Cocaine and depressive disorders: When standard clinical diagnosis is insufficient

Trastorno por uso de cocaína y depresión: cuando el diagnóstico clínico no es suficiente

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Abstract

Background: Cocaine use is a growing global health problem and patients with cocaine use disorders (CUD) present several complications, including high rates of major depression. There are two types of major depressive disorder (MDD) in these subjects: primary major depressive disorder (P-MDD) and cocaine-induced major depressive disorder (CI-MDD). To improve treatment, it is necessary to distinguish between both types. The aim of this study was to assess the differences in depressive symptomatology criteria (P-MDD vs CI-MDD) in CUD patients. *Methods:* Secondary data analysis was carried out with a cross-sectional sample of 160 patients presenting CUD and MDD. Clinical assessment was performed using the Psychiatric Research Interview for Substance and Mental Disorders (PRISM). A differential diagnosis was obtained between P-MDD and CI-MDD. *Results:* Men represented 80% of the sample, the mean age was 38.61 years, and 64.5% had elementary studies. CI-MDD diagnosis (61.3%) was more frequent than P-MDD (38.7%). There was a younger age of CUD onset in CI-MDD patients. In addition, 79.4% of the patients had another substance use disorder diagnosed. The criterion *"Changes in weight or appetite"* was more prevalent (57.1%) in P-MDD group. *Conclusions:* We found differences in the criterion *"Changes in weight or appetite"*. Further research is needed in this field in order to establish a differential diagnosis and thus provide better treatment for CUD individuals.
Keywords: Dual diagnosis; Cocaine use disorder; Cocaine-related disorders; Depressive disorder; Induced depression.

Resumen

Antecedentes: El consumo de cocaína es un creciente problema de salud en todo el mundo y los pacientes con trastorno por consumo de cocaína (TCC) presentan una alta comorbilidad con el trastorno depresivo mayor (TDM). Existen dos tipos de TDM: trastorno depresivo mayor primario (TDM-P) y trastorno depresivo mayor inducido por cocaína (TDM-IC). El objetivo de este estudio es evaluar las diferencias en la sintomatología depresiva (TDM-P vs. TDM- IC) en los pacientes con TCC para mejorar su tratamiento. *Métodos:* Se llevó a cabo un análisis secundario en una muestra transversal de 160 pacientes que presentaban TCC y TDM. La evaluación clínica, así como el diagnóstico diferencial entre TDM-P y TDM-IC se realizó utilizando la entrevista PRISM. *Resultados:* Los hombres representaron el 80% de la muestra con una edad media de 38,61 años y el 64,5% sólo tenía estudios elementales. El diagnóstico de TDM-IC (61,3%) fue más frecuente que el de TDM-P (38,7%). Los pacientes con TDM-IC mostraron una edad de aparición más temprana para el TCC. El 79.4% de los pacientes cumplían criterios para otro trastorno por consumo de sustancias. Únicamente el criterio *"Cambios en el peso o en el apetito"* fue estadísticamente más frecuente (57,1%) en los pacientes con TDM-P. *Conclusiones:* Existen diferencias en el criterio *"Cambios en el peso o apetito"* entre TDM-P y TDM-IC. Se necesita más investigación a fin de obtener un diagnóstico diferencial entre los dos tipos de depresión y proporcionar un mejor tratamiento para los pacientes con TCC.
Palabras clave: Patología dual; Trastorno por uso de cocaína; Trastornos relacionados con el uso de cocaína; Trastorno depresivo; Trastorno depresivo inducido.

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Globally, cocaine is one of the most widely used illicit stimulant and represents an increasing health problem. Its annual prevalence for use in Europe is early 1% (United Nations Office on Drugs and Crime (UNODC), 2016a) and among persons treated for drug use, 8.4% receive treatment for cocaine as main drug (United Nations Office on Drugs and Crime (UNODC), 2016b).

Patients diagnosed with cocaine use disorder (CUD) experience several complications including medical problems, family and social impairment, unemployment, and physical and sexual trauma. These issues are particularly marked in high risk populations such as women, older adults, and polysubstance users (John & Wu, 2017). Moreover, a number of studies in CUD populations have reported an elevated prevalence, over 40%, of comorbid psychiatric disorders (Araos et al., 2014; Herrero, Domingo-Salvany, Brugal, Torrens, & Itinere Investigators, 2011; Herrero, Domingo-Salvany, Torrens, Brugal, & ITINERE Investigators, 2008). The most frequent are mood disorders, including major depressive disorders (MDD), followed by anxiety and psychotic disorders (Araos et al., 2017; Lai, Cleary, Sitharthan, & Hunt, 2015).

Comorbid depression in CUD patients presents more severe clinical features than those found in patients with a single diagnosis. They include: poorer course of both pathologies (Magidson, Wang, Lejuez, Iza, & Blanco, 2013), earlier age of onset of depression, greater number of depressive symptoms and elevated functional impairment (Cohn et al., 2011), augmented social and personal impairment, and higher risk of suicide and other psychiatric conditions (Davis, Uezato, Newell, & Frazier, 2008).

Contingency management has been proved as a highly effective treatment for substance use disorders with or without mood disorders (Garcia-Fernandez, Secades-Villa, Garcia-Rodríguez, Peña-Suarez & Sanchez-Hervas, 2013). At present, the relevance of differentiating between induced and primary depression among substance users, has been highlighted and among antidepressant drugs, only Desipramine has demonstrated its efficacy improving depressive symptoms in cocaine users (Tirado-Muñoz, Farré, Mestre-Pintó, Szerman & Torrens, 2018).

The accurate diagnosis of comorbid depression is hindered by the overlapping of symptoms. Nowadays, emphasis is placed on nosological decision-making supported by evidence and the translational vision of research in both main classifications (ICD and DSM) (Bobes, Flórez, Seijo & Bobes, 2019). According to DSM-IV-TR (American Psychiatric Association (APA), 2000) and DSM-5 (American Psychiatric Association (APA)., 2013) criteria, two different conditions are considered for the diagnosis of comorbid disorders: primary disorder when is not substance or medically induced and substance-induced disorder when the symptoms are considered unreasonable, due to their severity or characteristics, with respect to those that appear as a result of intoxication or withdrawal. Furthermore, the expected effects are symptoms that appear as a result of the intoxication/withdrawal of a given substance and are considered physiological in relation to the pharmacological prospective of the substance and must be considered. In order to achieve an accurate diagnosis, clinicians should collect current and past history of substance consumption, all lifetime pathological symptoms and their clinical and temporal course.

There is increasing literature describing the differences and clinical relevance between primary and induced depression in substance use disorder (SUD) populations. In general terms, individuals with a SUD and induced depression exhibit greater consumption (Cohn et al., 2011; Davis et al., 2008) and poorer prognosis (Magidson et al., 2013; Tirado-Muñoz, Farré, Mestre-Pintó, Szerman, & Torrens, 2017). Moreover, such patients present higher impairment including risk of suicide (Conner et al., 2014), more hospitalizations, and have been prescribed more medication throughout life (Schuckit et al., 1997). In the case of alcohol, each type of depressive episode can be considered as two different diseases since P-MDD patients' present greater familial risk to develop a primary episode, while this association is not present for the induced episodes (Raimo and Schuckit, 1998).

These two types of depressive episodes are also found in CUD population: primary major depressive disorder (P-MDD) and cocaine-induced depressive disorder (CI-MDD). Leventhal et al (2006) found that CUD patients with a P-MDD diagnosis reported affective impairment more frequently than those with CI-MDD. It is thus crucial to distinguish between the two types of episodes due to implications in prognosis and treatment which must be adapted accordingly (Foulds et al., 2015; Tirado Muñoz et al., 2017). The prevalence of each type of depressive episode is unclear. In a systematic review comparing both types among patients with varying SUD, those with a CUD diagnosis showed more induced episodes than primary ones (Dakwar et al., 2011). Some studies have found a relationship between duration of use, frequency and age of consumption onset, and the probability of developing a cocaine-induced depressive episode (Herrero et al., 2008). With regard to treatment outcomes, a CI-MDD diagnosis has been observed to increase the risk of relapse with less time from discharge to relapse (Samet et al., 2013).

The aim of the study is to emphasize in the specific clinical characteristics including the depressive criteria that characterize each type of depressive episode, primary and induced, in patients with a CUD diagnosis to improve the diagnostic accuracy.

Material and Methods

Participants and recruitment

The present work is a secondary data analysis composed of a cross-sectional sample of 160 CUD individuals. Pa-

tients were recruited from out treatment facilities located in Barcelona and Málaga and in public therapeutic communities located in Andalucía in order to evaluate psychiatric comorbidities and search for biomarkers of cocaine addiction. The distribution of the participants, according to the medical service where they were recruited, was 103 (64.4%) outpatients and 57 (35.6%) from the therapeutic community.

Participation in the study was voluntary and subjects were required to meet eligibility criteria. The inclusion criteria for these studies were to be over 18 years old and seeking treatment for cocaine use. Exclusion criteria were language barriers or cognitive impairment to complete the clinical assessments. Patients who presented both types of depression (primary and induced) throughout their lives were also excluded.

Ethics statement

Written informed consent was obtained from each participant after a complete description of the study and responses to any queries provided. The study and protocols for recruitment were approved by the Ethics Committee from each participating center.

Clinical assessments

Participants were evaluated using the Spanish version of the *Psychiatric Research Interview for Substance and Mental Diseases* (PRISM) according to "Diagnostic and Statistical Manual of Mental Disorders-4th Edition-Text Revision" (DSMIV-TR) criteria. The PRISM is a semi-structured psychiatric research interview to diagnose psychiatric disorders among substance users that has demonstrated good psychometric properties in terms of test-retest reliability, inter-rater reliability, and validity for primary MDD and substance-induced MDD, with kappa ranging from 0.66 and 0.75 (Hasin et al., 2006; Torrens, Serrano, Astals, Pérez-Domínguez &Martín-Santos, 2004). All the interviews were performed by trained and experienced psychologists. In order to achieve the differential diagnosis in MDD it explores all depressive symptom criteria and consumption history. A time-line of each disorder and their symptoms is recorded to establish the relationship between them and differentiate among a primary disorder, an induced disorder or the expected effects of consumption. The length of each interview administration was between 2 and 3 hours depending of the subject assessed.

Statistical analysis

Descriptive analyses were used to characterize the samples. The estimations of the rates for each variable were described in frequencies and percentages. Group comparisons (P-MDD and CI-MDD) were performed using Student's t-test for continuous variables and the chi-square test for categorical ones. All estimates were performed with the SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) to analyze the data considering a significance level of 95% (p<0.05).

Results

Socio-demographic and clinical characteristics.

A total of 160 participants with CUD (80% men, mean age 38.61 years) were studied. According to the diagnosis of the comorbid lifetime depressive episode, 62 (38.7%) patients presented a P-MDD diagnosis and 98 (61.3%) a CI-MDD one.

Table 1 shows the sociodemographic and clinical description of the sample. The average participant was a 38-year-old, unemployed, male, receiving outpatient treatment. Significant differences were observed between the two groups with respect to the age of onset of CUD (p=0.039) with the CI-MDD group being younger at the time of initiation. No other significant differences were reported between P-MDD and CI-MDD patients.

In addition to these variables, 79.4% of the CUD patients with P-MDD or CI-MDD, were diagnosed with comorbid substance disorders (e.g., alcohol, heroin, cannabis, benzodiazepines, hallucinogens, or other stimulants). Alcohol was the substance with the highest prevalence (55.0%), followed by heroin (37.5%), and cannabis (36.3%).

Depressive diagnosis criteria

The comparison of diagnostic criteria for the worst episode of depression between P-MDD and CI-MDD is shown in Table 2.

No differences were found between groups for the first two criteria; meeting at least one of them was necessary to diagnose a major depression disorder. Prevalence in both groups was high and quite similar: 95.2% P-MDD patients and 98% CI-MDD met criterion 1 *(Depressed mood most of the day, nearly every day)* whilst 95.2% P-MDD and 93.8% CI-MDD met criterion 2 *(Markedly diminished interest or pleasure).*

Although we observed similar criteria between two types of depressive disorder, the statistical analysis revealed differences. For instance, significant ones were found in criterion 3 *(Significant weight or appetite loss/gain)* with a higher prevalence in P-MDD patients (57.1%) than CI-MDD (42.9%) (p=0.008).

Discussion

The purpose of this study was to characterize P-MDD and CI-MDD according the differences in clinical characteristics and depressive symptomatology in CUD patients. Main differences were found in some depressive symptoms and the age of CUD onset.

With respect to symptomatology we observed that criterion 3 (significant weight loss/gain when not dieting or increased/decreased appetite) was more prevalent in

Table 1. *Baseline, sociodemographic, and clinical characteristics of the study sample.*

Variables	Total N = 160	Primary Major Depressive Disorder N = 62 (38.7%)	Cocaine-Induced Depressive Disorder N = 98 (61.3%)	p Value
Sociodemographic Variables				
Age *[mean (SD)]*	38.61 (8.73)	39.24 (8.69)	38.20 (8.77)	0.465
Sex *[N (%)]*				
Women	32 (20)	15 (24.2)	17 (17.3)	0.292
Men	128 (80)	47 (75.8)	81 (82.7)	
Educational Level*[N (%)]*				
Elementary	103 (64.4)	40 (64.5)	63 (64.3)	0.968
Secondary	43 (26.9)	17 (27.4)	26 (26.5)	
University	14 (8.8)	5 (8.1)	9 (9.2)	
Work Status *[N (%)]*				
Employed	52 (32.5)	22 (35.5)	30 (30.6)	
Unemployed	78 (48.8)	25 (40.3)	53 (54.1)	0.291
Pensioner	27 (16.9)	14 (22.6)	13 (13.3)	
Hospice	3 (1.9)	1 (1.6)	2 (2)	
Criminal Record *[N (%)]*				
No	81 (50.6)	33 (53.2)	48 (49)	0.601
Yes	79 (49.4)	29 (46.8)	50 (51)	
Clinical Variables				
Depression Age of onset** *[mean (SD)]*	30.29 (12.5)	32.74 (11.52)	28.44 (13.04)	0.171
Number of depressive episodes** *[mean (SD)]*	3.14 (2.46)	2.57 (2.1)	3.6 (2.65)	0.099
Cocaine Use Disorder Age of onset *[mean (SD)]*	25.09 (8.16)	26.24 (8.63)	24.04 (7.71)	**0.039**
Length of CUD *[mean (SD)]*	13.52 (8.42)	12.47 (8.46)	14.16 (8.37)	0.220
Another Substance Use Disorder *[N (%)]*	127 (79.4)	48 (77.4)	79 (80.6)	0.690
Alcohol	88 (55)	34 (38.6)	54 (61.4)	0.974
Cannabis	58 (36.3)	20 (34.5)	38 (65.5)	0.403
Hallucinogens	18 (11.3)	7 (38.9)	11 (61.1)	0.990
Sedatives	36 (22.5)	12 (33.3)	24 (66.7)	0.449
Stimulants	17 (10.6)	8 (47.1)	9 (52.9)	0.457
Opioids	2 (1.3)	2 (100)	-	0.074
Heroin	60 (37.5)	19 (31.7)	41 (68.3)	0.154

Note. [a] p-value from Student's t-test; [b]p-value from Fisher's exact test or chi-square test.
**Primary Major Depressive Disorder (N=27); Cocaine-Induced Depressive Disorder (N=36)

P-MDD patients. This finding does not always concur with the limited literature: Some authors have reported that P-MDD patients showed frequently changes in weight/appetite (Cohn et al., 2011) whilst others have found the contrary, a greater prevalence in CI-MDD patients (Schuckit et al., 2007)

Regarding sociodemographic variables, P-MDD and CI-MDD patients have similar characteristics. Nevertheless, the age of CUD onset is lower in the CI-MDD, a finding which can be of use to clinicians for an accurate diagnosis. In SUD studies younger onset age has been correlated with long-term consequences (Grant & Dawson, 1998), and is a crucial factor in the development of this disorder (Jordan & Andersen, 2017). Due to our non-representative sample size we did not observe gender differences, nevertheless, some authors have reported a greater prevalence of P-MDD in women, and substance-induced depressive episodes in men (Dakwar et al., 2011).

With respect to prognosis, differences were found in the literature between P-MDD and CI-MDD. There is some evidence referring to greater severity, frequency, and risk of relapse in substance-induced depressive episodes compared to primary depressive ones (Samet et al., 2013; Schuckit et al., 2007).

Although the present symptomatology is insufficient for accurate differential diagnosis, and there is a lack of knowledge regarding depressive stratification, studies in alcohol and other substance use disorders have shown differences in prevalence, risk factors, and treatment outcomes for P-MDD and CI-MDD (Langås, Malt, & Opjordsmoen, 2013; Nunes, Liu, Samet, Matseoane, & Hasin, 2006; Samet et al., 2013). Moreover, there is evidence that suggests that

Table 2. *Comparison between primary mayor depressive disorder and substance-induced depressive disorder (DSM-IV-TR) diagnostic criteria in the worst depressive episode criteria.*

	Diagnosis according DSM-IV-TR criteria		
Criteria	**Primary Major Depressive Disorder N = 62**	**Cocaine-Induced Depressive Disorder N = 98**	**p Value**
Depressed mood most of the day, nearly every day (› 2 weeks)	59 (95.2)	96 (98.0)	0.322
Markedly diminished interest or pleasure in almost all activities most of the day, nearly every day	59 (95.2)	92 (93.9)	0.731
Significant weight loss/gain when not dieting or decreased appetite	46 (57.1)	52 (42.9)	0.008
Insomnia or hypersomnia nearly every day	45 (72.6)	64 (65.3)	0.336
Psychomotor agitation/retardation nearly every day	40 (64.5)	54 (55.1)	0.239
Fatigue or loss of energy nearly every day	45 (72.6)	73 (74.5)	0.789
Feelings of worthlessness or excessive inappropriate guilt nearly every day	53 (85.5)	84 (85.7)	0.968
Diminished ability to think or concentrate, or indecisiveness nearly every day	43 (69.4)	60 (61.2)	0.295
Recurrent thoughts of death, recurrent suicidal ideation or suicide attempt	37 (59.7)	58 (59.2)	0.951

P-MDD and CI-MDD are distinct conditions (Samet et al., 2013; Torrens Mèlich, 2008).

In addition, differences in biological mediators have been reported with specific changes in the serotonin and tryptophan profiles between P-MDD and CI-MDD (Keller et al., 2017). Despite the lack of information regarding their neurological pathways, clinicians treat the symptomatology profiles with either dopaminergic or serotoninergic pharmacotherapy (Saltiel & Silvershein, 2015). The genetic component has also been shown to be fundamental in research on substance use disorders (Yang, Han, Kranzler, Farrer, & Gelernter, 2011).

Due to their high prevalence, comorbid mental disorders have been extensively studied, specifically mood disorders in CUD. Our study underlines the importance of identifying the differences between P-MDD and CI-MDD in order to accurately diagnosis both types of depression.

Our study has some limitations. The first is the sample size which was relatively small for the detection of significant differences among variables. Moreover, women were under-represented as few of them seek treatment for substance use. Gender differences will need to be addressed in further research. Furthermore, the influence of other clinical variables such as body mass index or tobacco use could be explored. Finally, other environmental factors also could influence our data. Future investigation should take into account these limitations.

Our main strength is that the diagnostic procedures were performed with the PRISM interview which has demonstrated good reliability and validity for drug dependence and MDD diagnoses.

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Conflict of interest

The authors have no conflicts of interest.

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