is more important than part or all of the social commitments and activities undertaken by the individual, who starts to neglect or abandon them in order to favor the use. This pattern usually results in tolerance and abstinence syndrome⁶⁰ (D).

During abstinence, periods of intense craving for cocaine, together with other withdrawal symptoms, including fatigue, anhedonia, and depression, eventually lead back to drug use⁶¹ (C). In chronic users, abstinence syndrome is well observed, but it can appear even in those who used the drug for a few days, in a compulsive or binge use form⁶¹ (C). The syndrome is composed of three phases: crash, late dysphoric syndrome, and extinction. These phases represent the progression of signs and symptoms after the cessation of use and are described below⁶¹ (C):

- Phase I – Crash: a drastic reduction in mood and energy that happens about 15 to 30 minutes after the use of the drug, which persists for about eight hours and may extend for up to four days. The user may experience depression, anxiety, paranoia, and

an intense desire (craving) to return to drug use. Hypersomnia and aversion to the substance then occurs, and the person wakes up on a few occasions to eat in large quantities. This last step can last from eight hours to four days;

- Phase II – Late dysphoric syndrome: begins 12 to 96 hours after the substance use and may last from two to 12 weeks. In the first four days, there is the presence of sleepiness, craving for the drug, anhedonia, irritability, memory problems, and suicidal ideation. Relapses occur frequently as a way of relieving dysphoric symptoms;
- Phase III – Extinction: in this phase the dysphoric symptoms diminish or completely cease, and craving becomes intermittent.

Although cocaine withdrawal symptoms are less intense and appear to decrease linearly in hospital settings, in outpatient treatment they are more frequent, intense, and last longer⁶² (B). Trigger factors and conditioned stimuli have a great influence and represent a real potential for relapse in users⁶³ (B).

Psychiatric complications are the main reason for seeking medical attention among cocaine users⁴⁵ (B). They may result from acute intoxication and substance withdrawal^{64,65} (B). They worsen the prognosis and, if not detected, new relapses and treatment discontinuation can occur⁶⁶ (B).

In addition to using a broad pharmacological arsenal for the stabilization of psychiatric and medical conditions resulting from neural and sympathomimetic deregulation, it is necessary to manage the withdrawal symptoms^{67,68} (D). Disulfiram, still under study, has been used to alleviate drug craving and urgency⁶⁹ (A)⁷⁰(B), as well as modafinil^{71,72} (A). Topiramate is recommended to reduce the drug-seeking behavior^{73,74} (A)⁷⁵(B). Cocaine vaccines are being developed to reduce relapse, but are still far from being marketed⁷⁶ (A).

TOPIRAMATE

Topiramate's mechanism of action enhances the tone of the GABA neurotransmission system and inhibits the AMPA/kainate glutamate receptor system. This increase in inhibitory activity (GABA) and blockade of excitatory activity (glutamate) cause a reduction in dopamine release in the nucleus accumbens, part of the reward system. Thus, the pharmacological profile of topiramate, at least in theory, reduces the magnitude of cocaine's effects and drug-seeking behavior⁶⁷ (D). Although meta-analyses do not report a statistically significant positive response of this anticonvulsant in cocaine dependence treatment^{73,74} (A), studies with small samples, but placebo-controlled, have found that topiramate has a positive action on cocaine dependence⁷⁵ (B).

It has been found that, for many patients, the effect occurs at a dose of 200 mg, with best results at a dose of 300 to 400 mg/day⁷⁷ (D). The most frequently reported adverse effects are nervousness, abnormal thinking, impaired memory, nausea, weight loss, and language and concentration/attention disorders⁷⁸ (D).

DISULFIRAM

The pharmacological properties of disulfiram, which results in alcohol aversion, have been known since the 1930s, and became formally recognized and approved as a medication for alcohol dependence since the 1950s. This well-known substance for treating alcohol dependence appeared recently as the drug most supported by evidence for treating cocaine-dependent individuals⁶⁹ (A). There was a trend in favor of disulfiram compared to control, but not statistically significant in the assessment of reduced cocaine use, with RR = 0.82 (95% CI; 0.66-1.03). However, there is benefit in maintaining three or more consecutive weeks of abstinence, with RR = 1.88 (95% CI; 1.09-3.23)⁶⁹ (A).

In addition to inhibiting aldehyde dehydrogenase, a mechanism of aversive therapeutic action, which leaves the individual more attentive and organized, in order to prevent relapse and adverse effects of alcohol consumption⁷⁹ (B), disulfiram also acts on the dopamine system, inhibiting the conversion of dopamine into norepinephrine by blocking dopamine β -hydroxylase (DBH) and monoamine oxidase-B enzymes⁷⁷ (D).

The recommended daily dose of disulfiram is 250 to 500 mg/day. The drug action and metabolism are well tolerated and relatively safe, but contraindicated for patients with serious liver diseases, such as hepatitis and decompensated cirrhosis⁶⁷ (D) ⁶⁹(A). Patients should be well informed about the risks and effects of disulfiram secondary to alcohol intake. In these circumstances, the increase in aldehyde circulation causes changes ranging from physical and psychological discomfort, such as facial and chest flushing, feeling of warmth, nausea, anxiety, and panic reactions, to even more severe complications, such as respiratory depression, seizures, neurological disorders, cardiac arrhythmias, cardiogenic shock, and acute myocardial infarction, which may lead to death⁸⁰ (C). Thus, before starting treatment, it is recommended that a written informed consent is obtained from the patient with the approval of one of his relatives. Cognitive impairments or comorbidities that compromise the proper understanding of the risks involved and presence of suicidal or impulsive behaviors are, at the least, relative contraindications for this drug.

MODAFINIL

Modafinil is a central nervous system stimulant. Similar to cocaine, but in a milder form, modafinil blocks the reuptake of dopamine and noradrenaline, increasing its

concentration in the brain⁸¹ (A). The molecule can also increase the glutamate system activity, which is usually deficient due to the chronic use of cocaine. Such compensation could block the euphoric effects of cocaine and prevent the return of the drug-seeking behavior⁶⁷ (D). The drug appears to be well tolerated. The adverse events most commonly observed (5%) are headache, nausea, nervousness, anxiety, insomnia, diarrhea, dyspepsia, and dizziness⁷⁷ (D).

Open studies have found increased rates of treatment adherence and abstinence among patients treated with doses of 200 to 400 mg/day⁷⁷ (D). Despite the promising initial findings, meta-analyses have not confirmed these results on the use of stimulants such as modafinil and methylphenidate for treatment of cocaine users. They appear not to reduce cocaine use, despite the trend towards maintenance of abstinence, with RR = 1.41 (95% CI; 0.98-2.02; p = 0.07); therefore, all results showed no significant statistical difference⁸² (A). Thus, efficacy confirmation relies on the results of further studies.

RECOMMENDATION

Cocaine withdrawal symptoms are mainly psychological, particularly depressive and anxiety symptoms⁶¹ (C). Generally, these symptoms become more intense in the first 7 days, decreasing in intensity afterwards. They appear to be less intense when the patient is in a protected environment⁶² (B). Disulfiram, at a dose of 250 to 500 mg/day presents benefit in the treatment of cocaine-dependent individuals, increasing the possibility of maintaining abstinence⁶⁹ (A). Modafinil at a dose of 200 to 400 mg/day has no statistically significant benefits, despite the tendency to maintain abstinence⁸² (A). Topiramate at a dose of 200 to 400 mg/day, so far, has not shown benefits for treating cocaine-dependent individuals^{73,74} (A).

5. HOW SHOULD THE INITIAL ASSESSMENT OF THE CRACK USER BE MADE?

Among illicit drug users, crack users are less likely to seek treatment⁸³ (B) ⁸⁴(C). They seek treatment in acute situations and prefer intervention approaches in hospital settings, with low adherence in the later outpatient stage^{23,85,86} (B). For cocaine users, treatment-seeking takes place around the sixth and seventh year of use, but earlier among crack users⁸⁷ (B).

The initial assessment is a very important moment that depends on the expertise of the professional or service, but requires an intensive approach given the degree of disruption caused by the substance consumption^{88,89} (B). Risk assessment should be prioritized in order to solve the critical problems, to promote the patient's mental balance through an active management, anticipating risk situations and resolving them promptly to avoid resuming consumption⁹⁰ (D).

Because crack consumption has been directly associated with HIV infection, HIV testing is essential⁹¹ (B).

RECOMMENDATION

Crack-dependent individuals require more intensive approaches due to the degree of disruption caused by substance consumption^{88,89} (B), in addition to having the lowest rates of adherence to treatment compared to patients using other substances⁹⁰ (D).

6. WHAT ARE THE PSYCHIATRIC COMORBIDITIES RELATED TO CRACK CONSUMPTION?

The prevalence of mental disorders is higher among crack users compared to users of inhaled cocaine and is correlated with age ($r = 0.124$), days of cocaine use per month ($r = 0.370$), number of years of regular crack use ($r = 0.109$), and severity of cocaine dependence ($r = 0.502$), all significant⁹² (B). This finding is associated with the severity of dependence and with combined psychosocial factors⁹³ (B). When crack users have a primary mental disorder, the vulnerability is increased and associated comorbidity was present in 36.4%²⁶ (B) to 42.5% of cases⁹⁴ (B).

Depression (26.6%) and anxiety (13%) are the most frequent psychiatric comorbidities, affecting almost half of the users⁹⁴(B). Depressive symptoms secondary to consumption are the most prevalent^{94,95}(B). The intensity of crack consumption appears to be directly related to the risk of developing depressive disorder in up to 64% of cases⁹⁶ (B). Depression affected almost all crack users who consume alcohol and are infected with HIV, totalling 73.5% of cases⁹⁷ (B). Increased risk of suicidal ideation or suicide attempt was observed among Brazilian users⁹⁸ (B).

Crack users consume alcohol less frequently and less heavily than inhaled cocaine users¹⁴ (B). Alcohol consumption is a predictor of severity and poor prognosis for the user of any substance, including crack⁹⁹ (B). In a four-year follow-up study, a greater chance of alcohol dependence was found among crack and alcohol users (67.9%) than in heavy alcohol users (13.6%), with OR = 12.3 for men and OR = 7.0 for women¹⁰⁰ (B). The presence of alcohol during cocaine consumption originates cocaethylene, an active metabolite responsible for a more intense and longer lasting action on the reward system, but it is more toxic than cocaine, which increases the risk of sudden death among users¹⁰¹ (B).

The multiuse of substances is common among crack users¹⁰² (D). Marijuana is used in order to reduce the anxiety and craving resulting from the use of crack¹⁰³ (C). There is also a group of users who use both crack and inhaled cocaine¹⁰⁴ (A) ¹⁴(B).

Personality disorders are common among illicit drug users and affect most drug and alcohol users, a common situation among crack users¹⁰⁵ (A) ⁹⁴(B). Antisocial

personality disorder and borderline personality disorders are the most common¹⁰⁶ (A) ⁸⁶(B). The greater the severity of the personality disorder, the worse the prognosis and more remote the chances of adherence to treatment¹⁰⁷ (D). On the other hand, patients with avoidant and schizoid personality disorders appear to have a less severe consumption and to be more likely to seek treatment¹⁰⁸ (B).

Schizophreniform symptoms, in most cases transient, are often observed in users of both crack and inhaled cocaine¹⁰⁶ (A).

RECOMMENDATION

The use of crack is often associated with psychiatric comorbidities^{105,106} (A) ^{94,96}(B), and when users present with a primary mental disorder, the association is even higher^{26,94} (B). Multiuse of substances is common¹⁰³ (D). Although crack users usually consume less alcohol than inhaled cocaine users⁸⁶ (B), alcohol consumption predicts severity and poor prognosis⁹⁹ (B).

7. DO URINE TESTS, HAIR ANALYSIS, AND NEUROIMAGING TECHNIQUES HELP IN THE DIAGNOSIS OF PROBLEMATIC USE AND DEPENDENCE ON CRACK?

Analysis of psychotropic substances in body fluids (urine, blood, saliva) and hair has two main purposes: (1) emergency diagnosis; (2) clinical management and monitoring of chronic use during treatment¹⁰⁹ (C). In addition to confirming the good evolution of the proposed treatment, repeated negative urine samples can be a motivation for the patient being treated¹¹⁰ (B).

There are ethical precepts for drug testing in patients:

- The use of a test to prove abstinence to third parties (judges, employers, family members) or even to provide security to the group that interacts with the user is not justified;
- The problematic user has great difficulty to self-determine abstinence, no matter how much he/she wants it, and to gain autonomy, because the addiction dominates his/hers behavior;
- The temporary use of compulsory methods of controlling and monitoring (testing and use of aversive drugs) aims to eliminate the addictive behavior in order to rectify, restore, and enhance the capacity for autonomy. It would be "mandating treatment in the name of autonomy"¹¹¹ (D).

Urine drug testing is indicated to detect the recent use of cocaine and crack, with the presence of the substance and its metabolites (even in the case of coca tea), for up to five days after the last intake^{112,113} (D). It uses anti-benzoyllecgonine (BZE) antibody, one of the major metabolites of cocaine¹¹⁴ (A), considered as true-positive when the presence of BZE is at or above 40%¹¹⁵ (A). It is indicated for high-risk situation management, which requires constant

monitoring for short periods, as constant testing tends to lose effectiveness and trouble the patient when too prolonged¹¹³ (D). When BZE measurement is performed by gas chromatography-mass spectrometry, there is a sensitivity of 97.6%, and specificity of 60.5%, with a positive predictive value of 71% and negative predictive value of 97%. Considering the pretest probability (prevalence) of 42%, and likelihood ratio of 2.5 (95% CI; 1.95-3.20) when BZE measurement is positive, there is an increase in post-test probability (or definite diagnosis) by 64%¹¹⁶ (B).

Hair analysis is a method to investigate the previous use of cocaine and to monitor sustained abstinence, which detects drug consumption with more sensitivity during the preceding 120 days, with the exception of the last 30 days¹¹⁷ (C) ¹¹³(D). It is specific for cocaine and co-caethylene, as its major metabolite, benzoylecgonine, can generate false-positive results and, therefore, it is not part of the method¹¹⁸ (D). Hair analysis may be performed by two methods: radioimmunoassay and gas chromatography-mass spectrometry¹¹⁷ (C). The first method has a sensitivity of 67.8% and specificity of 80.5%. Considering the same pretest probability (prevalence) of 42%, and likelihood ratio of 3.54 (95% CI; 2.31-15.42), positive hair analysis by radioimmunoassay increases the diagnostic certainty to 72%. The second method has a sensitivity of 75%, specificity of 97.4%, and likelihood ratio of 37.13 (95% CI; 9.27-147.06); therefore, the spectrometric hair analysis increases the likelihood of disease from 42% to 96%¹¹⁹ (B).

Caution should be exercised in interpreting hair analysis: (1) cocaine metabolites can be detected up to three months after withdrawal *versus* consecutive negative tests for cocaine in urine up to 90 days; (2) the hair does not grow uniformly throughout the scalp, which can give the false impression of consumption in last month; (3) there is the possibility of external contamination of hair by contact with the sweat of others or reduced substance or

the use of products for hair care, extremely remote possibilities. There is no statistically significant difference between male and female hair analysis. The median half-life of cocaine in hair is 1.5 months (95% CI; 1.1-1.8) for men and 1.5 months (95% CI; 1.2-1.8) for women¹²⁰ (B).

The neuroimaging test used to detect addiction consists of a set of non-invasive techniques used in studies of brain dysfunction secondary to drug use. The main findings related to cocaine use are shown in Box 2. Neuroimaging techniques have helped researchers to detect brain changes caused by other disorders that increase the vulnerability or potencialize the use of drugs of abuse¹²¹ (D). Despite the current and potential advances, neuroimaging does not have clinical indications for diagnosis and treatment of addiction^{122,123} (D).

RECOMMENDATION

Screening for cocaine and its metabolites in body fluids helps in the diagnosis of psychotropic substance acute intoxication and allows confirmation of abstinence during treatment¹¹⁰ (B).

Diagnosis of previous cocaine consumption up to 120 days, except for the last 30 days and/or prolonged withdrawal monitoring, can be done through hair analysis by radioimmunoassay¹¹⁹ (B) and by gas chromatography-mass spectrometry¹¹⁷ (C). To detect the use of cocaine and crack within the previous five days, the measurement of cocaine metabolites (BZE) in urine is performed¹¹⁶ (B). Despite the current and potential advances, neuroimaging does not have clinical indications for diagnosis and treatment of addiction^{122,123} (D).

8. WHAT ARE THE EFFECTS OF CRACK USE ON PREGNANCY AND ON THE NEWBORN?

Certain phenomena associated with cocaine use during pregnancy, such as the substance effects on pregnancy development for both mother (placenta, infections etc.) and

Box 2

Neurological changes resulting from acute and chronic use of cocaine

1. The acute use of cocaine decreases the mean consumption of glucose by the brain, causes acute decrease in blood flow to regions such as the prefrontal cortex and basal ganglia — all involved in behavior reinforcement of dependency.
2. The intensity of the euphoric effects of cocaine is directly proportional to the blockade of dopamine reuptake by the substance. This blocking is more intense if the chosen route of administration is the lung (crack), followed by intravenous and intranasal, which partly explains the crack's ability to generate more dependency. From this observation, drugs that occupy the dopamine transporter proteins, such as modafinil, have been studied in order to reduce the craving and positive effects of cocaine.
3. Among chronic users, the mean reduction of glucose consumption by neurons and blood hypoperfusion may last for weeks, months, or indefinitely. Reduction of dopaminergic receptors, particularly type 2 (D2) is also observed. There is reduced white matter integrity in the frontal cortex region, a change related to increased impulsivity in users.
4. Neuroimaging has contributed to the understanding of craving¹²⁴⁻¹²⁶ (C).

fetus, as well as the presence of withdrawal syndrome after birth have called the attention of researchers and health professionals.

It is known that cocaine increases the replication of HIV *in vitro* and that cells of chronic cocaine users favor viral replication and entry of opportunistic infections, when compared to non-users. Perinatal transmission can occur by three mechanisms:

1. Before birth, by transplacental infection.
2. During labor, by contact with the mother's fluids.
3. After birth, through breastfeeding.

Cocaine appears to increase the risk of HIV transmission at least by the first two mechanisms, as it increases viral replication and affects fetal immune development¹²⁷ (D). Infants born to crack users are more exposed to infections (OR = 3.09; 95% CI; 1.76-5.45), including hepatitis (OR = 13.46; 95% CI; 7.46-24.29), acquired immunodeficiency syndrome (OR = 12.37; 95% CI; 2.20- 69.51), and syphilis (OR = 8.84; 95% CI; 3.74-20.88)¹²⁸ (B).

Results regarding the impact of fetal exposure to cocaine are still inconsistent¹²⁹ (D). There is no evidence of a teratogenic syndrome¹³⁰ (D). Crack use during pregnancy appears not to lead, invariably, to the birth of infants with severe, persistent, and unusual damages—the “crack babies”¹³¹ (D).

The strongest evidence of damage related to cocaine use during pregnancy is the risk of premature birth and low birth weight^{128,132} (B). A follow-up study of crack users divided into two groups (with and without prenatal care) found intrauterine growth retardation and low birth weight in relation to the populational mean, regardless of the presence of pre-natal care¹³³ (B). Regarding infants born to crack users, there were 19% premature births, lower weight (536 grams), lower height (2.6 cm), and smaller head circumference (1.5 cm)¹³⁴ (B). Changes in the central nervous system are frequently seen, such as permanent alertness (OR = 7.78; 95% CI; 1.72-35.06), excessive sucking (OR = 3.58; 95% CI; 1.63-7.88), and autonomic instability such as tachycardia, sweating, labile pressure, hyperthermia (OR = 2.64; 95% CI; 1.17-5.95), frequent crying (OR = 2.44; 95% CI; 1.06-5.66), nervousness and/or tremor (OR = 2.17; 95% CI; 1.44-3.29), and irritability (OR = 1.81; 95% CI; 1.18-2.80)¹²⁸ (B).

A study of neurological disorders in infants born to crack users found a relationship between intensity of cocaine use and presence of neurological disorders, such as abnormalities in muscle tone and posture¹³⁵ (B), in addition to significant changes in behavior up to five years of age¹³⁶ (B).

Few studies have found differences between children of mothers who use crack and of non-users, both regarding complications at birth¹³⁷ (B) and development¹³⁸ (C). There is no convincing relationship between the use

of cocaine/crack during the prenatal period and toxic changes in child development, noting that the social, environmental, and psychosocial variables of the pregnant women (multiuse of drugs, education, maternal nutritional status etc.) play a decisive role in the occurrence of the behavioral and physical damage observed^{139,140} (A)^{141,142}(B). The socioenvironmental and psychosocial characteristics of the mother also appear to influence the pregnancy and fetus, along with cocaine consumption¹⁴³ (B). Children born to crack users are less breast-fed (OR = 0.26; 95% CI; 0.15-0.44), use more child protection services (OR = 48.92; 95% CI; 28.77-83.20), and often are not raised by the biological mother (OR = 18.70; 95% CI; 10.53-33.20)¹²⁸ (B).

Neonatal cocaine withdrawal syndrome is characterized by irritability, hypertonicity, tremors, mood swings, and continuous crying¹⁴⁴ (C). Withdrawal symptoms do not appear to be as common among children of cocaine users¹⁴⁵ (B). A study of pregnant crack/cocaine users performed urinalysis in all newborns and found the following: (1) infants whose mothers did not use cocaine for seven days or more probably showed symptoms of withdrawal *in utero*, without repercussion after delivery; (2) those positive for the substance for a day or less did not show withdrawal symptoms; (3) neonates positive for cocaine between the second and sixth day of birth had a higher incidence of neonatal withdrawal symptoms and were conditioned to the cocaine use by the mothers during the immediate period after childbirth¹⁴⁶ (C).

RECOMMENDATION

The use of crack during pregnancy leads to intrauterine growth retardation and low birth weight¹²⁸ (B), increases the risk of premature birth¹³⁴ (B), and exposes children to infections such as hepatitis, human immunodeficiency virus, and syphilis¹²⁸ (B).

Neonatal cocaine withdrawal syndrome is related to cocaine use by mothers during the immediate period after childbirth¹⁴⁶ (C), is infrequent¹⁴⁵, (B) and is characterized by irritability, hypertonicity, tremors, mood swings, and continuous crying¹⁴⁴ (C).

Children born to crack users are always alert, present with excessive sucking, autonomic instability, frequent crying, tremors, and irritability¹²⁸ (B). They also have muscle tone and postural abnormalities¹³⁵ (B) and behavioral changes up to the preschool period¹³⁶ (B).

9. DO CHILDREN OF CRACK USERS PRESENT WITH IMPAIRED NEUROLOGICAL AND COGNITIVE DEVELOPMENT?

The available evidence on the relationship between the exposure to cocaine/crack during pregnancy and presence of neurodevelopmental damage is still inconsistent and controversial.

From birth to age seven, the children of cocaine users present higher incidence of low birth weight and are twice as likely to be below the average height for their age¹⁴⁷ (B). Children aged 10 who were exposed to crack consumption in the first trimester of pregnancy have slower growth throughout childhood compared to controls of similar age not exposed to the drug, suggesting that intrauterine exposure to cocaine has a long lasting effect¹⁴⁸ (B). However, some studies found no relationship between cocaine use and development changes^{139,140} (A).

There seems to be some relationship between cocaine use during pregnancy and damage to cognitive and behavioral functioning¹⁴⁹(A) ^{136,150}(B), with a probability of cognitive impairment (OR = 1.98; 95% CI; 1.21-3.24; p = 0.006), without motor abnormalities. The potential reversibility of such changes is still unclear¹³² (B). Exposed children have lower language skills than those not exposed – a significant difference that remained stable over the first three years of life¹⁵¹ (A). A similar study found no relationship¹⁵² (A); thus there is still controversy on this subject.

The interaction between intrauterine exposure to cocaine and quality of the mother's environment was assessed in a four-year follow-up study of infants exposed and not exposed to the substance during pregnancy. No difference was found in the indexes of general intelligence and cognitive performance between groups, but the exposed group had more specific cognitive impairments (verbal performance, attention, IQ test/arithmetic, and acquisition of new knowledge)¹⁵³ (A). Nevertheless, the influence of environmental factors may never be disregarded, as the same study compared the exposed children sent to well-structured foster homes with those raised by their biological parents (users and nonusers), finding a better school performance among the first.

RECOMMENDATION

Children of crack users have a reduced weight and height development¹⁴⁷ (B), but there is still controversy on the damage to psychomotor and cognitive development, as there are studies that found no relationship^{139,140,152} (A), while others found cognitive and behavioral impairments, but not motor¹⁴⁹ (A).

10. IS THERE EVIDENCE THAT GENETIC FACTORS HAVE A ROLE IN CRACK ABUSE AND ADDICTION?

Several genetic associations related to cocaine dependence are being studied — a highly prevalent disorder involving multiple genes¹⁵⁴ (B). Because a part of cocaine addicts consists of multi-drug users, multiple genes have been studied. Regions of human chromosomes 4, 5, 9 to 11, and 17 are more likely to have genes susceptible to substances, and there is moderate to high heritability for

most vices¹⁵⁵ (B). The heritability rate of addictive use of stimulants, sedatives, and heroin for men is 0.33, 0.27, and 0.54, respectively¹⁵⁶ (B).

It is also known that the earlier the exposure to cocaine in animals, the greater the impairment of maturation and the onset of mental and behavioral disorders¹⁵⁷⁻¹⁵⁹ (D). In these animal models, there is evidence of the different chromosomal combinations of alleles and also of the alleles related to cocaine use^{160,161} (D).

Based on genetic studies of cocaine users, pharmacogenetic studies have proposed some substances for the treatment of cocaine addiction, such as disulfiram and methylphenidate¹⁶² (D).

By studying siblings of cocaine abusers, it was found that probands have proportional risk for cocaine addiction (HR = 1.71; 95% CI; 1.29-2.27)¹⁶³ (B).

RECOMMENDATION

There is evidence of familial transmission of cocaine dependence^{154,163}(B) and high to moderate heritability for most addictions¹⁵⁶ (B). The knowledge that genetic factors contribute to abuse and facilitate the development of crack dependence is being used in pharmacogenetic research in order to provide specific treatments for cocaine-dependent individuals¹⁶² (D).

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