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Clinical differences between cocaine-induced psychotic disorder and psychotic symptoms in cocaine-dependent patients

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Abstract

The aim of this study is to compare the clinical characteristics of three groups of patients in treatment for cocaine dependence: patients without any psychotic symptoms (NS), patients with transient psychotic symptoms (PS) and patients with cocaine- induced psychotic disorder (CIPD). An observational and retrospective study of 150 cocaine-dependent patients undergoing treatment in the Drug Unit of the Psychiatry Department of University Hospital Vall d'Hebron in Barcelona (Spain) using these three groups, NS, PS and CIPD, was performed. All patients were evaluated with the PRISM interview. ANOVA, Chi-square tests and multivariate multinomial regression analysis were used to perform statistical analyses. Seven patients with a primary psychotic disorder were discharged. Forty-six patients (32.1%) did not report any psychotic symptoms. Ninety-seven patients (67.9%) presented with a history of any cocaine- induced psychotic symptom and were considered as the cocaine-induced psychotic (CIP) group. Among them, 39 (27.3%) were included in the PS group, and 58 (40.6%) were included in the CIPD group. A history of imprisonment was found significantly more frequently in the PS than the NS group. The distribution of age at onset of dependence, lifetime cannabis abuse or dependence and imprisonment were significantly different between the NS and CIPD groups. We conclude that in cocaine- dependent patients, clinicians should be advised about the risk of development of psychotic symptoms. The presence of some psychotic symptoms could increase the potential risks of disturbing behaviours.

Keywords

Cocaine, cocaine-induced psychosis, cocaine-induced psychotic disorder, dependence, PRISM, psychotic symptoms, psychosis

1. Introduction

Cocaine consumption in Europe has been increasing, achieving a higher prevalence than in the United States, although a mild stabilization has been detected in recent years (European Monitoring Centre for Drugs Addiction, 2012; United Nations Office on Drug and Crime, 2012). Comorbidity of cocaine use disorders with psychiatric disorders has been extensively reported (Brady et al., 1991; Satel and Edell, 1991; Barlett et al., 1997; Kalayasiri et al., 2006a; Tang et al., 2007; Herrero et al., 2008; Roncero et al., 2012; Roncero et al., 2013a). One of the most serious co-morbidities with cocaine use disorders is the presence of psychotic symptoms. Cocaine-Induced Psychotic Disorder (CIPD) has been found in 5% of young cocaine users (Herrero et al., 2008), and in cocaine dependent patients treated in therapeutic community, the prevalence of CIPD was 11.5% (Vergara-Moragues et al., 2012). In clinical settings, psychotic symptoms have been found to occur in between 29% and 86.5% of cocaine-dependent patients (Brady et al., 1991; Satel and Edell, 1991; Barlett et al., 1997; Kalayasiri et al., 2006a; Tang et al., 2007; Roncero et al., 2012; Vorspan et al., 2012, Roncero et al., 2013a), but actual figures remain unclear because the samples are not similar, and the instruments and approach used in the evaluation process are not comparable (Roncero et al., 2012).

There is a controversy between the diagnosis of psychotic symptoms secondary to cocaine intoxication and the DSM-IV diagnosis of CIPD (Boutros and Bowers, 1996; Caton et al., 2007). Some authors, after studying psychotic symptoms in cocaine users, classified the induced psychotic episodes in two types. The first, called "transient psychotic episodes", is experienced during consumption. In this case, the symptoms are gone after a binge or a crash phase. The other type is named "persistent psychotic episodes", in which the psychotic symptomatology can persist for as long as days after a crash phase and the severity of the symptoms is higher than in transient psychotic symptoms. This type is considered authentic CIPD (Satel and Edell, 1991).

The DSM-IV describes substance-induced psychotic disorders as being associated

with prominent hallucinations or delusions and specifies that hallucinations should not be included if the person has insight that they are substance induced. They also should not be included when there is evidence that the symptoms developed during or within a month of substance intoxication. This diagnosis should be made instead of a diagnosis of substance intoxication only when the symptoms are sufficiently severe to warrant independent clinical attention. The criteria between substance-induced psychotic disorders and substance intoxication are differentiated as the duration of symptoms, their severity and hallucinations occur in the absence of intact reality testing. There are some criticisms about the narrow definition of CIPD, and this has led to the suggestion of a broader classification based on association rather than causation for DSM-5 (Mathias et al., 2008). Cocaine-induced psychosis (CIP) has been suggested for psychotic symptoms related to cocaine use (Brady et al., 1991; Satel and Edell, 1991; Roncero et al., 2012).

Some risks factors are associated with transient psychosis related to cocaine use: amount of cocaine consumed (Floyd et al., 2006; Kalayasiri et al., 2006a; Mahoney et al., 2008; Vorspan et al., 2012; Roncero et al., 2013a), age of onset of use (Cubells et al., 2005; Kalayasiri et al., 2006a; Floyd et al., 2006; Kalayasiri et al., 2010; Vorspan et al., 2012) and co-morbidity with attention deficit hyperactivity disorder (ADHD) (Tang et al., 2007; Roncero et al, 2013b). With respect to borderline personality disorder (BPD), antisocial personality disorder (APD) (Kranzler et al., 1994; Roncero et al., 2013a) and drug use (smoked or intravenous) (Mooney et al., 2006, Kalayasiri et al., 2006b; Vorspan et al., 2012; Roncero et al., 2013c), the association remains unclear. Some authors have linked psychotic symptoms with these variables, but others reject these associations. The clinical factors associated with transient cocaine-induced psychotic symptoms are well-described in the current literature, but studies about the clinical factors associated with CIPD are lacking.

Therefore, knowledge of the clinical features of cocaine-dependent patients who have developed transient psychotic symptoms or CIPD may be relevant not only for diagnostic information but also for evaluating therapeutic interventions to be applied in each case.

The aim of this study is to compare the clinical characteristics of three groups of patients in treatment for cocaine dependence: patients without any psychotic symptoms (NS), patients with transient psychotic symptoms (PS) and patients with CIPD. We hypothesized that there is a gradient of severity in which the presence of PS is more severe than NS, and the presence of CIPD is more severe than both NS and PS.

2. Methods

2.1. Design

We used a cross-sectional design in an observational study. Patients were assessed during two visits. Initially, patients were evaluated by a psychiatrist, who collected demographic and consumption data, and (if applicable) gave a diagnosis of cocaine dependence disorder according to DSM-IV-TR criteria. Subsequently, they were interviewed by a psychologist trained in the administration of the diagnostic interview described below.

2.2. Sample

The 150 participants were patients undergoing treatment at the Drug Unit of the Department of Psychiatry at the University Hospital Vall d'Hebron in Barcelona (Spain) between February 2007 and August 2010. Inclusion criteria included being over 18 years of age, having a diagnosis of cocaine dependence and following a treatment regimen as an outpatient or an inpatient at the drug unit of the hospital. Each patient signed the corresponding informed consent approved by the ethics committee of the hospital and received no financial compensation for their participation.

Exclusion criteria included the presence of primary psychotic or bipolar I disorders, being intoxicated at the time of the interview, having severe somatic disorders and not sufficient language proficiency.

According to these criteria, one patient was not evaluated because they came intoxicated to the evaluation visit. Seven patients were excluded due to the existence of a primary psychotic disorder. The total sample of the study was composed of 143 patients.

2.3. Assessments and measures

In addition to socio-demographic and consumption variables, the Spanish Version of the Psychiatric Research Interview for Substance and Mental Disorders (PRISM) (Torrens et al, 2004; Hasin et al., 1996) was administered. This interview, based on DSM-IV, diagnoses approximately 20 Axis I and II disorders. It was designed specifically to differentiate primary mental disorders and induced effects of intoxication and withdrawal in subjects with high consumption of alcohol and other substances. The main feature of this instrument is to add specific guidelines for evaluation and classification requirements such as frequency, duration of symptoms and explicit exclusion criteria, to determine the temporal relationship between psychiatric symptoms and substance use. According to the psychotic disorders section of the instrument, the sample was divided into three study groups. In Group I, the patients had no psychotic symptoms (NS) in their lifetime. In Group II, the patients had psychotic symptoms but were aware that these symptoms were caused by substance use (PS) in their lifetime. In Group III, patients had psychotic symptoms and were not aware that they were caused by substance (CIPD) in their lifetime. Finally, we included the cocaine-induced psychosis group (CIP) if a patient were included in the PS or CIPD groups. According to PRISM criteria, to diagnose CIPD the delusions have to be clear, they have to last more than 1 h and disagree with the cultural context of the patients.

To diagnose hallucinations, they have to be clear, last more than 1 h and disagree with the cultural context of the patients, but they do not have to be present while the patients are sleeping or awake; additionally, the patients have to act according to the hallucinations.

2.4. Statistical analysis

As psychotic symptoms were included in the definition of study groups, they were simply described in terms of frequencies. ANOVA and Chi-square tests where used to compare the socio-demographic and clinical characteristics of the sample and comorbidities between study groups. The Chi-square test was considered not applicable, due to insufficient representation in the sample, when at least one cell content was less than 5.

To reduce the presence of some false positive effects, Bonferroni corrections for multiple tests were performed grouping socio-demographic and comorbidity variables. Only the variables that exceeded the respective *p* values were entered in a second analysis. These variables were used in a multivariate multinomial regression analysis as predictors, using stepwise entrance of variables to perform an exploratory analysis including a polynomial variable including CIPD, PS or NS as dependent variables. To provide information on the adjustment of the resulting model, sensitivity (capacity to detect subjects among categories) and specificity (capacity to detect subjects not included in categories) parameters were reported. All statistical tests were two-tailed. SPSS Version 18.0 for Windows was used in all analyses.

3. Results

Of the 143 participants, 46 patients (32.1%) in the sample did not report any psychotic symptoms, 97 (67.9%) presented with a history of any cocaine-induced psychotic symptom, 39 (27.3%) were included in the PS group and 58

(40.6%) in the CIPD group. Socio-demographic data were collected, as shown in Table 1. Statistically significant differences among study groups where found in the following variables: age at onset of cocaine addiction, duration of dependence, imprisonment and completion of primary studies.

We found that 37.1 % of the sample presented three or more substance use disorders, and comorbidities can also be observed in Table 1. Regarding other substances, cannabis, alcohol and hallucinogens were found to be statistically significant. No significant differences in Axis I disorder analysis was found. Differences that were statistically significant for both Axis II disorders (antisocial and borderline personality disorders) were found, but they were no longer statistically significant following the Bonferroni corrections.

Table 1. *Sociodemographic and comorbities clinical data*

		Total N=143		**NS N=46 (32,1%)**		**PS N= 39 (27.3%)**		**CIPD N= 58 (40.6%)**		**Significance**	
		N	**%/SD**	**N**	**%/SD**	**N**	**%/SD**	**N**	**%/SD**		
Age (years)		34.28	±8.01	35.74	±7.25	35.21	±8.79	32.50	±7.83	F =2.504	p=0.085
Sex (men)		117	81.8	38	82.6	29	74.4	50	86.2	χ^2=2,229	p=0.328
Marital status	Single	81	56.6	24	52,2	23	59	34	58,6	χ^2=6.042	p=0.196
	Couple	36	25.2	17	37,0	8	20,5	11	19		
	Divorced	26	18.2	5	10,9	8	20,5	13	22,4		
Not finished primary studies		29	20.3	3	10.3	12	41.4	14	24.6	na	
Active (employed or studying)		60	42.0	20	33.3	18	30	22	36,7	χ^2=0.712	p=0.071
Living alone		16	11.3	3	6.5	5	12.8	8	14	na	
Ever imprisoned		66	46.2	11	23.9	24	61.5	31	53.4	χ^2=.14.112	p=0.001
Age at onset of addiction (years)		24.78	±7.44	27,74	±6.41	25.72	±8.24	21.79	±6.60	F=9.656	p<0.0001
Duration of dependence (years)		7.69	±6.97	5.67	±5.84	6.85	±5.82	9.84	±7.95	F=5.267	p=0.006
Grams consumed/ week last month		3.66	±8.30	2.69	±6.80	2.19	±4.52	5.61	±11.08	F=2.045	p=0.134

Nasal airway		110	88	60	95	32	88.9	40	81	χ^2=3.764	p=0.152
Lifetime SUD (Abuse or dep.)	Opiates	33	23.1	8	17.4	8	20.5	17	29.3	χ^2=2.252	p=0.324
	Alcohol	109	76.2	27	58.7	32	82.1	50	86.2	χ^2=11.719	p=0.003
	Sedative	25	17.5	4	8.7	7	17.9	14	24.1	χ^2=4.249	p=0.120
	Cannabis	64	44.8	9	19.6	19	48.7	36	62.1	χ^2=19.085	p<0.0001
	Other stimulants	23	16.1	5	10.9	5	12.8	13	22.4	χ^2 2.956	p= 0.228
	Hallucinogens	41	28.7	5	10.9	9	23.1	27	46.6	χ^2=16.792	p<0.0001
Lifetime any SUD (ex. cocaine)*		119	83.2	29	63.0	36	92.3	54	93.1	χ^2=19.771	p<0.0001
Lifetime axis I	Major depression	19	13.3	9	19.6	4	10.3	6	10.3	χ^2=2.320	p=0.313
	Anxiety disorder	6	4.2	4	8.7	1	2.6	1	1.7	na	
	ADHD childhood	42	29.4	11	23.9	8	20.5	23	39.7	χ^2=5.093	p=0.078
	Eating disorders	7	4.9	2	4.3	3	7.7	2	3.4	na	
	Substance Induced mood disorder	40	28.0	9	19.6	13	33.3	18	31	χ^2=2.440	p=0.295
Lifetime any axis I		66	46.2	21	45.7	19	48.7	26	44.8	χ^2=0.149	p=0.928
Lifetime axis II	Antisocial (APD)	22	15.4	3	6.5	4	10.3	15	25.9	χ^2=8.455	p=0.015
	Borderline (BPD)	34	23.8	8	17.4	6	15.4	20	34.5	χ^2=6.207	p=0.045
Lifetime any axis II		44	30.8	10	21.7	10	25.6	24	41.4	χ^2=5.307	p=0.07

NS. No psychotic symptoms PS.- Psychotic Symptoms CIPD.- Cocaine Induced Psychotic Disorder. Disorders were described when at least 5 patients met criteria. Na. Chi Square test was considered not applicable when one or more of the cells had an unexpected count less than 5

*-*This includes any substance moreover of those presented above.- Miinum significance after bonferroini adjustment: Co-morbidities data: 0.05/14= 0.0036, Sociodemographic data: 0.05/9 = 0.006.*

Delusions and hallucinations in the PS and CIPD groups are described in Table 2.

Table 2. *Hallucinations and Delusions*

		Total N= 97 (67.95%)		**PS N= 39 (27.3%)**		**CIPD N= 58 (40.6%)**	
		N	**%**	**N**	**%**	**N**	**%**
Delusions							
Self-referential		25	17.5	13	33.3	25	43.1
Persecution		50	35	7	17.9	50	86.2
Grandiosity		3	2.1	-		3	5,2
Somatic		2	1.4	-		2	3,4
Depressant		-		-		-	
Jealous		11	7.7	-		11	19.0
Bizarre		1	1.7	-		1	1.7
Hallucinations							
Auditive	no insight	4	2.8	-		4	6,9
	insight*	51	35.7	22	56,4	29	50
Visual	no insight	5	3.5	-		5	8.6,
	insight*	55	38.5	28	71,8	27	46.6
Tactile	no insight	3	2,1	-		3	5,2
	insight*	42	29.4	17	43,6	25	43,1
Olfactory	no insight	2	1.4	-		2	3.4
	insight*	8	5.6	3	7.7	5	8,6

Ps Psychotic Symptoms CIPD Cocaine induced psychotic disorder

[*] *The symptom was present but the subject was aware that it was induced by drug use.*

The multinomial regression model using stepwise entrance of variables was conducted to analyse all variables from the previous bivariate analysis that remained statistically significant after Bonferroni correction. These variables included lifetime alcohol use, cannabis and hallucinogens abuse or dependence, age at onset, years of dependence and history of imprisonment. The resulting model was statistically significant (χ^2=52.486, p<0.0001), with the R^2 higher for the first model (Cox=0.307). Sensibility was 71.7% for the NS group, 30.8% for the PS group and 77.6% for the CIPD group. Specificity was 35.0% for the NS group, 13.3% for the PS group and 51.7% for the CIPD group.

Imprisonment was found to be significantly more frequent in the PS than the NS group.

The distribution of age at onset of dependence, lifetime cannabis abuse or dependence and imprisonment were significantly different between the NS and CIPD groups. Finally, no statistically significant differences were found between PS and CIPD (see table 3).

Table 3. *Multinomial Regression*

	PS vs. NS					CIPD vs. NS					CIPD vs. PS				
	W	**Sig.**	**Oald R**	**95% IC**		**W**	**Sig.**	**O ald R**	**95% IC**		**W**	**Sig.**	**O ald R**	**95% IC**	
Age onset of dependence						4.493	0.034	0.928	0.865	0.994	3.156	0.076	1.061	0.994	1.133
Duratio n of dependence						3.355	0.067	1.064	0.996	1.137					
Alcohol															
Cannabis	0.021	0.887	0.382	27.	1.149	4.345	0.037	0.322	0.111	0.935					
Hallucinogens															
Ever imprisoned	8.153	0.004	0.243	0.092	0.642	4.181	0.041	0.366	0.140	0.959					

4. Discussion

The present study describes the presence of psychotic symptomatology in cocaine- dependent subjects and explores the relationship between cocaine-induced psychotic disorder and clinical features. Of the total sample, 67.9% of the subjects presented with a history of any cocaine-induced psychotic symptomatology, as determined by the presence of a positive item in the PRISM interview. These results are consistent with other clinical sample studies reporting a prevalence between 29% and 86.5% (Manschreck et al., 1988; Brady et al., 1991; Satel and Edell, 1991; Barlett et al., 1997; Kalayasiri et al., 2006a; Tang et al., 2007; Vorspan et al., 2012; Roncero et al., 2013a, Roncero et al., 2013b). PRISM has never been used to study CIPD in cocaine- dependent patients who are seeking treatment in

outpatient clinics; therefore, the results are difficult to compare.

The 40% of CIPD, as diagnosed by the PRISM interview is very high if the results are compared with a sample of cocaine-dependent patients seeking treatment in a therapeutic community (11.5%) (Vergara-Morales et al., 2012; Vergara-Moragues et al., 2013) and from cocaine users recruited outside the health-care services (5%) measured with the same instrument (Herrero et al., 2008). Differences compared with the patients from the therapeutic community may be because patients who are able to adhere to therapeutic community treatment tend to have less psychopathology compared with patients who leave treatment (De Leon et al., 1973; Ravndal, 1991; Vergara-Moragues et al., 2012). Recent studies have demonstrated that there is a higher treatment success (measured by length of stay in days, type of discharge and therapeutic community outcome clinical impression) among people without psychopathological comorbidity (Vergara-Moragues et al., 2013). Furthermore, in the sample of Vergara-Moragues et al. (2012), the PRISM interview was administered after 15-20 days in the therapeutic community, and these patients may be more severe, with a higher prevalence of subjects with cocaine (or other)-induced psychotic disorders who dropped out of the treatment in the first 15-20 days. Additionally, the higher prevalence of CIPD reported in the study with regular cocaine users who are seeking treatment also evaluated with PRISM (Herrero et al., 2008) may be due to the sample characteristics.

We studied cocaine- dependent patients who are seeking treatment in a health centre of a general hospital, whereas the other study was conducted with cocaine users not seeking treatment. However, to confirm our findings, it would be interesting to perform another study in another clinical sample seeking treatment.

PRISM was used in this study because it is a precise instrument to differentiate between primary psychotic disorders and those induced by substances. For this reason and following the DSM-IV criteria, patients with hallucinations that are

recognized as caused by the consumption of the drug are not included in the group of CIPD. This could explain why one-third of patients who experience only psychotic symptoms associated with cocaine consumption (PS) cannot be diagnosed with a CIPD following the PRISM criteria. In our sample, the CIPD group was not aware that these perceptions are caused by consumption and they behaved accordingly with them.

Factors related with the risk of having only induced PS or CIPD are not well known (Roncero et al., 2012; Roncero et al., 2013a). It has been hypothesized that the existence of clinical psychotic disorders slows or reduces the risk of developing cocaine dependence (Brousse et al., 2010). In our sample, CIPD presence is associated with a lower age of onset of addiction, more years of duration of addiction and a history of imprisonment.

Our results regarding the younger age of onset of cocaine dependence confirm previous studies (Barlett et al., 1997; Cubells et al., 2005; Kalayasiri et al., 2006a; Floyd et al., 2006; Lichlyter et al., 2011). The lower onset age is in the CIPD group in comparison with the PS group, whereas those with a later onset of cocaine addiction are mostly in the NS group, and this lower onset age is consistent with the previous literature. Additionally, the number of years of regular cocaine use has been described previously in other studies (Brady et al., 1991; Roncero et al., 2013a; Lichlyter et al., 2011). However, these two factors (years of regular use and age of onset of cocaine dependence) can be linked.

Patients with only psychotic symptoms (61.5%) have a higher history of imprisionment than patients without any psychotic symptoms (23.9 %) or patients of the CIPD group (53.4%). This may be because consumption could be linked to hostile behaviours. It has been suggested that stimulant use could generate psychotic symptoms that manifest as hostility. These symptoms contributes to a perception of the environment as hostile and a threatening place as well as

increasing impulsivity. The cocaine-induced psychotic symptoms trigger hostile behaviours (Tang et al., 2007; Lapworth et al., 2009). This finding allows us to affirm that the presence of psychotic symptomatology could be a criterion for severity of cocaine dependence because even patients who do not meet the criteria for CIPD and preserve their view of reality may have behavioural disorders. However, patients in the PS group have a more prominent history of arrest than the CIPD group, and it could be hypothesized that patients with PS end up in jail and CIPD end up in the hospital. However, this hypothesis should be tested so that one may link the time in which the patients had taken the substance and have been imprisoned or confined to the hospital. Furthermore, we find a lower average occurrence of imprisonment in the CIPD group even though there is a higher average occurrence of antisocial personality disorder (25.9 %) compared with the PS group (10.3%).

CIPD is also associated with cannabis, hallucinogen and alcohol use disorders. The psychotic symptoms association with cannabis use disorder is consistent with preliminary reports that showed an association with cannabis use (Kalayasiri et al., 2010) or cannabis dependence (Roncero et al., 2013a). Additionally, adolescent onset of cannabis use has been described as increasing the risk of having psychotic symptoms in cocaine-dependent individuals (Kalayasiri et al., 2010), and this seems to confirm our results.

We described the presence of psychotic symptoms in association with the consumption of hallucinogens. However, we must be very cautious in interpreting this finding because hallucinogen use obviously caused hallucinations (Assad and Shapiro, 1986; Paparelli et al., 2011).

Further, the alcohol-induced psychotic syndrome is well known, with a lifetime prevalence of 0.5%. It has been described that this is related to a younger age of onset of alcohol dependence (Perala et al., 2010), so it could explain our finding

regarding the association of CIPD with alcohol-use disorders.

When reviewing literature in reference to the relationship with other Axis I mental disorders, it is noted that some studies conclude that there has been a relationship between psychotic disorders and any mental disorders in cocaine-dependent patients. Unlike previous studies associating it with adult ADHD (Manschreck et al., 1988; Tang et al., 2007; Roncero et al., 2013b), we failed to detect any relationship between psychotic symptoms and ADHD in childhood. This difference could be because we measured only childhood ADHD in the current study because the ADHD adult section of PRISM has been validated recently (Ramos-Quiroga et al., 2012). Furthermore, in another study by our research group we failed to detect an association between adult ADHD and any psychotic disorder in cocaine-dependent adults (Daigre et al., 2013).

Co-morbid Axis II disorders are prevalent in cocaine users. Several studies found prevalences ranging from 30 to 70% in inpatient samples, with antisocial (ASPD) and borderline personality disorders being the most frequent. Regarding Axis II disorders, the presence of psychotic symptoms was not associated with personality disorders (Kranzel et al., 1994). In the sample, neither the presence of psychotic symptoms nor cocaine-induced psychotic disorder is associated with any personality disorders, although it should be noted that there is a tendency, and it seems to be a gradient of ASPD: CIPD group (25.9%), PS group (10%) and NS group (6.5%). This is consistent with previous work associated with the coexistence of ASPD in a clinical population in treatment (Vergara-Moragues et al., 2012; Roncero et al., 2013a). However, this point should be re-studied in the future.

In the present study, we hypothesized that there is a gradient of severity in which the presence of PS is more severe than NS, and the presence of CIPD is more severe than both NS and PS. After obtaining the results, we conclude that the hypothesis is only partially confirmed because following the results of multivariate analysis, the NS group presents less severity than the PS and CIPD groups, but

there were no statistically significant differences between patients with PS and CIPD.

The similarities between the PS and CIPD groups are probably due to them sharing severity factors associated with present symptoms, regardless of intensity, which would be a common first step. For these reasons, those who present with PS or CIPD tend to have grater severity of addiction, expressed a younger age of onset of dependence and greater comorbidity with other addictions and personality disorders. We probably failed to find differences between PS and CIPD in the multivariate analysis because development of the full disorder could be associated with other factors such as genetic influence or even the phase the disease during evaluation. Thus, these factors should be researched in future studies. Regardless, the most important step for clinicians is to be able to identify CIP; clinically, it is less relevant to differentiate between people who meet diagnostic criteria of CIPD and those who do not.

Cautious clinical management of an addict patient with psychotic symptomatology is necessary to discern in which cases the mental disorder is independent of substance use and when it is induced by the drug. It is also necessary to then differentiate between the full syndrome and only the presence of symptoms. The process is complex because during both intoxication and withdrawal, psychotic symptoms may occur.

One of the strong points of this study is the use of PRISM as a PS and CIPD evaluation instrument, as diagnoses using this instrument are very comprehensive. Previously, PRISM has been used to study outcomes over two years among patients admitted to emergency departments with early-phase primary or substance-induced psychosis (Drake et al., 2011), but there are no others studies using PRISM in cocaine-dependent patients seeking treatment. Comparing the subjects in the PS and CIPD groups with those patients without

any symptoms could lead to the identification of the sickest patients: the PS and CIPD groups are more often composed of poly-drug users, they have an early cocaine addiction onset, and the years of duration of dependence are longer and they have more of a criminal background than the NS group. These are indicative of the severity of addiction when assessing patient's severity.

Limitations of the study should be noted. We included in the analyses the amount of cocaine and the route used, but we did not consider the time in which this consumption contributes to psychotic symptoms. This should be considered in the design of future studies.

This paper shows that both the presence of CIPD diagnosed by the PRISM interview and the only presence of PS are very common in cocaine-dependent patients. There are differences between patients who develop a clinically isolated and complete syndrome. Those who develop the full syndrome are more severe, as they have begun poly-drug use and have an earlier onset of addiction and the addiction has lasted longer. Moreover, patients with PS are proven to have major legal problems. Regardless, the most important step for clinicians is to be able to identify CIP.

The high frequency of CIPD or PS in cocaine-dependent patients seeking treatment should be noted. Furthermore, the presence of some psychotic symptoms could increase the potential risks of a disturbing behaviour, posing a threat to the patients themselves and/or others. Clinicians should be advised about the risk of developing psychotic symptoms in cocaine-dependent patients.

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References

Asaad, G., Shapiro, B., 1986. Hallucinations: Theoretical and clinical overview. The American Journal of Psychiatry, 143(9), 1088-1097.

Bartlett, E., Hallin, A., Chapman, B., Angrist, B.,1997. Selective sensitization to the psychosis-inducing effects of cocaine: A possible marker for addiction relapse vulnerability? Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology, 16(1), 77-82.

Boutros, N. N., Bowers, M. B.,Jr., 1996. Chronic substance-induced psychotic disorders: State of the literature. The Journal of Neuropsychiatry and Clinical Neurosciences, 8(3), 262-269.

Brady, K. T., Lydiard, R. B., Malcolm, R., Ballenger, J. C., 1991. Cocaine-induced psychosis. The Journal of Clinical Psychiatry, 52(12), 509-512.

Brousse, G., Vorspan, F., Ksouda, K., Bloch, V., Peoc'h, K., Laplanche, J. L., Mouly, S., Schmidt, J., Llorca, PM., Lepine, JP. 2010. Could the inter-individual variability in cocaine-induced psychotic effects influence the development of cocaine addiction? towards a new pharmacogenetic approach to addictions. Medical Hypotheses, 75(6), 600-604.

Caton, C. L., Hasin, D. S., Shrout, P. E., Drake, R. E., Dominguez, B., First, M. B., Samet, S., Schanzer, B. Stability of early-phase primary psychotic disorders with concurrent substance use and substance-induced psychosis. The British Journal of Psychiatry: The Journal of Mental Science, 190, 105-111.

Cubells, J. F., Feinn, R., Pearson, D., Burda, J., Tang, Y., Farrer, L. A., Gelernter, J., Kranzler, HR. 2005. 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 and Alcohol Dependence,

80(1), 23-33.

Daigre, C., Roncero, C., Grau-López, L., Martínez-Luna, N., Prat, L., Valero, S., Tejedor, R., Ramos-Quiroga, J., Casas, M., 2013. Attention deficit hyperactivity disorder in cocaine-dependent adults: a psychiatric comorbidity analysis. American Journal on Addiction;22(5):466-73.

De Leon G. 1989. Psychopathology and substance abuse: what is being learned from research in therapeutic communities. Journal of Psychoactive Drugs 21(2):177-88.

De Leon G, Skodol A, Rosenthal MS. Phoenix House. Changes in psychopathological signs of resident drug addicts. Archives of General Psychiatry. 1973;28(1):131-5.

Drake, R.E., Caton, C.L., Xie, H., Hsu, E., Gorroochurn, P., Samet, S., Hasin, D.S., 2011. A prospective 2-year study of emergency department patients with early-phase primary psychosis or substance-induced psychosis. The American Journal of Psychiatry 168, 742-748.

EMCDDA, Lisbon, November 2012 http://www.emcdda.europa.eu/publications/annual-report/2012

Floyd, A. G., Boutros, N. N., Struve, F. A., Wolf, E., Oliwa, G. M., 2006. Risk factors for experiencing psychosis during cocaine use: A preliminary report. Journal of Psychiatric Research, 40(2), 178-182.

Hasin, D. S., Trautman, K. D., Miele, G. M., Samet, S., Smith, M., Endicott, J., 1996. Psychiatric research interview for substance and mental disorders (PRISM): Reliability for substance abusers. The American Journal of Psychiatry, 153(9), 1195-1201.

Herrero, M. J., Domingo-Salvany, A., Torrens, M., Brugal, M. T., Gutierrez, F., Itinere Investigators, 2008. Personality profile in young current regular users of cocaine. Substance Use & Misuse, 43(10), 1378-1394.

Kalayasiri, R., Kranzler, H.R., Weiss, R., Brady, K., Gueorguieva, R., Panhuysen, C., Yang, B.Z., Farrer, L., Gelernter, J., Malison, R.T., 2006a. Risk factors for cocaine-induced paranoia in cocaine-dependent sibling pairs. Drug and Alcohol Dependence 84, 77-84.

Kalayasiri, R., Sughondhabirom, A., Gueorguieva, R., Coric, V., Lynch, W.J., Morgan, P.T., Cubells, J.F., Malison, R.T., 2006b. Self-reported paranoia during laboratory "binge" cocaine self-administration in humans. Pharmacology, Biochemistry, and Behavior 83, 249-256.

Kalayasiri, R., Gelernter, J., Farrer, L., Weiss, R., Brady, K., Gueorguieva, R., Kranzler, H.R., Malison, R.T., 2010. Adolescent cannabis use increases risk for cocaine-induced paranoia. Drug Alcohol Depend. 107, 196-201.

Kranzler, H. R., Satel, S., Apter, A., 1994. Personality disorders and associated features in cocaine-dependent inpatients. Comprehensive Psychiatry, 35(5), 335-340.

Lapworth, K., Dawe, S., Davis, P., Kavanagh, D., Young, R., Saunders, J., 2009. Impulsivity and positive psychotic symptoms influence hostility in methamphetamine users. Addictive Behaviors, 34(4), 380-385.

Lichlyter, B., Purdon, S., Tibbo, P., 2011. Predictors of psychosis severity in individuals with primary stimulant addictions. Addictive Behaviors, 36(1-2), 137-139.

Mahoney, J. J.,3rd, Kalechstein, A. D., De La Garza, R.,2nd, Newton, T. F., 2008. Presence and persistence of psychotic symptoms in cocaine- versus methamphetamine-dependent participants. The American Journal on Addictions / American Academy of Psychiatrists in Alcoholism and Addictions, 17(2), 83-98.

Manschreck, T. C., Laughery, J. A., Weisstein, C. C., Allen, D., Humblestone, B., Neville, M., Podlewski, H., Mitra, N., 1988. Characteristics of freebase cocaine psychosis. The Yale Journal of Biology and Medicine, 61(2), 115-122.

Mathias, S., Lubman, D. I., Hides, L., 2008. Substance-induced psychosis: A diagnostic conundrum. The Journal of Clinical Psychiatry, 69(3), 358-367.

Mooney, M., Sofuoglu, M., Dudish-Poulsen, S., Hatsukami, D. K., 2006. Preliminary observations of paranoia in a human laboratory study of cocaine. Addictive Behaviors, 31(7), 1245-1251.

Paparelli, A., Di Forti, M., Morrison, P., Murray, R., 2011. Drug-induced psychosis: how to avoid star gazing in schizophrenia research by looking at more obvious sources of light. Frontiers in Behavioral Neuroscience, 17;5:1.

Perala, J., Kuoppasalmi, K., Pirkola, S., Harkanen, T., Saarni, S., Tuulio-Henriksson, A., 2010. Alcohol-induced psychotic disorder and delirium in the general population. The British Journal of Psychiatry : The Journal of Mental Science, 197(3), 200-206.

Ravndal E., Vaglum P. 1991. Psychopathology and substance abuse as predictors of program completion in a therapeutic community for drug abusers: a prospective study. Acta Psychiatrica Scandinava ;83(3):217-22.

Ramos-Quiroga, JA., Diaz-Digon, L., Comin, M., Bosch, R., Palomar, G., Chalita, JP., Roncero, C., Nogueira, M., Torrens, M., Casas, M.,2012 Criteria and Concurrent Validity of Adult ADHD Section of the Psychiatry Research Interview for Substance and Mental Disorders. Journal of Attention Disorders (in press).

Roncero, C., Ros-Cucurull, E., Daigre, C., Casas, M., 2012. Prevalence and risk factors of psychotic symptoms in cocaine-dependent patients. Actas Españolas de Psiquiatría. 40, 187-197.

Roncero, C., Daigre, C., Gonzalvo, B., Valero, S., Castells, X., Grau-Lopez, L., Eiroa-Orosa, F.J., Casas, M., 2013a. Risk factors for cocaine-induced psychosis in cocaine-dependent patients. European Psychiatry: The Journal of the Association of European Psychiatrists.28, 141-146.

Roncero, C., Daigre, C., Grau-López, L., Rodríguez-Cintas, L., Pérez-Pazos, J., Barral, C., Gonzalvo, B., Corominas, M., Casas, M., 2013b. Cocaine-induced psychosis and impulsivity in cocaine-dependent patients. Journal of Addition Diseases 32, 1-11 DOI:10.1080/10550887.2013.824330

Roncero, C., Martinez-Luna, N., Daigre, C., Grau-Lopez, L., Gonzalvo, B., Perez-Pazos, J., Casas, M., 2013c. Psychotic symptoms of cocaine self-injectors in a harm reduction program. Substance Abuse 34, 118-121.

Satel, S. L., Edell, W. S., 1991. Cocaine-induced paranoia and psychosis proneness. The American Journal of Psychiatry, 148(12), 1708-1711.

Tang, Y. L., Kranzler, H. R., Gelernter, J., Farrer, L. A., Cubells, J. F., 2007. Comorbid psychiatric diagnoses and their association with cocaine-induced psychosis in cocaine-dependent subjects. The American Journal on Addictions / American Academy of Psychiatrists in Alcoholism and Addictions, 16(5), 343-351.

Torrens, M., Serrano, D., Astals, M., Perez-Dominguez, G., Martin-Santos, R., 2004. Diagnosing comorbid psychiatric disorders in substance abusers: Validity of the spanish versions of the psychiatric research interview for substance and mental disorders and the structured clinical interview for DSM-IV. The American Journal of Psychiatry, 161(7), 1231-1237.

UNODC, World Drug Report 2012 (United Nations publication, Sales No. E.12.XI.1). www.unodc.org/documents/data-and.../WDR_2012_web_small.pdf

Vergara-Moragues, E. González-Saiz F., Lozano O., Betanzos P., Fernández F., Bilbao-Acebos I., Pérez M., Verdejo A., 2012. Psychiatric comorbidity in cocaine users treated in therapeutic community: Substance-induced versus independent disorders. Psychiatry Research. 30;200(2-3):734-41.

Vergara-Moragues, E., González-Saiz, F., Lozano-Rojas, O., Fernández Calderón, F.,Verdejo García, A., Betanzos Espinosa, P., Bilbao Acedos, I., Pérez García, M. 2013. [Relationship between psychopathological comorbidity and outcomes variables in-treatment cocaine dependent subject in therapeutic community]. Adicciones 25(2):128-36.

Vorspan, F., Brousse, G., Bloch, V., Bellais, L., Romo, L., Guillem, E., Coeuru, P., Lépine, JP. 2012. Cocaine-induced psychotic symptoms in french cocaine addicts. Psychiatry Research, 200, 1074-1076.