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Prevalence and risk factors of psychotic symptoms in cocaine-dependent patients

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Objectives. Cocaine consumption can induce transient psychotic symptoms expressed as paranoia or hallucinations. This work reviews that evidence and tries to obtain data regarding frequency of psychotic symptoms or cocaine induced psychosis (CIP), risks or associated factors.

Method. Systematic review of studies found in PubMed database published until January 2011 where cocaine induced paranoia was present.

Results. Cocaine induced paranoia has a particular clinical presentation. It needs to be clearly identified due to its harmful consequences. The prevalence is between 12% in clinical studies and 100% in experimental studies. The following are considered potential risk factors: age of first use and length, amount of substance, route of administration, body mass index, genetic factors, personal vulnerability and comorbidity with AXIS I (psychosis, ADHD) and AXIS II disorders (antisocial personality disorder).

Conclusions. It is needed to research with larger samples of cocaine users of different countries and contexts, in order to identify and detail what variables are closely related in the development of cocaine induced paranoia, so the population at risk can be treated earlier.

Key words: Psychosis, Cocaine, Cocaine induced psychosis, Dependence, Risk factors

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Prevalencia y factores de riesgo asociados a la presencia de clínica psicótica en dependientes de cocaína

Objetivos. El consumo de cocaína puede inducir la aparición de sintomatología psicótica transitoria en forma de paranoia y alucinaciones. Este trabajo revisa la frecuencia

de aparición de sintomatología psicótica en pacientes consumidores de cocaína y los factores de riesgo o asociados a su presentación.

Metodología. Búsqueda sistemática en base de datos de *Pubmed* de los artículos publicados hasta enero de 2011, inclusive, sobre aparición de sintomatología psicótica en contexto de consumo de cocaína.

Resultados. La psicosis inducida por cocaína es un cuadro clínicamente característico, que debe ser identificado y diferenciado de otras psicosis. Se han detectado presencia de síntomas psicóticos de entre el 12% en estudios clínicos descriptivos y de hasta del 100% en estudios de laboratorio. Se consideran posibles factores de riesgo: la edad de inicio del consumo, su duración y gravedad, la vía utilizada, el índice de masa corporal, factores genéticos y vulnerabilidad interpersonal asociada, así como la comorbilidad con otros trastornos psiquiátricos tanto del Eje I (psicosis crónicas, TDAH) como del Eje II, principalmente con el Trastorno antisocial de la personalidad.

Conclusiones. Se debe continuar investigando con muestras más amplias de población consumidora, incorporando en mayor medida población de diferentes países y contextos, para poder identificar y concretar qué variables son las más estrechamente implicadas en la aparición de sintomatología psicótica. Ello permitirá identificar a la población de riesgo, con el fin de realizar una intervención precoz.

Palabras clave: Psicosis, Cocaína, Trastorno psicótico inducido, Dependencia, Factores de riesgo

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INTRODUCTION

According to the data of the 2011 United Nations Office on Drugs and Crime,¹ cocaine consumption worldwide is located in the fourth place, with prevalence between 0.3 and 0.5% of the adult population between 15 and 64 years. Cocaine is the second most consumed illegal drug after

cannabis in both Spain and Europe. Its consumption and demand for treatment have increased in recent years in our country until becoming the leader in Europe in number of consumers.² It is considered that cocaine could be replacing the use of other stimulants.

The prevalence of cocaine consumption in the year 2008 in Spain was 3% for the population between 15- 64 years.³ According to European data, cocaine consumption is mainly concentrated in young adults between 15 -34 years, finding numbers above 25.4% of use of the substance in individuals in said age range.⁴ Cocaine is the substance mentioned most in the emergency setting and that which causes the greatest number of admissions for hospital treatment in relation to abuse or dependence (41.7% of the total).⁵

Cocaine dependence is a chronic disorder marked by relapses and elevated comorbidity. It is an important worldwide health problem due to the multiple associated somatic, legal, social, cognitive and psychological complications.⁶

The spectrum of medical manifestations associated to cocaine consumption is wide and may cause potentially fatal complications such as pulmonary infections, respiratory failure, hemorrhaging, heart diseases, acute myocardial infarction, seizure episodes, agitation or even sudden death.⁷⁻⁹

Furthermore, it is known that a considerable proportion of cocaine consumers have other mental disorders associated to consumption, (up to 42.5%), mainly affective disorders (26.6%) and anxious spectrum disorders (13%).¹⁰

Psychotic symptoms are one of the most common complications produced by cocaine consumption, whether acute or chronic. The appearance of psychotic symptoms in cocaine consumers or paranoia induced at any time of life is frequent.^{6, 11} This could be due to the fact that cocaine consumers have a greater risk of developing psychotic symptoms as a psychopathological complication, transitory paranoia being the most common picture. Said symptoms may appear also during periods of abstinence.^{6, 12}

However, the presence of psychotic symptoms is not a universal fact and their prevalence has not been definitively clarified as of yet.¹¹ There is wide variability in its prevalence, this ranging according to different works from 6.9% in consumers who do not seek treatment,¹⁰ 12% in patients hospitalized in any type of department of a General Hospital,⁸ up to 100% in experimental studies¹³ of consumers who meet substance dependence criteria. Such a wide range found in the prevalence data may be because the different studies are not comparable regarding methodological variability, possible presence of biases in the sample studied, differences in design and any instruments used, etc.¹⁴

There are few existing studies regarding the appearance of psychotic symptoms and cocaine consumption and those that do exist are less systematic than those focused on other substances. This study has aimed to review the previous investigations that describe the prevalence of psychotic symptoms and the risk factors associated to their appearance, in cocaine dependents.

MATERIAL AND METHODS

Research articles have been included in this review work after conducting a systematized and extensive review in the computerized database of *Medline*. The existing scientific literature published during the last four decades, specifically up to and including January 2011, was included in order to cover all of the available studies up to the date. This search was made using the following keywords: psicosis (psychosis), cocaína (cocaine), trastorno psicótico inducido (cocaine induced psychosis or paranoia), dependencia (dependence) and factores de riesgo (risk factors). The *MESH* terms available have been combined and the references to other pertinent articles available were reviewed.

This is a review of observational and experimental studies conducted in the human population that describe or investigate the presence of psychotic symptoms in the cocaine consumer population. Age range, gender or race were not used as selection criteria. Articles were not excluded based on sample size, presence or not of a control group of the sample being studied, or date of publication, as well as the language used. Of the articles found, those that did not include aspects related to epidemiology, symptoms, risk factors, prognoses and evolution as well as case series, were ruled out as they did not provide directionality nor did they evaluate the evolution over time.

A total of 26 original articles published between 1988 in 2011 were selected and analyzed. Of these, 21 were conducted in the United States, 3 in Spain, 1 in the Bahamas and 1 in Japan. Furthermore, nine of them were experimental and had been carried out in the outpatient laboratory or hospital setting during an admission. The remaining studies are descriptive carried out in clinical context based on epidemiological studies performed by interviews to the consumer population. Studies that included all the cocaine consumption pathways were compiled, in distinctively, and others that focused on the pulmonary pathway (crack) or intravenously, exclusively.

RESULTS

Of the 26 articles analyzed, most of the studies had been conducted in the USA, 9 of them experimental (table 1). These were conducted under outpatient laboratory or

hospital setting conditions during an admission. The remaining studies were descriptive conducted in clinical context studies conducted by interviews in the consumer population (table 2). Studies that included all the cocaine consumption pathways were compiled, in distinctively, and others that focused on the pulmonary pathway (crack) or intravenously, exclusively. There was variability in the size of the sample studied, going from 19 to 420 patients (Tables 1 and 2).

It has been hypothesized that there may be psychotic symptoms in the general population. In this sense, Freeman et al.¹⁵ described up to 18.6% of the psychotic symptoms of self-referential nuance and 1.8% of references of individuals on the existence of complots against them in the English population during the year prior to the study conducted. In said study, paranoia was associated to use, being single, poverty, health problems, low IQ, scarce social support, stress, depressed mood, suicide alleviation, cannabis and alcohol abuse, increase of the need for medical care and appearance of other associated psychiatric disorders.

However, as mentioned, the prevalence of the appearance of psychotic symptoms in the consumer population attended in care sites varies according to the studies from 12% to 100% in the descriptive studies^{8, 16} and from 34% to 100% in the experimental ones.^{13, 17}

On the neurobiological level, cocaine acts directly, producing dopamine reuptake blockade. This seems to be the fundamental, but not the only cause, of the psychotic symptoms.¹⁸ Dopaminergic release would be initially responsible for the positive symptoms and the subsequent degeneration of the neurons per se of the dopaminergic system, which would lead to the appearance of the negative symptoms.¹⁹ Furthermore, it has been demonstrated in preclinical studies that environmental stressant factors can produce increased dopamine and glutamate release in the mesolimbic projections and in the medial prefrontal cortex, which could also be involved in the origin of the psychotic symptoms. That is, the appearance of psychotic symptoms in the context of cocaine intoxication is not only due to having exceeding a certain threshold nor to the amount consumed

Table 1 Experimental studies on psychotic symptoms in cocaine consumers

STUDY	N	PREV	PLACE	PATHWAY	RESULTS
Rosse et al. 1994 ²⁹	62	70%	Admission U. USA	Pulmonary (crack)	Induced psychotic symptoms (IPS) generally precede compulsive search for cocaine.
Rosse et al. 1995 ⁵¹	44	64%	Admission.U USA	Pulmonary (crack)	Subjects with IPS have higher levels of anxiety and hyperarousal
Cubells et al. 2000 ⁴²	256	60%	Outpatient USA	All	The haplotype associated to low DBH activity is related with IPS.
Boutros et al. 2002 ¹⁷	30	34%	Admission.U USA	All	Decrease of P50 sensory gate is related with development of IPS and presence of attention deficit with its severity.
Malcolm et al. 2004 ²⁶	23	35%	Laboratory USA	Pulmonary (crack)	There is a negative correlation between previous sensibilization of suffering IPS with the risk of relapse in cocaine consumption.
Kalayasiri et al. 2007 ¹³	28	43 %	Laboratory Multicentric USA	Intravenous	In laboratory conditions, IPS is dose-dependent. Accumulative use of cocaine is a risk factor.
Kalayasiri et al. 2007 ³⁹	31	100%	Laboratory USA	Intravenous	Individuals homozygous for the allele responsible for very low activity of DBH have more propensity to IPS during the administration of cocaine.
Mooney et al. 2006 ³⁵	44	67%	Laboratory Multicentric USA	Pulmonary (crack)	Male gender and older age are risk factors for suffering IPS.
Boutros et al. 2006 ⁴⁵	68	71%	Laboratory USA	All	P50, N100 and P200 sensory gating are deficient in cocaine dependents. All the latencies were increased in patients with background of IPS.

PREV: Prevalence, U.: Unit, IPS: Cocaine induced psychotic symptoms

Table 2 Descriptive studies on psychotic symptoms in cocaine consumers

STUDY	N	PREV	PLACE	PATHWAY	RESULTS
Manschreck et al. 1988 ³⁸	106	29%	Admission U. Bahamas	Pulmonary (Base)	Among those having IPS, comorbidity was observed with Axis I, violent behaviors and greater amount of cocaine consumption.
Satel et al. 1991 ²²	50	68%	Outpatient USA	All	In vulnerable individuals, there is non-specific limbic sensibilization, which leads to IPS after the continued use of cocaine. Dose and pathway used have no effect.
Satel et al. 1991 ⁵⁴	20	68%	Outpatient USA	All	Appearance of IPS is a risk factor for subsequent development of a psychosis. Important consumers who experience IPS during intoxication have greater risk of developing psychosis than those who do not experience it.
Gelernter et al. 1994 ⁴³	103	54%	Outpatient USA	All	Certain DAT genotypes predispose to suffering IPS in white population.
Rosse et al. 1994 ⁴⁸	72	54.8%	Outpatient USA	Pulmonary (crack)	IPS appears in similar proportion in cocaine dependences in the Phencyclidine Drug (PCP) ones. With PCP, there is more proportion of sensorial-perceptive disorders than delusional type. With cocaine, suspicion and paranoia predominate.
Bartlett et al. 1997 ²⁴	40	47.5%	Outpatient USA	All	IPS is related with the sensibilization and this, in turn, with the number of relapses in consumption.
Yui et al. 1999 ²⁵	79	67%	Prison	All	There is pathological sensibilization of the neuronal systems that are an important factor of relapse of IPS, both for cocaine and amphetamines and other stimulants.
Harris et al. 2000 ¹⁶	19	100%	Emergencies USA	All	Patients with IPS have predominately positive symptoms, although also substantially negative one, which is related to greater stay in emergency services and admissions.
Rosse et al. 2005 ⁴⁶	69	80%	Admission.U USA	Pulmonary (crack)	Low BMI has been related with the development of IPS and elevated BMI is considered a protector factor.
Floyd et al. 2006 ³³	51	71%	Outpatient Multicentric USA	All	IPS is more severe if consumption initiates in early ages (17-20y) when cerebral development is more vulnerable.
Kalayasiri et al. 2006 ³²	420	65%	Outpatient USA	All	Severity of dependence, early onset of consumption, pulmonary pathway and less consumption during the previous year are risk factors for the appearance of IPS.
Sopeña et al. 2007 ⁸	170	12%	Medical or psychiatric admission U. Spain	All	Manifestations associated to cocaine consumption, both medical and psychiatric, are extensive: they cause potentially fatal complications.
Tang et al. 2007 ⁴⁷	243	75%	Outpatient	All	Multiple consumption and psychiatric disorders are very frequent among cocaine dependents are associated to greater frequency and severity of IPS. In consumers, comorbid ADHD increases that of presenting it, suggesting a common base.
Mahoney et al. 2008 ¹²	42	67%	Outpatient USA	All	IPS by cocaine is less frequent than that induced by PCP, although both have elevated prevalence.
Herrero et al. 2008 ¹⁰	139	6,9%	Naturalistic (street)	All	Untreated youth, between 18 and 30 years, have cocaine induced psychotic disorder, evaluated by semistructured interview PRISM.

Table 2	Continuation				
STUDY	N	PREV	PLACE	PATHWAY	RESULTS
Manschreck et al, 1988 ³⁸	106	29%	Admission.U USA.	All	IPS is common among chronic consumers, the amount consumed and duration of consumption are related with its appearance.
Satel et al, 1991 ²²	50	68%	Outpatient Spain	All	There is an association between the appearance of psychotic symptoms and the amount consumed, dependence on cannabis and antisocial personality disorder.

PREV: Prevalence, U.: Unit, IPS: Cocaine induced psychotic symptoms

nor the time that consumption has been occurring. The precipitant of this disorder is the interaction of cocaine and the setting with an already vulnerable individual, that is, with some previous alteration to consumption that predisposes the subject to suffering paranoia, probably in the dopaminergic circuit of the limbic system, although the exact cerebral localization is still unknown.²⁰

Once a cocaine-induced psychotic picture appears, the likelihood that it will reappear with consumption is greater as the time of cocaine consumption increases.^{21, 22} Furthermore, severity of the symptoms is greater and is associated to a lower amount of substance consumed.^{21, 22} This phenomenon is known as "sensibilization"²³ and could also be responsible for a dopamine dysregulation that would induce the craving and a greater number of relapses.^{24, 25}

It has been postulated that there is a negative correlation between previous sensibilization to suffering an induced psychotic disorder and risk of relapse in cocaine consumption.²⁶ However, it should be stated that said sensibilization phenomenon only affects the psychotic symptoms and not other effects of the cocaine consumption in the individual.²⁴ Therefore, the cocaine consumers who experience sensibilization to the psychotogenic properties generally have less craving and are capable of reducing both cocaine consumption and that of other toxic substances.²⁶ In vulnerable individuals, there is a nonspecific limbic sensibilization that leads to the induced disorder, although in this case, neither the dose nor the route used would be influencing factors.²²

Clinical characteristics of the cocaine psychoses

The clinical characteristics of cocaine psychosis are very similar in the different subjects. They are generally preceded by a period of suspicion, distrust, compulsive behaviors and dysphoria, which commonly occur with a significant component of aggressiveness and agitation.^{6, 11} Transient paranoia is the

most characteristic of the symptoms,¹⁴ this occurring in 90% of the cases, with harm and jealous-type contents, the most frequent delusion being that of feeling oneself surrounded by agents of the law or by people who want to steal their substance. The presence of alterations in the affective sphere is common. Almost all the delusional and hallucinatory symptoms accompanying them are directly related with consumption behaviors and may even occur at one hour.²⁷

Hallucinations are not uncommon. They are generally vivid and isolated and consistent with the thought content.¹¹ In those having hallucinations, the auditory ones are the most frequently, these appearing in 83% (sounds from people who are following them...) followed, in a lesser frequency, by the visual ones (spies in the windows, etc) and tactile ones.^{11, 21} The descriptions of the cenesthetic hallucinations are classic; in up to 38% of the patients, such as having the skin infested of parasites or cenesthetic in form of formication, up to 21% in which the patient has the belief of having the parasite under the skin. These hallucinatory pictures are typical of cocaine psychosis. Even when there is criticism of it by the individual, it could be classified as cocaine hallucinosis.²⁷

The clinical picture is generally self-limited and abates without the need to initiate treatment in the hours following the end of the consumption, remission of the symptoms being typical after 24-48 hours of abstinence.^{11, 28} Rarely, it is possible that the symptoms prolong beyond the *crash* period (picture of hypersomnia that follows the recent abstinence). However, an increase in emergencies and the number of admissions associated to the predominance of negative symptoms has been observed (appearing less frequently than the positive ones in the context of cocaine consumption).¹⁶

It has been observed that cocaine consumers without primary psychotic disorder, who consult in psychiatric emergency services, have more severe hallucinatory pictures than schizophrenic patients without added substance use disorder.⁷

Behavioral alterations such as aggressivity/agitated behavior, repetitive or stereotypical behaviors or unusual sexual behaviors have been correlated with cocaine induced hallucinations and delusions.²⁸ It has been demonstrated that the appearance of violent behaviors, heteroaggressivity and criminal acts appears more frequently in individuals who have an associated disorder due to substance use with a psychosis than in those affected by each one of the disorders independently, with the legal and social repercussions these entail.²⁸

Frequently, they also have motor stereotypes. It is described that 27% mimic tasks or gestures without meaning, such as rummaging the zone that surrounds them, expecting to find drugs or pinching their skin.²¹ Regarding the cocaine-induced compulsive search associated to the acute intoxication episode in patients with chronic cocaine consumption, more than 50% of the patients studied have compulsive searching, always associated to crack consumption and with a search behavior of at least 90 minutes.²⁹ The patients search for pieces of crack that they believe may have fallen or been shifted from their original site accidentally or by third parties, around the place in which the patient had been consuming it. It has also been observed how they inspect furniture, the area of consumption, pockets, clothes in general, shoes and even socks. They carefully examine everything that physically reminds them of the crack such as food remains, small-sized stones, pieces of soap, etc. Most of the patients are aware that they are searching in vain and they have several grades of resistance to the search impulse promoted by the excessive belief that cocaine may be found nearby in this setting. After, Rosse et al.²⁹ did not find a clear relationship between said search in the presence of craving and they suggested that the induced psychotic disorder generally precedes the compulsive search

for cocaine, both during the life of consumption of the individual as during the bingeing.

Risk factors associated to consumption

All the associated factors or risk factors of appearance of psychotic symptoms in cocaine consumers are not exactly known (Table 3). Cocaine acts on the specific neurotransmitter pathways.^{18, 19} Thus, studying the mechanism by which the substances affect said pathways and produce psychotic symptoms may provide keys to the psychopathology of the psychosis. However, it has been hypothesized that the appearance of a cocaine-induced psychotic disorder, after the first consumption, could be associated to a lower risk of developing a subsequent addiction.³⁰

Age and duration of consumption

It has been described that early-onset of consumption is a risk factor for the appearance of psychotic symptoms.^{21, 31, 32} It has been observed that if cocaine consumption initiates at early ages (17 -20 years) or in periods of brain development, in which the individual is more vulnerable, the severity of the induced psychotic disorder may be increased.^{24, 33} Age may be related with the consumption route since age is lower in those who inject crack in comparison with those who inject other drugs in patients who use the intravenous route.³⁴

In another sense, Mooney et al.³⁵ described that older patients have a greater risk of developing symptoms, which is in agreement with two recent studies. In the first study, it is described that the patients who have psychotic symptoms generally have a longer history of cocaine dependence¹⁴ and

Table 3	Factors associated to the development of psychotic symptoms, in cocaine dependents
Age of onset of consumption Consumption pathway Dose/amount consumed Neurophysiological Genetic	With greater consensus
Age of patient Duration (years) of consumption Body Mass Index Gender Race Consumption pattern Consumption/dependence on other drugs: cannabis Comorbidity with other Axis I Disorders: (ADHD, Psychosis) Comorbidity with Axis II Disorders: ASPD	In study /with less consensus
ADHD: Attention Deficit Hyperactivity Disorder. ASPD: Antisocial Personality Disorder	

in the second one, it is indicated that the severity of the symptoms evaluated by the PANSS is related to more years of exposure/consumption of stimulant substances.³¹ However, other authors disagree,²⁶ since they have suggested that the number of years of active consumption did not have a relationship with the risk of suffering psychotic symptoms, within the context of cocaine intoxication.

Gender

The prototype of an individual who develops induced psychotic symptoms is generally a man,^{21, 35} this being considered a risk factor although according to some authors,¹² women have more risk of developing said symptoms.

Consumption pathway

The importance of the consumption pathway has been stressed since this affects the absorption speed and therefore determines the onset and duration of the effects as well as the substance's blood concentration.³⁶ Consumers who use the intravenous route suffer paranoia and hallucinations more acutely and suddenly in comparison with other consumption pathways, followed by freebase form of consumption via the lung.^{21, 36} This could be more related to the amount of the cocaine consumed than to the specific consumption pathway used.³⁷ That is, the greater addictive capacity of the cocaine and the need to increase the amount when said pathways are used would be explained because the intravenous and respiratory pathways show a more rapid absorption speed and therefore produce a more intense and shorter effect than the nasal, topical and oral administration.

When cocaine has been administered via the lung, under experimental conditions in the laboratory, in a sample of cocaine consumer patients using this via, it has been observed that up to 67% have reported paranoia/suspicion after its administration.³⁵ When the intravenous route has been used experimentally, this has occurred in 100% of the administrations.¹³

Dosage

Manschreck et al.³⁸ postulated that the patients who had induced psychotic symptoms consumed greater amounts of cocaine than those who did not have them. Satel et al.²² did not find this relation. However, in different works, Brady et al.²¹ and Kalyasari et al. have supported this, both in clinical studies³² and in two laboratory studies.^{13, 39} In this sense, they have described that the presence of induced-psychotic symptoms is dose-dependent and that the accumulative use of cocaine supposes a risk factor.¹³

Recently, it has been described that the patients with psychotic symptoms had consumed important amounts of cocaine during the week prior to initiating the treatment (a mean of 12 grams per week) versus the mean of 6 grams/week among those who did not report psychotic symptoms.¹⁴

However, in relation to the dose, Kalayasiri et al.³² have also described the reduction of cocaine consumption during the previous year as a risk factor to the appearance of psychotic symptoms, which could be explained by the sensibilization phenomena.²³

Genetic factors

The importance of the influence of genetic factors both for cocaine dependence⁴⁰ and the greater vulnerability for the development of psychotic symptoms is known.^{32, 41} Greater risk has been associated with different genetic variants. In this sense, individuals homozygous for an allele for very low DBH activity have greater propensity to suffering psychotic symptoms within the context of cocaine consumption.⁴² There is also evidence that suggests the influence of the dopamine transporter protein (DAT) in this phenomenon. This is blocked by the cocaine, thus producing an increase in the availability of dopamine. In this sense, some DAT genotypes could predispose to the appearance of induced paranoia in the white population.⁴³ However, it has not been possible to relate other polymorphisms, such as that of the COMT, with cocaine induced psychoses in cannabis consumers.⁴⁴ Neither have been linked with neurotrophic factors.⁴⁰

The genetic variants may not only influence the development of psychotic symptoms. Brousse et al.³⁰ hypothesized that the appearance of a cocaine-induced psychotic disorder after the first consumption could be associated with a lower risk of developing an addiction subsequently. This protector effect would be associated to the presence of one or more polymorphisms.

Neurobiological vulnerability

In a study performed under laboratory conditions, it was observed that the P50, P100 and P200 sensory gating were deficient in cocaine-dependent individuals and that all the latencies were found to be increased in patients with induced psychotic disorder background and that the presence of attention deficit was related to its severity.⁴⁵ Therefore, even though the neurophysiological vulnerability factors of an individual to suffer an induced psychotic disorder are not fully known, the deficits in sensory gating and in attention capacity, which are also altered in idiopathic psychosis, could be considered factors involved in such vulnerability.¹⁷

Body mass index

Low body mass index (BMI) has been related with greater risk of appearance of an induced psychotic disorder while high BMI has only been considered as a protective factor.⁴⁶

Comorbidity with the use of other substances

It is well known that multiple consumption of substances and comorbidity with other psychiatric disorders are very frequent among cocaine consumer individuals¹⁰ and that this fact is associated to greater frequency in the appearance of induced psychotic disorder and greater severity of its presentation.⁴⁷

The induced-psychotic disorder that appears within the context of cocaine consumption has some specific characteristics in relation to that produced by other substances that facilitate the differential diagnosis. Induced psychotic disorder appears in similar proportion in cocaine and/or phencyclidine drug (PCP) dependents. However, the latter has more prevalence of sensorial perceptive alterations than delusional ones, contrary to that induced by cocaine in which suspicion and paranoia predominate.⁴⁸

It has been described that the severity of psychotic symptoms induced by stimulant substances (cocaine and methamphetamine) is related with earlier and more prolonged exposure to them. When methamphetamine consumption-induced disorder is compared with the cocaine-induced, the latter appears less frequently. However, the prevalences of both disorders are very elevated.³¹ In this sense, the appearance of an induced disorder within the context of methamphetamine consumption in patients with impulsive personality traits contributes to increasing the patient's aggressivity, which may culminate in behavioral alterations.⁴⁹ Said alterations, including aggressivity, have also been associated to cocaine-induced psychosis in cocaine dependents,²⁸ and therefore it can be assumed that there is a similar physiopathological development.

There are several studies on the comorbidity of cannabis consumption and the presence or not of cocaine-induced psychiatric disorder. Tang et al.⁴⁷ described that there were statistically significant differences in the frequency of appearance of psychotic disorder induced in cocaine consumers according to their consumption of cannabis. However, this finding disappears when adjusting for gender and age. Subsequently, Kalayasiri et al.⁴⁴ described that cannabis consumption increased risk of suffering psychiatric disorder induced in cocaine dependent patients, among the adolescent population. Roncero et al.¹⁴ observed that cocaine-dependent patients, who had induced psychotic symptoms, tended to also be cannabis-dependent more frequently than those who did not have said symptoms.

Comorbidity with other disorders on the Axis I

Newcomb et al.⁵⁰ stated that comorbidity was observed with other psychiatric disorders in the long-duration chronic consumer population. This did not stand out in consumers of smaller amounts of cocaine or with less dependence evolution time. Manschreck et al.³⁸ observed that patients who had psychotic symptoms within the context of cocaine consumption had comorbidity with other major psychiatric disorders (psychosis, ADHD, etc.). Rosse et al.⁵¹ performed the first study on the levels of anxiety and arousal in patients with crack-induced psychotic disorder. They concluded that these patients had greater levels of anxiety and hyperarousal than the rest of the individuals.

Comorbidity with other psychopathological alterations seems to affect the appearance of psychotic symptoms. Their is a bidirectional relation between cocaine consumption and psychotic disorders.^{47, 52-55} Cocaine could be involved as an etiologic factor related with chronic psychoses, it being known that those individuals who experience transient paranoia during acute intoxication may have a greater risk of developing psychosis than those who consume cocaine and do not experience it.⁵⁴ That is, the presence of a cocaine-induced psychotic disorder is considered a risk factor for the development of a subsequent psychosis.⁵⁴ That is why cocaine has been considered as a partial inductor drug of a model of psychosis.⁴⁷ However, on the contrary to cannabis and amphetamines, there are few studies, although it is accepted that cocaine can precipitate the appearance of psychosis in vulnerable patients.^{52, 53} On the contrary, patients diagnosed of psychotic disorders generally have more history of substance consumption, particularly cocaine and amphetamines, than the general population.^{53, 55} Cocaine consumption has also been related with worse evolution of the psychotic disease, greater number of decompensations and relapses, worse treatment compliance and worse response to conventional neuroleptic treatment.⁵⁵

Another disorder that has been associated with the presence of psychotic symptoms is the presence of comorbidity ADHD. This seems to increase the risk of presenting an induced psychotic disorder in consumers, suggesting a common base for said phenomenon.⁴⁷ Cases of presence of psychotic symptoms and cocaine consumer patients and with ADHD who receive disulfiram have been described, a dose-response relation being hypothesized.⁵⁶ All this suggests the importance of detecting this comorbidity in cocaine consumers, in which it has been postulated that the Barkley scale is useful in discrimination of symptoms suggestive of ADHD.⁵⁷

Comorbidity with Axis II disorders

Comorbidity with Axis II disorders is especially prevalent in cocaine consumer population.¹⁴ Differences have even

described in the personality traits of individuals associated to cocaine consumption.⁵⁸ Several studies have found prevalences going from 30 to 70%, the most prevalent ones being borderline personality disorder and antisocial personality disorder (ASPD).^{14, 59}

A common origin has been hypothesized for the development of behavioral disorders and psychotic symptoms.²⁸ In any case, some personality disorders may act as risk factors for the development of a psychosis. Cocaine-induced psychotic disorder may be related with hostile behaviors and with ASPD. In this sense, a pattern has been suggested in which the stimulant substances in patients with impulsive personality traits and through the appearance of psychotic symptoms would contribute to creating a hostile perception of the environment and to precipitating behavior alterations and aggressivity in the patients.⁴⁹ Kranzler et al.⁶⁰ compared the frequency of appearance of cocaine induced psychotic disorder in patients with and without the personality disorder and did not find significant differences. In spite of this, the relation between personality disorders and cocaine induced psychotic symptoms has not been sufficiently analyzed. Recently, it has been documented that there is greater presence of antisocial personality disorder in cocaine dependents who have a history of having had psychotic symptoms. Thus, the presence of this disorder in these patients should be carefully evaluated.¹⁴

CONCLUSIONS

There is an important variability in the studies performed in cocaine consumers and dependents on the epidemiological data and risk factors associated to the presence of psychotic symptoms or induced psychotic disorder. The variation in the results is because some of the studies are not comparable among them due to differences in the type of sample, type of study, consumption pathway chosen, methodology used, existence of potential biases and even the definition adopted in regards to the concept of "psychosis" or of psychotic symptoms, accepted by the different investigators.

It can be concluded that a substantial part of the cocaine consumer clinical population (from 29 to 75%) experience psychotic symptoms at some time in their life. Even when the studies are conducted under special situations, such as in emergency facilities, the prevalence reaches 100% of the cases. In the case of the experimental studies, psychotic symptoms have been detected in 35% to 100% of the cases.

The following have been described as possible risk factors: early age of onset of consumption, its duration and severity, pathway used (intravenous and pulmonary), low body mass index, genetic factors and neurophysiological vulnerability, comorbidity with other psychiatric disorders

of Axis I (cannabis dependence, chronic psychosis and ADHD) and Axis II (principally with antisocial personality disorder).

Investigation should be continued with larger samples, incorporating a non-USA population to a greater extent. More naturalistic and follow-up studies should be made that make it possible to clearly identify and specify which variables are most closely involved in the appearance of psychotic symptoms, in cocaine consumer patients. This would make it possible to identify the at risk population in order to make an early intervention.

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REFERENCES

1. UNODC (United Nations Office on drugs and crime). Disponible en <http://www.unodc.org/>, accedido el 1-07-2011.
2. European Monitoring Centre for Drugs and Drug Addiction. 2009. Annual report on the state of the drugs problem in Europe. Lisbon 2009. Disponible en <http://www.emcdda.europa.eu/news/2011/2>, accedido el 1-07-2011.
3. Observatorio Español de Drogas. Plan Nacional sobre drogas (PND). Delegación del Gobierno para el Plan Nacional sobre drogas. Disponible en <http://www.pnsd.msc.es/Categoria2/observa/home.htm>, accedido el 1-07-2011.
4. European Monitoring Centre for Drugs and Drug Addiction. 2008. Annual report on the state of the drugs problem in Europe. Lisbon 2008. Disponible en <http://www.emcdda.europa.eu/news/2011/2>, accedido el 1-07-2011.
5. Programa de actuación frente a la cocaína 2007-2010. Observatorio Español de Drogas. Plan Nacional sobre drogas (PND). Delegación del Gobierno para el Plan Nacional sobre drogas. Disponible en <http://www.pnsd.msc.es/Categoria2/observa/home.htm>, accedido el 1-07-2011.
6. Karila L, Petit A, Phan O, Reynaud M. [Cocaine induced psychotic disorders: a review]. *Rev Med Liege*. 2010;65(11):623-7.
7. Serper MR, Chou JC, Allen MH, Czobor P, Cancro R. Symptomatic overlap of cocaine intoxication and acute schizophrenia at emergency presentation. *Schizophr Bull*. 1999;25:387-94.
8. Sopena B, Rivera A, Rodríguez-Domínguez M, Rodríguez-Rodríguez M, Argibay A, Maure B, et al. Complicaciones relacionadas con el consumo de cocaína que precisaron ingreso hospitalario. *Rev Clin Esp*. 2008;208(1):12-7.
9. Brody SL, Slovis CM, Wrenn KD. Cocaine-related medical problems: consecutive series of 233 patients. *Am J Med*. 1990; 88(4):325-31.
10. Herrero MJ, Domingo-Salvany A, Torrens M, Brugal MT; ITINERE Investigators. Psychiatric comorbidity in young cocaine users: induced versus independent disorders. *Addiction*. 2008;103(2):

- 284-93.
11. Roncero C, Ramos JA, Collazos F, Casas M. Complicaciones psicóticas del consumo de cocaína. *Adicciones*. 2001;13(Supl. 2):179-85.
 12. Mahoney JJ 3rd, Kalechstein AD, De La Garza R 2nd, Newton TF. Presence and persistence of psychotic symptoms in cocaine-versus methamphetamine-dependent participants. *Am J Addict*. 2008;17(2):83-98.
 13. Kalayasiri R, Sughondhabrirom A, Gueorguieva R, Coric V, Lynch W, Morgan P, et al. Self-reported paranoia during laboratory "binge" cocaine self-administration in humans. *Pharmacology, Biochemistry and Behaviour*. 2006;83(2):249-56.
 14. Roncero C, Daigre C, Gonzalvo B, Valero S, Castells X, Grau-López L, et al. Risk factors for cocaine-induced psychosis in cocaine-dependent patients. *Eur Psychiatry*. 2011;doi: 10.1016/j.eurpsy.2011.06.012.
 15. Freeman D, McManus S, Brugha T, Meltzer H, Jenkins R, Bebbington P. Concomitants of paranoia in the general population. *Psychol Med*. 2010;24:1-14.
 16. Harris D, Batki SL. Stimulant Psychosis: Symptom Profile and Acute Clinical Course. *Am J Addiction*. 2000;9:28-37.
 17. Boutros NN, Gelernter J, Gooding DC, Cubells J, Young A, Krystal JH, et al. Sensory gating and psychosis vulnerability in cocaine-dependent individuals: preliminary data. *Biol Psychiatry*. 2002;15;51(8):683-6.
 18. Volkow ND, Wang GJ, Fischman MW, Foltin R, Fowler JS, Franceschi D, et al. Effects of route of administration on cocaine induced dopamine transporter blockade in the human brain. *Life Sciences*. 2000;67(12):1507-15.
 19. Lieberman JA, Kinon BJ, Loebel AD. Dopamine mechanisms in idiopathic and drug induced psychosis. *Schizophrenia Bulletin*. 1990;6;97-110.
 20. Horger Horger BA, Nishimura MC, Armanini MP, Wang L-C, Poulsen KT, Rosenblad C, et al. Neurturin exerts potent actions on survival and function of midbrain dopaminergic neurons. *J Neurosci*. 1998;18:4929-37.
 21. Brady KT, Lydiard RB, Malcolm R, Ballenger JC. Cocaine induced psychosis. *Journal of Clinical Psychiatry*. 1991;52:509-12.
 22. Satel SL, Southwick SM, Gawin FH. Clinical Features of Cocaine-Induced Paranoia. *Am J Psychiatry*. 1991;148(4):495-8.
 23. Post RM, Kopanda RT. Cocaine, kindling and psychosis. *Am J Psychiatry*. 1976;133:627-34.
 24. Bartlett E, Hallin A, Chapman B, Angrist B. Selective Sensitization to the Psychosis-Inducing Effects of Cocaine: A possible Marker for Addiction Relapse Vulnerability? *Neuropsychopharmacology*. 1997;16(1):305-15.
 25. Yui K, Goto K, Ikemoto S, Ishiguro T, Angrist B, Duncan GE, et al. Neurobiological basis of relapse prediction in stimulant-induced psychosis and schizophrenia: the role of sensitization. *Molecular Psychiatry*. 1999;4:512-23.
 26. Reid MS, Ciple D, O'Leary S, Branchey M, Buydens-Branchey L, Angrist B. Sensitization to the Psychosis-Inducing Effects of Cocaine Compared with Measures of Cocaine Craving and Cue Reactivity. *Am J Addiction*. 2004;13:305-15.
 27. Diagnostic and statistical manual of mental disorders (4th ed; text revised). American Psychiatric Association 2000. Barcelona: Masson, 2002.
 28. Tang YL, Kranzler HR, Gelernter J, Farrer LA, Pearson D, Cubells JF. Transient cocaine-associated behavioral symptoms rated with a new instrument, the scale for assessment of positive symptoms for cocaine-induced psychosis (SAPS-CIP). *Am J Addict*. 2009;18(5):339-45.
 29. Rosse RB, Fay-McCarthy M, Collins JP Jr, Alim TN, Deutsch SI. The relationship between cocaine-induced paranoia and compulsive foraging: a preliminary report. *Addiction*. 1994;89(9):1097-104.
 30. Brousse G, Vorspan F, Ksouda K, Bloch V, Peoc'h K, Laplanche JL, et al. Could the inter-individual variability in cocaine-induced psychotic effects influence the development of cocaine addiction? Towards a new pharmacogenetic approach to addictions. *Med Hypotheses*. 2010;75(6):600-4.
 31. Lidlyter B, Purdon S, Tibbo P. Predictors of psychosis severity in individuals with primary stimulant addictions. *Addict Behavior*. 2011;36(1-2):137-9.
 32. Kalayasiri R, Kranzler HR, Weiss R, Brady K, Gueorguieva R, Panhuysen C, et al. Risk factors for cocaine-induced paranoia in cocaine-dependent sibling pairs. *Drug Alcohol Depend Journal*. 2006;84(1):77-84.
 33. Floyd AG, Boutros NN, Struve FA, Wolf E, Oliwa GM. Risk factors for experiencing psychosis during cocaine use: a preliminary report. *J Psychiatr Res*. 2006;40(2):178-82.
 34. Buchanan D, Tooze JA, Shaw S, Kinzly M, Heimer R, Singer M. Demographic, HIV risk behavior, and health status characteristics of "crack" cocaine injectors compared to other injection drug users in three New England cities. *Drug Alcohol Depend*. 2006;81(3):221-9.
 35. Mooney M, Sofuoglu M, Dudish-Poulsen S, Hatsukami DK. Preliminary observations of paranoia in a human laboratory study of cocaine. *Addict Behavior*. 2006;31:1245-51.
 36. Jeffcoat AR, Perez-Reyes M, Hill JM, Sadler BM, Cook CE. Cocaine disposition in humans after intravenous injection, nasal insufflation (snorting), or smoking. *Drug Metab Dispos*. 1989;17(2):153-9.
 37. Kaye S, Darke S. Injecting and non-injecting cocaine use in Sydney, Australia: physical and psychological morbidity. *Drug Alcohol Rev*. 2004;23(4):391-8.
 38. Manschreck TC, Laughery JA, Weisstein CC, Allen D, Humblestone B, Neville M, et al. Characteristics of freebase cocaine psychosis. *Yale J Biol Med*. 1988;61(2):115-22.
 39. Kalayasiri R, Sughondhabrirom A, Gueorguieva R, Coric V, Lynch WJ, Lappalainen J, et al. Dopamine beta-hydroxylase gene (DbetaH) -1021C-->T influences self-reported paranoia during cocaine self-administration. *Biol Psychiatry*. 2007;61(11):1310-3.
 40. Fernández-Castillo N, Ribasés M, Roncero C, Casas M, Gonzalvo B, Cormand B. Association study between the DAT1, DBH and DRD2 genes and cocaine dependence in a Spanish sample. *Psychiatr Genet*. 2010;20(6):317-20.
 41. Cubells JF, Feinn R, Pearson D, Burda J, Tang Y, Farrer LA, et al. Rating the severity and character of transient cocaine-induced delusions and hallucinations with a new instrument, the Scale for Assessment of Positive Symptoms for Cocaine-Induced Psychosis (SAPS-CIP). *Drug Alcohol Dependence*. 2005;80(1):23-33.
 42. Cubells JF, Kranzler HR, McCance-Katz E, Anderson GM, Malison RT, Price LH, et al. A haplotype at the DBH locus, associated with low plasma dopamine beta-hydroxylase activity, also associates with cocaine-induced paranoia. *Mol Psychiatry*. 2000;5(1):56-63.
 43. Gelernter J, Kranzler HR, Satel SL, Rao PA. Genetic association between dopamine transporter protein alleles and cocaine-induced paranoia. *Neuropsychopharmacology* 1994;11(3):195-200.
 44. Kalayasiri R, Gelernter J, Farrer L, Weiss R, Brady K, Gueorguieva R, et al. Adolescent cannabis use increases risk for cocaine-induced paranoia. *Drug Alcohol Dependence*. 2010;107(2-3):196-201.
 45. Boutros NN, Gooding D, Sundaresan K, Burroughs S, Johanson,

- CE. Cocaine-dependence and cocaine-induced paranoia and mid-latency auditory evoked responses and sensory gating. *Psychiatry research*. 2006;145:147-54.
46. Rosse R, Deutsch S, Chilton M. Cocaine addicts prone to cocaine-induced psychosis have lower body mass index than cocaine addicts resistant to cocaine-induced psychosis--Implications for the cocaine model of psychosis proneness. *Isr J Psychiatry Relat Sci*. 2005;42(1):45-50.
47. Tang YL, Kranzler HR, Gelernter J, Farrer LA, Cubells JF. Comorbid psychiatric diagnoses and their association with cocaine-induced psychosis in cocaine-dependent subjects *Am J Addict*. 2007;16(5):343-51.
48. Rosse RB, Collins JP, Fay-McCarthy M, Alim TN, Wyatt RJ, Deutsch SI. Phenomenologic comparison of the idiopathic psychosis of schizophrenia and drug-induced cocaine and phencyclidine psychoses: A retrospective study. *Clinical Neuropharmacology*. 1994;17(4):359-69.
49. Lapworth K, Dawe S. Impulsivity and positive psychotic symptoms influence hostility in methamphetamine users. *Addict Behavior*. 2009;34(4):380-5.
50. Newcomb MD, Bentler PM, Fahy B. Cocaine use and psychopathology: associations among young adults. *Int J Addict*. 1987;22(12):1167-88.
51. Rosse RB, Alim TN, Johri SK, Hess AL, Deutsch SI. Anxiety and pupil reactivity in cocaine dependent subjects endorsing cocaine-induced paranoia: preliminary report. *Addiction*. 1995;90(7):981-4.
52. Barnett JH, Werners U, Secher SM, Hill KE, Brazil R, Masson K, et al. Substance use in population-based clinic sample of people with first-episode psychosis. *British Journal of Psychiatry*. 2007;190:515-20.
53. Ringen PA, Melle I, Birkenaes AB, Engh JA, Faerden A, Jónsdóttir H, et al. Illicit drug use in patients with psychotic disorders compared with that in the general population: a cross-sectional study. *Acta Psychiatr Scand*. 2008;117:133-8.
54. Satel SL, Edell WS. Cocaine-induced paranoia and psychosis proneness. *Am J Psychiatry*. 1991;148(12):1708-11.
55. Roncero C, Barral C, Grau-Lopez L, Bachiller D, Szerman N, Casas M, et al. Protocols of dual diagnosis intervention in schizophrenia. *Addictive Disorders & Their Treatment*. 2011;10(3):131-54.
56. Grau-López L, Roncero C, Navarro MC, Casas, M. Psychosis induced by the interaction between disulfiram and methylphenidate may be dose dependent. *Substance Abuse*. 2012;33(2):186-8.
57. Vergara-Moragues E, González-Saiz F, Lozano Rojas O, Bilbao Acedos I, Fernández Calderón F, Betanzos Espinosa P, et al. Diagnosing Adult Attention Deficit/Hyperactivity Disorder in Patients with Cocaine Dependence: Discriminant Validity of Barkley Executive Dysfunction Symptoms. *Eur Addict Res*. 2011;17(6):279-84.
58. Sáiz PA, González MP, Paredes B, Martínez S, Delgado JM. Personalidad y uso-abuso de cocaína. *Adicciones*. 2001;13(suppl 2):47-60.
59. Frances RJ, Miller S, Mack AH, editors. *Clinical textbook of addictive disorders*. 3rd ed., New York: The Guilford Press, 2005.
60. Kranzler HR, Satel S, Apter A. Personality disorders and associated features in cocaine-dependent inpatients. *Compr Psychiatry*. 1994;35(5):335-40.