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An International Perspective and Review of Cocaine-Induced Psychosis: A Call to Action

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ABSTRACT. Cocaine use can induce transient psychotic symptoms that include suspiciousness, paranoia, hallucinations, and other cocaine-related behaviors. In this commentary, the authors provide an international perspective while reviewing the recent advances in epidemiology, clinical features, and risk factors related to cocaine-induced psychosis exhibited by patients with cocaine use disorders. In some settings, the occurrence of cocaine-induced psychosis has been shown to be as high as 86.5%. Many risk factors have been linked with cocaine-induced psychosis, including the quantity of cocaine consumed, lifetime amount of cocaine use, onset of cocaine dependence, years of use, routes of administration, other substance use disorder comorbidity, weight, gender, comorbidity with other medical and mental health disorders, genetics, and pharmacological interactions. Research has shown that the evaluation of cocaine-induced psychosis in patients with cocaine use is clinically relevant, especially in those patients who consume high amounts of cocaine, have a cannabis dependence history, have antisocial personality disorder, use administration routes other than intranasal, or exhibit attention-deficit/hyperactivity disorder (ADHD) comorbidity. Currently, the literature lacks information regarding the evolution of cocaine dependence or cocaine-dependent patients' risk for developing schizophrenia or other psychotic disorders. Furthermore, clinicians still do not have an evidence-based pharmacological approach to management of cocaine dependence available to them. Additional research is also needed regarding risk factors such as neurobiological markers and personality traits. Finally, we recommend the development of an integrative model including all of the risk factors and protective factors for cocaine-induced psychosis.

Keywords: Cocaine, cocaine dependence, cocaine-induced psychosis (CIP), psychosis, psychotic symptoms, risk factors

INTRODUCTION

Cocaine use is a problem around the world,¹ with particularly high rates of use in the United States (US)² and Europe.³ Cocaine use is associated with a variety of mental disorders^{4,5} and can exacerbate the morbidity and treatment of preexisting

mental disorders.^{6–8} Cocaine consumption can induce transient psychotic symptoms,^{8–11} behavioral symptoms,^{8,12} or a complete induced psychosis.¹³ Behavioral alterations have not been considered across all studies because of the difficulties of relying on patient recall and reporting. Different definitions have been used for describing these symptoms (see Table 1). According to the DSM-5 (*Diagnostic and Statistical Manual of Mental Disorders*, 5th edition), cocaine-induced psychotic disorder refers to psychological changes (e.g., euphoria, hypervigilance, interpersonal sensibility, impaired judgment) during recent use or shortly after cocaine use, with signs or symptoms that are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance.¹⁴ Previously, we reviewed the relevant cocaine-induced psychosis literature published up to April, 2011.⁷ This article seeks to provide an update on the more recent advances in epidemiology, clinical features, and risk factors related to

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TABLE 1
Cocaine Use and Psychosis: Definitions

Definition	Concept
Cocaine physical dependence according to the DSM-5	A pattern of cocaine use leading to clinically significant impairment or distress occurring within a 12-month period as manifested by at least 2 of the following: <ul style="list-style-type: none"> • Cocaine often taken in larger amounts or over a longer period of time than was intended • There is a persistent desire or unsuccessful efforts to cut down or control cocaine use • A great deal of time is spent in activities necessary to obtain the cocaine, use, or recover from its effects • Craving or a strong desire or urge to use cocaine • Recurrent cocaine use resulting in a failure to fulfill major role obligations at work, school, or home • Continued cocaine use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cocaine • Important social, occupational, or recreational activities are given up or reduced because of cocaine use • Recurrent cocaine use in situations in which it is physically hazardous • Use is continued despite the knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by cocaine • Tolerance • Withdrawal
Cocaine intoxication with psychotic symptoms or cocaine intoxication with perceptual disturbances according to the DSM-5	Recent use of cocaine with psychological changes (e.g., euphoria, hypervigilance, interpersonal sensibility, impaired judgment) that developed during, or shortly after, cocaine use with signs or symptoms (e.g., tachycardia, papillary dilation, psychomotor agitation or retardation) that are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance.
Cocaine-induced psychotic disorder according to the DSM-5	A complex diagnosis characterized by the presence of delusions and/or hallucinations during or soon after substance intoxication or withdrawal or after exposure to cocaine. The patient has no insight to the symptoms. The disturbance causes clinically significant distress or impairment in social, occupational or other important areas of functioning.
Cocaine-induced paranoia	Paranoia developed during or shortly after use of cocaine with intact reality testing or auditory, visual, or tactile illusions occurring in the absence of a delirium.
Cocaine-induced psychosis (CIP)	Transient psychotic symptoms, expressed as paranoia or hallucinations induced by cocaine. CIP symptoms can appear with cocaine intoxication, and they can also be present in psychotic disorders induced by cocaine. The patient can maintain intact reality testing and is conscious of cocaine's effect.
Behavior alterations induced by cocaine	Clinically significant problematic behavioral developed during or shortly after use of cocaine.
Cocaine-associated risk behaviors	Cocaine consumption can be linked with hostile behaviors and high impulsivity. It had been suggested that this occurs through psychotic symptoms. This contributes to a perception of the environment as a threatening place as well as through increasing impulsivity, triggering risky behaviors.

cocaine-induced psychosis. Finally, we offer some suggestions for future research in this area and propose a model of risk factors for developing cocaine-induced psychotic behavior.

CURRENT UNDERSTANDING OF COCAINE-INDUCED PSYCHOSIS

Prevalence

The presence of any psychotic symptoms during cocaine use is common,⁷ but this does not always occur with cocaine intake and is avoided by abstinence.¹⁵⁻¹⁸ In addition to the risks associated with cocaine-induced psychosis symptoms, some studies observed that drug-dependent patients with cocaine-induced paranoia are at

a higher risk of developing psychotic disorders.^{15,19} In psychiatry settings, studies have reported a prevalence of psychotic symptoms induced by cocaine use ranging between 29% and 86.5%.^{7,10} The prevalence of cocaine-induced psychotic disorders ranges from 6.9%²⁰ in young cocaine users not seeking treatment to 11.5% in cocaine-dependent patients under treatment in therapeutic community²¹ or 40.6% in outpatients clinics.¹³

The first studies focused on this issue were published in the late 1980s, with the majority of them originating from the US.⁷ Manschreck and colleagues reported a cocaine-induced psychosis prevalence of 29% in patients hospitalized for cocaine use.²² Brady et al. found that cocaine-induced paranoia was present in 53% of cocaine-dependent subjects.¹¹ Bartlett and colleagues observed cocaine-induced psychosis in 47.5% of cocaine-dependent patients.²³

In the last decade, 3 large studies have been published in the US. Kalayasiri and colleagues observed cocaine-induced

psychosis in 65% of cocaine-dependent patients.²⁴ Cubells et al. and Tang et al. reported cocaine-induced psychosis in 75% of adult cocaine-dependent individuals.^{16,17} Recently, Zayats and colleagues described a prevalence of 67.6% in European American and 70.2% in African American cocaine-dependent patients.²⁵ Finally, Gilder et al. indicated a prevalence of 29% in 286 stimulant-dependent patients.²⁶ However, in this study, only 16.6% of patients were “pure cocaine-dependent patients,” whereas the rest of the participants used methamphetamine alone or in addition to cocaine.²⁶ Controlled laboratory studies of cocaine use (intravenous or smoked) by a healthy patient with a history of cocaine dependence reported a prevalence of cocaine-induced psychosis ranging between 43%²⁴ and 100%.^{27,28} In European countries, the past 4 years have included studies describing a cocaine-induced psychosis prevalence ranging from 29% to 86.5%. The studies were from Spain,^{8,9,20,21,28–30} France,^{10,31} and Martinique (French West Indies).³²

We attribute the variety of estimates regarding prevalence of cocaine-induced psychosis to the variability and bias in the samples, study design limitations, and the difficulty in comparing the various instruments used to measure psychosis. It should be noted that although the study samples included between 20 and 2292 patients, only 9 clinical samples included more than 150 patients.^{9,12,13,17,21,25,26,29,33} Furthermore, the number of participants in controlled experimental studies was limited.^{24,27,28,34}

Assessment

The most commonly used instruments to assess cocaine-induced psychotic symptoms and induced psychotic disorder are the Cocaine Experience Questionnaire (CEQ),^{15,16,32} the Scale for Assessment of Positive Symptoms for Cocaine-Induced Psychosis (SAPS-CIP),^{15,16,29–32} questionnaires designed ad hoc,^{8,9,17} and the Psychiatric Research Interview for Substance and Mental Disorders (PRISM).^{13,30,33} The PRISM was designed specifically to differentiate among primary mental disorders and induced ones.^{35,36}

Clinical Features

One of the first systematic studies of cocaine-induced psychosis involved 55 cocaine-dependent patients who were consecutively admitted for treatment.¹¹ Twenty-nine patients reported psychotic symptoms. Ninety percent developed paranoid delusions directly related to drug use, 96% experienced hallucinations (83% auditory, 38% visual, and 21% tactile), and 29% of subjects developed transient behavioral stereotypes.¹¹ Satel and colleagues reported that 68% of 50 cocaine-dependent patients developed paranoid episodes during cocaine intoxication, 53% of those with paranoid ideation developed checking behaviors, and 38% of the patients had harmed themselves.³⁷

In the first European study to measure cocaine-induced psychosis, 173 cocaine-dependent patients were evaluated, and 53.8% reported psychotic symptoms while under the influence of cocaine. The most frequently reported symptom was paranoid beliefs and suspiciousness (43.9%). Patients also reported auditory hallucinations (30.9%), visual hallucinations (26.1%), and tactile hallucinations (10.3%). Motor alterations were not evaluated.⁹ The same research group conducted another study in which clinical features were observed directly by trained staff in a

self-injection room offered as part of a harm reduction program.⁸ The study included a sample of 21 cocaine-dependent patients with a total of 375 cocaine intravenous intakes. Psychotic symptoms were noted in 62% of the patients and in 21% of the drug intakes. Symptoms observed in the patients included illusions (28.6% of patients), hallucinations (38.1%), delusions (47.6%), and self-reference beliefs with insight (42.9%). Other motor and behavioral symptoms noted in patients were trembling (66.7%), stereotyped movements (66.7%), and behavioral alterations (23.8%). Psychotic symptoms as a percentage of the 375 cocaine self-injections were illusions (6.4%), hallucinations (5.3%), delusions (9.3%), and self-reference beliefs with insight (9.1%). Other motor and behavioral symptoms as a percentage of total cocaine self-injections were trembling (57.9%), stereotyped movements (24%), and behavioral alterations (6.1%).⁸

In the second large European study by Vorspan and colleagues, involving 105 participants with cocaine addiction, the prevalence of psychotic symptoms was 86.5%.¹⁰ The symptoms reported were auditory hallucinations (44%); visual hallucinations (42%); tactile hallucinations (32%); olfactory hallucinations (23%); paranoid ideation (55%); delusion of jealousy (13%); delusion of having sinned (15%); delusion of grandiosity (30%); delusions about religion (6%); somatic delusion or dysmorphophobia (22%); delusion of reference (28%); delusion of influence (13%); thought broadcasting, insertion, or withdrawal (25%); agitated behavior or aggression (41%); repetitive stereotyped movements (58%); unusual social or sexual behavior (65%); and ritualized cocaine intake (preparation of self or place where cocaine was issued) (48%).

Recently, we studied the presence of psychotic symptoms in a large sample of 287 cocaine-dependent patients.²⁶ Psychotic symptoms of any sort were reported in 59.9% of the sample (see Table 2). Despite the fact that motor alterations were not evaluated, symptoms could have been underestimated.²⁹

Risk Factors for Cocaine-Induced Psychosis

Quantity of cocaine consumed. Initially, the literature reported that the quantity of use did not appear to predispose users to cocaine-induced paranoia.³⁷ However, it is currently accepted that quantity is positively related to cocaine-induced psychosis.^{9,18,24,27,38} In a study of 16 individuals diagnosed with crack dependence and reporting polysubstance use, the amount of cocaine consumed and psychotic symptoms decreased after 3 weeks of treatment, and there was a significant correlation between psychotic symptoms and dose reduction.³¹

TABLE 2
Psychotic Symptoms Lifetime Prevalence

Symptoms reported	%
Any psychotic symptoms	59.9
Referential believes	38.6
Delusion of persecution	27.2
Any hallucinations	28.3
Auditory hallucinations	23.6
Visual hallucinations	13.3
Kinesthetic hallucinations	7.8

Note. Based on Roncero et al.²⁹

Lifetime amount of cocaine use. Although the lifetime amount of cocaine use or amount of cocaine used in the month preceding admission did not differ significantly between those patients with and without psychosis, Brady et al. reported that those with psychosis had used significantly more cocaine in the year prior to admission and had used cocaine for a longer period of time.¹¹ Additionally, Cubells and colleagues reported significant positive correlations between the severity of hallucinations and delusion and the lifetime number of episodes of cocaine use, which could be related with lifetime amount of cocaine use.¹⁶

The onset of cocaine dependence. Using cocaine at an early age or during vulnerable periods of brain development may lead to increased severity of cocaine-induced psychosis,^{11,23,24,38} and the severity of psychosis appears to be related to an earlier exposure to stimulants in general.³⁹ There is a negative correlation between symptom severity and age of initiation of cocaine use.¹⁶

Years of use. Controversy still exists regarding the relationship between years of use and the risk of developing cocaine-induced psychosis. Reid et al. found that the number of years of cocaine use did not correlate with cocaine-induced psychosis.⁴⁰ However, a higher number of years of daily stimulant use has been associated with stimulant-associated psychosis.²⁶ Furthermore, in experimental research under controlled laboratory conditions, patients who reported feeling paranoid/suspicious were more likely to be older.²⁸ As well, the severity of the psychosis appears to be related to having used stimulants for a longer period of time.³⁹

Routes of administration. Intravenous use of cocaine has been correlated with stimulant-associated psychosis.²⁶ Previously, various routes of administration, from nasal insufflation to smoking, were reported to increase the risk of cocaine-induced psychosis.²⁴ Recent research indicates that intravenous cocaine use seems to lead to the appearance of psychotic symptoms.⁸

Substance use disorder comorbidity. Cannabis use in particular seems to play a mediating role in the development of cocaine-induced psychosis.⁷ In some studies, the presence of a comorbid substance use disorder (SUD) has not been significant after adjusting for age and sex.¹⁷ In other studies, the initiation of cannabis use in adolescence increased the risk of cocaine-induced psychosis in cocaine-dependent individuals,²⁴ and cannabis dependence lifetime history was linked with psychotic symptoms.⁹ Recently, it has been reported that early cannabis use is associated with the occurrence and the severity of psychotic symptoms during cocaine intoxication in those with a comorbid SUD.³² In a sample of cocaine self-injectors, a higher prevalence of psychotic symptoms was noted in those using cannabis in the previous month, using more benzodiazepines, or using less methadone.⁸

Body weight. A low body mass index (BMI) could increase the risk for cocaine-induced psychosis in crack users, and a high BMI could be a protective factor.⁴¹

Gender. The results have been inconsistent regarding the influence of gender on the risk of developing cocaine-induced psychosis. Males were significantly more likely than females to develop psychotic symptoms in some studies,^{11,28} but others found that women had a higher risk of developing symptoms.¹⁸

Comorbid Axis I disorders. Some comorbid Axis I disorders, such as psychosis or attention-deficit/hyperactivity disorder (ADHD), have been found to be related to cocaine-induced psychosis.⁷ Previous psychosis has been reported to be associated with psychotic symptoms.²² ADHD, a common diagnosis in cocaine-dependent patients,⁴² has been associated either with the

categorical presence of cocaine-induced psychosis^{17,29} or stimulant-associated psychosis.²⁶

Comorbid Axis II disorders. People who use cocaine are frequently diagnosed with comorbid Axis II disorders. The prevalence of these disorders in inpatient samples is reported to be between 30% and 70%, with antisocial personality disorder and borderline personality disorder being the most common.^{29,43} Kranzler et al. did not find significant differences in the frequency of cocaine-induced psychosis between individuals with and without personality disorders.¹⁹ However, others found that cocaine-induced psychosis could be linked to hostile behavior⁷ and antisocial personality disorder.^{7,9} Stimulants may generate hostility through psychotic symptoms.^{17,44}

Genetic influence. A few retrospective studies have investigated the association between certain genetic attributes and cocaine-induced psychosis.⁴⁵⁻⁴⁷ Dopamine transporter (DAT) allele 9 has been linked to a predisposition for paranoia in people who use cocaine.⁴⁵ Cocaine-induced psychosis has also been associated with a haplotype of the DBH locus (Del-a) that produces low levels of dopamine beta-hydroxylase (DbetaH),⁴⁶ and a prospective study found that individuals homozygous for the "very-low-activity" T allele (-1021C→T) at DbetaH are more likely to exhibit paranoia during cocaine administration.⁴⁸ Kalayasiri and colleagues could not find an association between polymorphic variation in the catechol-O-methyl transferase gene (COMT) and the risk of developing cocaine-induced psychosis.⁴⁷ However, these results require independent replication,⁴⁵ there are differences between races,^{25,49} and some studies fail to detect any significant genetic differences between cocaine-dependent patients with or without cocaine-induced psychosis.⁵⁰⁻⁵²

Pharmacological interactions. The interactions between cocaine with other illegal drugs or with drugs used to treat cocaine dependence or other comorbid conditions can lead to psychotic symptoms. Mainly, these include drugs with dopaminergic system activity.⁷ Farooque and Elliott reported a patient who developed psychosis after she was prescribed bupropion for having a low energy level.⁵³ Additionally, the interaction between disulfiram and cocaine can lead to psychotic symptoms,⁵⁴ and there are some case reports about the association of disulfiram⁵⁵ and/or methylphenidate treatment with the presence of psychotic symptoms in cocaine-dependent patient.⁵⁶⁻⁵⁸

FUTURE AND NEXT STEPS

The relationship between cocaine use/dependence and the presence of psychotic symptoms has received much attention in the addiction field. It is well known that cocaine use is associated with the occurrence of transient psychotic symptoms.⁷ However, there is a clear need for further research, as indicated by the discordant studies mentioned above and the remaining questions and gaps in knowledge.

First, there is controversy regarding even the definitions of the psychotic symptoms. Transient psychotic symptoms occur during consumption, and symptoms disappear after a binge or a crash phase. This is in contrast to the "persistent psychotic episodes," where symptoms may be present for days after a crash phase, and their severity is greater than transient psychotic symptoms. This episode type is considered to be "authentic" cocaine-induced

psychotic disorder.¹⁵ However, not all of these concepts are included in DSM-5,¹⁴ and there is not a universal consensus regarding these definitions. Although symptoms seem to be concordant across all the studies, there is also a lack of trials comparing differences in psychotic symptoms based on different routes of administration of cocaine.

The presence of psychotic symptoms clearly influences quality of life and may affect cocaine dependence evolution in people who use cocaine. Psychiatric comorbidity predicts cocaine-dependent individuals' shorter time in residential treatment.³³ Further, patients with psychotic symptoms have a higher history of detentions than patients without any psychotic symptoms.¹³ Prospective studies regarding the influence of psychotic symptoms on treatment or other clinical features are needed. It is also unclear whether the presence of psychotic symptoms is linked with the future presence of schizophrenia or persistent psychosis.

There are many well-known risk factors for cocaine-induced psychosis in cocaine-dependent patients,⁷ but other factors remain controversial or have not been studied. Researchers have looked for neurobiological markers related to the risk of developing cocaine-induced psychosis. However, many studies have failed to find an association or have not been replicated. In order to avoid bias, this kind of research should be done in multinational studies using a standardized interview for cocaine-dependent patients. Persons who use cocaine have an increased risk of developing psychotic symptoms if they have a deficit of P50 sensory gating and attention deficits³⁴ and prolonged latency of the evoked potentials (P50, N100, P200).⁵⁹ Recently, a correlation between psychosis proneness and sensory gating in cocaine-dependent patients was found.⁶⁰ However, these studies have only involved small sample sizes and should be replicated on a larger scale. Neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), could play a role in the transient psychotic symptoms associated with cocaine consumption. Cocaine-dependent patients with cocaine-induced psychosis exhibit a significant decrease in serum brain-derived neurotrophic factor levels, sharing some of the deficiencies that characterize schizophrenia and psychosis.⁶¹ However, it is unknown whether neurotrophic factor levels act as a risk factor or a protective factor or if the changes in the BDNF levels are the same no matter the route of administration.

Knowledge gaps exist regarding the influence of the personality traits or disorders on the presence of cocaine-induced psychosis. As mentioned earlier, antisocial personality disorder has been proposed as a risk factor for cocaine-induced psychosis,⁹ but other studies have failed to find this association.^{12,13,19} To our knowledge, there is very little research about the relationship between cocaine-induced psychosis and a dimensional approach to personality in cocaine-dependent patients. Similarly, further research is also needed in the area of impulsivity (or subtypes of impulsivity) and its influence on the presence of psychotic symptoms. Cocaine-dependent patients with higher impulsivity or cognitive impulsivity levels were more likely to exhibit cocaine-induced psychosis.²⁹ This association could be mediated by the "binge" cocaine use pattern; however, this variable has not been studied in large clinical samples.

Additional research is needed regarding pharmacological interactions. Some case reports have been published about the influence of various medications on the presence of psychotic

symptoms.^{53–58} However, the degree of influence of pharmacological treatment (e.g., dopaminergic drugs) on the presence of psychotic symptoms in cocaine-dependent patients is not well known.

Finally, it is necessary to integrate the current knowledge about all of these risk factors. Previously, we proposed a risk factor model for developing cocaine-induced psychosis.⁹ We found that the amount of cocaine consumed, cannabis dependence history, route of administration, and antisocial personality disorder were associated with cocaine-induced psychosis. Future integrative models should incorporate new knowledge regarding other factors, such as some of the neurobiological markers, routes of cocaine use, lifetime ADHD, and personality dimensions.

CONCLUSION

Although many unknowns remain regarding the risk factors linked to cocaine-induced psychosis, and we do not have a complete integrative model, the evaluation of cocaine-induced psychosis in cocaine-addicted patients is clinically relevant. It is particularly important for those patients consuming high amounts of cocaine, exhibiting cannabis dependence history, using routes other than intranasal, or with comorbid antisocial personality disorder or ADHD. The systematic evaluation of psychotic symptoms can be beneficial for the patient and the community by preventing psychotic states and hostile behavior and its associated negative consequences.

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AUTHOR CONTRIBUTIONS

Dr. Roncero and Dr. Casas designed the objective of the study. Dr. Roncero and Dr. Daigre wrote the first and last manuscript drafts. The other authors contributed to the literature review and provided critical revisions to all of the versions of the manuscript.

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