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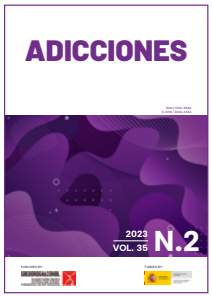

ORIGINAL

Differences between substance-induced psychotic disorders and non-substance-induced psychotic disorders and diagnostic stability

Diferencias y estabilidad diagnóstica entre trastornos psicóticos inducidos por sustancias y trastornos psicóticos no inducidos

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Abstract

Several hypotheses have been proposed to explain the comorbidity between psychotic disorders and substance use, one of them being the capacity of some to induce psychotic symptoms, although the transition from psychotic episodes induced by substances to schizophrenia has been less studied. In this study, differential variables between patients with induced and non-induced psychosis are determined, and the evolution and change of diagnosis of those induced to schizophrenia in the follow-up is analyzed. This is an observational case-control study with 238 patients admitted to the acute care unit for psychotic episodes between December 2003 and September 2011. The group of non-substance-induced psychotic disorders (NSIPD) included 127 patients, with 111 in the substance-induced (SIPD) group, according to the International Classification of Diseases. Sociodemographic and clinical characteristics, personal and family history, substance use, diagnostic stability and progression were compared. The NSIPD group showed higher scores in severity and in negative symptoms and more family history of psychosis. The SIPD group presented more personal history of personality disorder and family history of addictions and more positive symptoms At 6 years of follow-up, 40.9% of ISDP changed to a diagnosis of schizophrenia, presenting more family history of psychotic disorders and worse progression with more visits to the emergency department and readmissions, than subjects who maintained diagnostic stability. Therefore, special attention should be paid to this group of patients because of the potential severity and the increased risk of developing a chronic psychotic disorder.

Key words: substance-induced psychotic disorder, psychosis, addiction, schizophrenia, diagnostic stability

Resumen

Se han propuesto distintas hipótesis para explicar la comorbilidad entre trastornos psicóticos y por consumo de sustancias, siendo una de ellas la capacidad de algunas de inducir cuadros psicóticos, aunque la transición de episodios psicóticos inducidos por sustancias a esquizofrenia ha sido menos estudiada. En este trabajo se determinan variables diferenciales entre individuos con psicosis inducidas y no inducidas, y se analiza la evolución y el cambio de diagnóstico de las inducidas a esquizofrenia en el seguimiento. Es un estudio observacional de casos y controles con 238 pacientes ingresados en la unidad de agudos de un Hospital General de Madrid (España) por episodios psicóticos entre diciembre de 2003 y septiembre de 2011. Se incluyeron 127 en el grupo de trastornos psicóticos no inducidos por sustancias (TPNIS) y 111 en el de inducidos por sustancias (TPIS), según la Clasificación Internacional de Enfermedades. Se compararon características sociodemográficas, clínicas, antecedentes personales y familiares, de consumo de sustancias, estabilidad diagnóstica y evolución. El grupo de TPNIS presentó mayores puntuaciones en gravedad y sintomatología negativa mientras que el de TPIS tuvo más antecedentes personales de trastorno de personalidad y familiares de adicciones, y más sintomatología positiva. A los seis años un 40,9% de TPIS cambió a diagnóstico de esquizofrenia, presentando más antecedentes familiares de trastornos psicóticos y de adicciones, y una peor evolución con más visitas a urgencias y reingresos que los sujetos con estabilidad diagnóstica. Por tanto, habrá que prestar especial atención a este grupo de sujetos por su potencial gravedad y por el mayor riesgo de desarrollar un trastorno psicótico crónico.

Palabras clave: trastorno psicótico inducido por sustancias, psicosis, adicción, esquizofrenia, estabilidad diagnóstica

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The relationship between substance use and psychotic disorders continues to be debated in academic and clinical circles (Mathias, Lubman & Hides, 2008), despite the well-known potential of drugs of abuse, including alcohol, cannabis or cocaine, to induce psychotic symptoms in vulnerable people (Paparelli, Di Forti, Morrison & Murray, 2011; Rognli, Berge, Håkansson & Bramness, 2015; Soyka, 2008; Zawilska & Wojcieszak, 2013). The use of psychoactive substances can trigger psychotic symptoms of different types, including acute intoxication, withdrawal, intoxication or withdrawal delirium, affective disorders with substance-induced psychotic symptoms and substance-induced psychotic disorders (SIPD) (Keshavan & Kaneko, 2013). SIPD has been described as a group of psychotic phenomena appearing when a psychoactive substance is used or in the two weeks following use, persisting for at least 48 hours and not lasting more than six months (World Health Organization, 1992). Symptoms sometimes remain despite cessation of use (Chen et al., 2003; Schuckit, 2006). It is difficult for clinicians to distinguish between primary or non-substance-induced psychotic disorders (NSIPD) and comorbid substance-use disorders, and SIPDs (Mathias et al., 2008).

It has been shown that the regular use of psychoactive substances, especially cannabis, can induce psychotic experiences which are usually transitory in nature (Gage, Hickman & Zammit, 2016) and linked to the development of schizophrenia in vulnerable individuals (Callaghan et al., 2012; Fonseca-Pedrero, Lucas-Molina, Pérez-Albéniz, Inchausti & Ortuño-Sierra, 2020; García Álvarez, Gomar, García-Portilla & Bobes, 2019; Semple, McIntosh & Lawrie, 2005). Comorbid substance use disorder is present in 55% of first psychotic episodes (Abdel-Baki, Ouellet-Plamondon, Salvat, Grar & Potvin, 2017; Myles, Myles & Large, 2015), and significant comorbidity is in turn also found between schizophrenia and substance use disorders (Caton et al., 2005), with cannabis being the most studied drug. With regard to other psychoactive substances, it has been argued that although alcohol dependence predicts psychotic experiences, it does not cause psychosis per se (Soyka, 2008). Similarly, although amphetamine-induced psychosis is well documented, the extent to which amphetamine contributes as a cause of schizophrenia itself remains doubtful (Chaudhury, Krishna, & Kumar, 2016). Research on cocaine and opioids as a risk factor for schizophrenia is limited (Gregg, Barrowclough & Haddock, 2007).

Thus, the ability to distinguish between primary and substance-induced psychosis is important in understanding the development of the disease and planning adequate treatment, particularly in the early stages (Arias et al., 2013; Fiorentini et al., 2011). Some studies have focused on investigating risk factors, both sociodemographic and clinical, which explain the diagnostic instability of SIPD (Caton et al., 2007; Mathias et al., 2008; Mauri, Di Pace, Reggiori, Paletta & Colasanti, 2017; Niemi-Pynttäri et al., 2013; Sara, Burgess, Malhi, Whiteford & Hall, 2014; Starzer, Nordentoft & Hjorthøj, 2018), reaching the conclusion that there is likely no specific psychopathology of induced psychotic disorders (Baldacchino et al., 2012; Chaudhury et al., 2016).

In some cases, chronic psychoses will develop after psychoactive substance-induced psychoses; however, the risk factors associated with SIPDs for inducing permanent mental disorder are unclear (Chen, Hsieh, Chang, Hung, & Chan, 2015). Studies examining the diagnostic stability of first psychotic episodes have yielded mixed results (Fusar-Poli et al., 2016), the influence of drug use on the progression from induced psychoses to schizophrenia has hardly been researched, and in the majority of studies substance use is usually a criterion for exclusion (Pedrós, Martí, Gutiérrez, Tenias & Ruescas, 2009). However, in recent years, several investigations have been carried out to assess the conversion of SIPD to schizophrenia or bipolar disorder. (Alderson et al., 2017; Chen et al., 2015; Mauri et al., 2017; Niemi-Pynttäri et al., 2013; Sara et al., 2014; Shah, Chand, Bandawar, Benegal & Murthy, 2017; Starzer et al., 2018). Four of them found a heightened risk of conversion to schizophrenia from SIPD (Alderson et al., 2017; Chen et al., 2015; Niemi-Pynttäri et al., 2013; Sara et al., 2014; Starzer et al., 2018), with varying results. Alderson et al. (2017) reported a 17.3% risk of changing to schizophrenia within 5 years, with half such cases occurring in the first two years and 80% in the first 5 years after the diagnosis of substance-induced psychosis. Sara et al. (2014) found a 46% conversion rate to schizophrenia in 11 years of follow-up, and a cohort investigation at 11 years of follow-up reported figures of 22.5% (Chen et al., 2015). On the other hand, an investigation comparing SIPD, NSIPD and comorbid substance use disorder found similar percentages of diagnostic stability and schizophrenia diagnosis at follow-up (Mauri et al., 2017). By substance, it has been suggested that the cumulative risk of conversion from SIPD to schizophrenia spectrum disorders may be 46% for cannabis, 30% for amphetamines and 5% for alcohol, with conversion occurring within three years (Niemi-Pynttäri et al., 2013). However, research aimed at studying the variables influencing the relationship between cannabis use and the risk of psychosis is scarce (Fonseca-Pedrero et al., 2020), which also occurs with other substances.

The distinction between substance-induced psychosis and primary psychotic disorder is important because of the different approaches to treatment required. Nevertheless, there are few studies on the differences between the two conditions and on the longitudinal diagnostic stability in individuals with substance-induced psychosis. The objective of this study was thus to compare sociodemographic and clinical characteristics, as well as personal and family history of psychiatry and use of psychoactive substances, between subjects

with substance-induced psychotic disorders and those with non-induced psychotic disorders to find out the proportion of individuals with SIPD whose diagnosis changed to schizophrenia and to study the progression. We hypothesise that there will differences between individuals with induced and primary psychoses, although research results are currently mixed, and that the group with induced psychoses which change diagnosis will present a worse progression.

Method

Participants

This is an observational study of cases and controls, with the cases comprising a group of patients with substance-induced psychotic disorders (SIPD), and the controls a group of subjects with non-substance-induced psychotic disorders (NSIPD) without substance abuse or dependence, excluding tobacco. A total of 238 individuals took part, with 127 in the NSIPD group diagnosed as schizophrenia free (F20) according to the International Classification of Diseases (ICD-10), of whom 51 had nicotine dependence. The group of SIPD subjects included 111 participants, 71 (68.3%) with psychotic disorder due to cannabinoid use (F12.5), 14 (13.5%) with psychotic disorder due to cocaine use (F14.5), three (2.9%) with a psychotic disorder due to alcohol (F10.5), and 16 (15.4%) with a psychotic disorder due to polydrug use or other psychotropic substances (F19.5). The ages of the SIPD group ranged from 18 to 50 years, with a mean of 29.64 years (SD = 7.21), while the NSIPD group was aged 18 to 72 years, with a mean of 40.61 years (SD = 13.23).

Sociodemographic and clinical characteristics, as well as personal and family psychiatric history and use of addictive substances, diagnostic stability and progression were analyzed.

Study procedure

Subjects admitted to the acute unit of the Fundación Alcorcón University Hospital (Madrid) with psychotic episodes were recruited prospectively in the period between November 2003 and September 2011, subject to meeting inclusion criteria and agreeing to participate by signing the informed consent. Those who were assigned to the main researcher were selected. This sample was considered representative of the total number of individuals hospitalized for psychotic episodes since all were consecutively assigned on admission to the psychiatrists of the unit, including the principal researcher.

The inclusion criteria were being older than 18 years of age, living in the Fundación Alcorcón University Hospital's health area, having had a psychotic episode with psychiatric hospitalization between November 2003 and September 2011, and not suffering from comorbid organic brain pathology. The exclusion criteria were belonging to another health area, presenting comorbid organic brain pathology and rejecting participation or not signing the informed consent. In the NSIPD group, in addition to the above, the presence of substance use disorder, except tobacco, was an exclusion criterion.

Sociodemographic variables, personal and family history, and substance use data were obtained during hospitalization when the patients were recruited, through an initial clinical interview on the first day of admission between the main investigator (experienced psychiatrist from the unit), the patient, and his relatives when these were available. This first interview also included an assessment of psychotic symptoms with the Positive and Negative Syndrome Scale (PANSS) for schizophrenia and of severity with the Global Clinical Impressions scale (CGI). In the final clinical interview before discharge, the main investigator diagnosed personality disorder, substance addiction, if any, or psychotic disorder, according to ICD-10 diagnostic criteria.

The follow-up variables were collected periodically until November 2011 and retrospectively and cross-sectionally in June 2017 through the systematic review of computerized medical records. The final diagnosis, substance use and follow-up variables, such as the number of hospitalizations or visits to the emergency department in the period between November 2011 and June 2017, were obtained from the annotations in the computerized medical record of the reference professionals and from the successive emergency department visits and psychiatric hospitalizations. Since the Fundación Alcorcón University Hospital is the principal hospital for this health area, patients usually go to there in case of emergency or for psychiatric admission, so the computerized history includes all episodes. A total of 27 subjects were excluded for declining to participate and not signing informed consent; two cases were lost due to death from organic causes, ten changed addresses, and among the rest there was a high rate of missing data for variables.

To assess diagnostic stability, the SIPD group was divided into one labelled "stable diagnosis" and another "changing diagnosis", depending on whether or not their diagnosis remained the same as on recruitment.

Measurement instruments

- Positive and Negative Syndrome Scale for Schizophrenia (PANSS): Developed by Kay, Fiszbein and Opler (Kay, Fiszbein & Opler, 1987) and adapted to Spanish by Peralta and Cuesta (1994), this is one of the most widely used instruments for assessing symptomatology in patients diagnosed with schizophrenia. It is a hetero-applied scale using a semi-structured interview of about 45 minutes in length. In its original version it is made up of 30 items grouped into three factors: positive syndrome (consisting of 7 items), negative syndrome (7 items) and general psychopathology (16 items). Scores for each item range from

1 (absent), 2 (minimal), 3 (mild), 4 (moderate), 5 (moderate-severe), 6 (severe), and 7 (extreme). The main psychometric properties are currently well documented (Kay, Opler & Lindenmayer, 1989; Kay & Sevy, 1990). Wallwork, Fortgang, Hashimoto, Weinberger and Dickinson (2012) proposed a five-factor model for the PANSS with factors labelled "positive," "negative," "cognitive," "depressed," and "excited." In a Spanish study, internal consistency for the five-factor model ranged from 0.59 (excited factor) to 0.90 (negative factor). Although the internal consistency of the excited factor is below the usually accepted limit of 0.70, being close to 0.60 it is an acceptable limit for short scales (Rodríguez-Jiménez et al., 2013).

- Global Clinical Impression Scale (CGI): This is used to assess the severity of the patient's disease, assessing the subject's psychopathology on four subscales: positive, negative, cognitive, depressive symptoms and an overall psychopathology score. Scores range from 0 to 7 points, with higher scores indicating greater severity (Kadouri, Coeeuble & Falissard, 2007).

Ethical aspects

Participation in the study was voluntary, hence all participants gave consent to participate in the project. The study was approved by the clinical research ethics committee (CEIC) of the Fundación Alcorcón University Hospital (Madrid) and funded by the National Plan on Drugs.

Statistical analysis

Means and standard deviations were used as descriptive statistics for quantitative variables, and frequencies for the qualitative ones. The quantitative variables were compared using Student's *t*-test, once they were found to be normal with the Kolmogorov-Smirnov test, and taking into account variance homogeneity using the Levene test. The *chi*-square test was used to compare the qualitative variables and, in cases where the conditions for this test were not met, Fisher's exact test was applied. For data analysis, the IBM Statistical Package for the Social Sciences (SPSS), version 23 (IBM SPSS, IBM Corp, Armonk, NY) was used. Statistical significance was set at $p < 0.05$ and degrees of freedom and effect sizes were calculated.

Results

Comparative analysis of SIPD and NSIPD

Sociodemographic data is shown in Table 1. Table 2 describes the comparison of the characteristics of disorder onset and the symptoms assessed using the PANSS and ICG scales. Family history of substance addiction and psychotic disorder are compared in Table 3. Diagnoses of personality disorder were higher in the SIPD group, as shown in Table 4, with statistically significant differences ($c^2 = 40.61$; $p < 0.01$) and 19.8% of personality disorders in the NSIPD group and 57.7% in the SIPD group. Table 5 shows substance use in subjects with SIPD at the time of recruitment.

Diagnostic stability and progression

Of the 44 subjects in the SIPD group from whom diagnostic data were obtained at follow-up, 18 (40.9%) changed diagnoses to NSIPD (comprising the "changing diagnosis" group), while 26 (59.1%) remained as SIPD ("stable diagnosis"). In the NSIPD group, 37 subjects had nicotine addiction and one was an occasional smoker. Substance use results for the SIPD group by diagnostic stability are detailed in Table 6, and the comparison of family history and follow-up variables in Table 7.

Discussion

The mean age of SIPD group cases was 29.64 years, while that of the NSIPD group was 40.61 years. This may be explained by the inclusion in the study of patients with chronic psychotic disorders of longer duration than in SIPD since this is not a study of first psychotic episodes. One study (Singal, Bhat, Srivastava & Prakash, 2015) obtained a mean age of 31.52 for their group of primary psychoses and 37.47 years for that of substance-induced psychosis, figures differing from the present study, which includes first psychotic episodes. Caton et al., (2005) found lower figures of 25 and 29 years respectively because they studied patients with psychosis in early stages. Males were significantly older than females in the SIPD group, which is consistent with previous studies (Seddon et al., 2016; Weibell et al., 2013). In the sociodemographic variables of marital status, cohabitation and type of residence, no statistically significant differences were found. Educational level was significantly higher in the SIPD group, in line with results of other research showing that this group of patients has higher scholastic achievement (Caton et al., 2007; Singal et al., 2015; Weibell et al., 2013). One study found that 89% of individuals with SIPD had secondary school level, compared to 64% of NSIPD (Singal et al., 2015). Unemployment affected 47.7% of the patients with SIPD, which may be a result of their worse overall functioning due to substance use and comorbidity with personality disorders. The number of pensioners is high in the NSIPD group probably because as they are more chronically ill, they had already been awarded a disability pension. No statistically significant differences were found in the age of first symptoms, initial diagnosis or first admission. The duration of the first psychiatric hospitalization was significantly longer for subjects with NSIPD than for patients with SIPD. This may be due to the fact that psychotic symptoms are usually transient in induced psychoses (Gage et al., 2016) and abate more rapidly during hospitalization and when psychoactive substance use ceases.

Table 1. ***Sociodemographic characteristics.***

		NSIPD n (%)	SIPD n (%)	c^2	p
Sex	Male	66 (52%)	98 (88.3%)	36.47	0.01
	Female	61 (48%)	13 (11.7%)		
Marital status	Single	86 (69.9%)	69 (69.7%)	0.12	0.94
	Married/with partner	27 (21.9%)	23 (23.2%)		
	Other	10 (8.2%)	7 (7.1%)		
Living arrangements	Birth family	66 (54.5%)	60 (61.2%)	5.64	0.23
	Own family	31 (25.6%)	21 (21.4%)		
	Alone	18 (14.9%)	9 (9.2%)		
	Institution	4 (3.3%)	2 (2.1%)		
	Other	2 (1.7%)	6 (6.1%)		
Level of education	No school	5 (4.5%)	2 (2.9%)	21.84	0.01
	Primary	71 (63.4%)	37 (54.4%)		
	Secondary	23 (20.5%)	23 (33.9%)		
	University	13 (11.6%)	6 (8.8%)		
Work situation	Homemaker	21 (17.6%)	7 (8%)	67.24	0.01
	Unemployed	18 (15.1%)	42 (47.7%)		
	Employed	19 (16.0%)	29 (33.0%)		
	Self-employed	32 (26.9%)	1 (1.1%)		
	Pensioner	26 (21.9%)	2 (2.3%)		
	Student	3 (2.5%)	6 (6.9%)		
	Other	0 (0.0%)	1 (1.1%)		
Residence	Urban	99 (80.5%)	68 (72.3%)	1.99	0.16
	Rural	24 (19.5%)	26 (27.7%)		

Table 2. ***Comparative analysis of characteristics of disorder onset, the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) and the Global Clinical Impression Scale (CGI).***

	NSIPD Mean (SD)	SIPD Mean (SD)	t	df	p	d
Age of first psychiatric symptomsa	24.6 (8.33)	26.3 (6.42)	-1.67	196.65	0.09	-0.23
Age of diagonis[a]	26.9 (9.32)	27.4 (6.61)	-0.48	178.83	0.63	-0.07
Age of first hospitalization[a]	30.2 (11.74)	27.9 (6.73)	1.76	180.35	0.08	0.23
Duration of first hospitalization[b]	19.9 (13.96)	13.3 (9.67)	4.07	203.55	0.01	0.52
PANSS-P	22.36 (7.49)	24.73 (5.53)	-2.55	189.95	0.01	-2.34
PANSS-N	23.60 (8.45)	12.53 (5.84)	10.69	184.31	0.01	11.07
PANSS-G	37.30 (9.47)	34.39 (0.53)	1.92	110.89	0.06	0.33
CGI	4.76 (0.71)	4.51 (0.53)	2.43	157	0.02	0.38

Note. a: years; b: days; df: degrees of freedom; d: Cohen's d; P: positive; N: negative; G: global.

Table 3. ***Comparative analysis of family history.***

Family history		NSIPD n (%)	SIPD n (%)	c^2	p	OR (CI 95%)
Psychotic disorder	Yes	21 (21.2%)	14 (21.2%)	0.00	0.99	1.01 (0.472.16)
	No	78 (78.8%)	52 (78.8%)			
Substance use disorder	Yes	13 (13.1%)	19 (28.8%)	6.21	0.01	2.67 (1.21-5.89)
	No	86 (86.9%)	47 (71.2%)			

Note. OR: Odds ratio; CI: Confidence interval.

Table 4. ***Percentages of personality disorder diagnosis in both groups.***

Personality disorder diagnosis	NSIPD n (%)	SIPD n (%)
Paranoid personality disorder (F60.0)	1 (1.1%)	2 (2.9%)
Schizoid personality disorder (F60.1)	7 (7.7%)	3 (4.4%)
Dissocial personality disorder (F60.2)	0 (0.0%)	2 (2.9%)
Emotional instability personality disorder (F60.3)	1 (1.1%)	16 (23.5%)
Histrionic personality disorder (F60.4)	0 (0.0%)	0 (0.0%)
Anankastic personality disorder (F60.5)	2 (2.2%)	0 (0.0%)
Anxious personality disorder (F60.6)	1 (1.1%)	1 (1.5%)
Dependent personality disorder (F60.7)	0 (0.0%)	0 (0.0%)
Other specific personality disorders (F60.8)	0 (0.0%)	0 (0.0%)
Unspecified personality disorder (F60.9)	6 (6.6%)	16 (23.5%)

Table 5. ***SIPD group substance use at admission.***

Substance type and level of use		n (%)
Tobacco	Not used	4 (5.1%)
	Occasional	1 (1.3%)
	Dependent	73 (93.6%)
Alcohol	Not used	41 (41.4%)
	Occasional	21 (21.2%)
	Dependent	37 (37.4%)
Cannabis	Not used	14 (13.9%)
	Occasional	1 (1.0%)
	Dependent	86 (85.2%)
Cocaine	Not used	53 (50.0%)
	Occasional	16 (15.1%)
	Dependent	37 (34.9%)
Opioids	Not used	90 (90.0%)
	Dependent	10 (10.0%)

Table 6. ***Comparison of substance use in the six-year follow-up.***

		Stable diagnosis n (%)	Changed diagnosis n (%)	c^2 / F	df	p
Nicotine dependence	No	26 (33.3%)	8 (36.4%)	0.34	1	0.85
	Yes	52 (66.7%)	15 (63.6%)			
Alcohol dependence	No	72 (92.3%)	17 (77.3%)	3.96	1	0.61
	Yes	6 (7.7%)	5 (22.7%)			
Cannabis dependence	No	68 (87.2%)	18 (81.8%)	0.41	1	0.50
	Yes	10 (12.8%)	4 (18.2%)			
Cocaine dependence	No	75 (96.2%)	21 (95.5%)	0.02	1	0.99
	Yes	3 (3.8%)	1 (4.5%)			
Opioid dependence	No	78 (100%)	21 (95.5%)	3.58	1	0.22
	Yes	0 (0.0%)	1 (4.5%)			

Note. df: degrees of freedom.

Table 7. ***Diagnostic stability: family history and progression.***

		Stable diagnosis	Changed diagnosis	c^2 / t	df	p	OR (CI 95%) / d
Family history of substance dependence[a]	No	76 (88.4%)	13 (59.1%)	10.34	1	0.01	5.26 (1.79-15.43)
	Si	10 (11.6%)	9 (40.9%)				
Family history of psychotic disorder[a]	No	72 (82.8%)	13 (59.1%)	5.73	1	0.02	3.23 (1.20-9.18)
	Si	15 (17.2%)	9 (40.9%)				
Hospitalizations in 6 years of follow-up[b]		0.6 (1.14)	1.8 (2.30)	-2.49	27.91	0.02	-1.15
Emergency visits in 6 years of follow-up[b]		1.3 (2.56)	2.6 (2.76)	-2.24	135	0.03	-1.27

Note. a: N (%); b: Mean (SD); df: degrees of freedom; d: Cohen's d; OR: Odds ratio; Ci: Confidence Interval.

A diagnosis of comorbid personality disorder was made with 57.7% of the patients in the SIPD group, with unstable personality disorder being the most frequent together with unspecified personality disorder, followed by schizoid, paranoid and dissocial disorders. In NSIPD, only 19.8% were diagnosed with a personality disorder, with schizoid disorder being the most frequent. These results are in line with the literature, which indicates that personality disorder diagnoses are more frequent in individuals with SIPD (Arias et al., 2013), especially antisocial disorders (Caton et al., 2005, 2007; Fiorentini et al., 2011), compared to the schizoid disorders most commonly associated with a schizophrenia diagnosis (Núñez & Gurpegui, 2002). It can be hypothesized that the presence of a personality disorder, especially those characterized by a high degree of impulsiveness and emotional instability, can predispose to substance use, which, in turn, could trigger psychosis in vulnerable subjects, or that these disorders have common brain substrates and mechanisms (Volkow, 2001). Therefore, it is essential to explore the presence of substance use and the existence of psychotic symptoms in individuals with personality disorders.

Patients with SIPD had greater family history of substance use disorder, with statistically significant differences compared to the NSIPD group, in line with previous research showing that a family history of substance abuse is predictive of SIPD (Caton et al., 2005, 2007). In contrast, no differences were found in the family history of psychotic disorder, which differs from the literature since it has been observed that individuals with primary psychosis have greater family history of mental illness (Caton et al., 2005, 2007). Singal et al. (2015) observed a family history of psychosis in 20% of NSIPD cases, double that of patients with induced psychosis. Therefore, the presence of a family history of psychosis should be taken into account in these SIPD patients since they could be at higher risk of progressing to schizophrenia.

Individuals in the SIPD group scored significantly higher on positive symptoms, while those with NSIPD had higher scores for negative symptoms and severity. This fact could be due to the presence in the NSIPD group of patients with chronic psychoses of greater progression, in which the presence of negative symptoms and greater seve-

rity can be expected, compared to induced psychoses. The findings in this regard in the literature are contradictory since on the one hand, it has been pointed out that SIPD have higher scores on positive symptoms than NSIPD (Caton et al., 2005; Fraser, Hides, Philips, Proctor & Lubman, 2012; Weibell et al., 2013), while on the other, that the latter would score higher in both positive and negative symptoms (Myles, Newall, Nielssen & Large, 2012; Seddon et al., 2016), with some even finding no differences (Møller & Linaker, 2004; Tosato et al., 2013).

In the following six years, 40.9% of the individuals belonging to the SIPD group changed to a diagnosis of schizophrenia. Various studies have provided figures for the diagnostic transition from substance-induced psychosis to schizophrenia of between 17% and 50% (Alderson et al., 2017; Arendt, Rosenberg, Foldager, Perto & Munk-Jorgensen, 2005; Chen et al., 2015; Crebbin, Mitford, Paxton & Turkington, 2009; Mauri et al., 2017; Niemi-Pynttäri et al., 2013; Sara et al., 2014; Shah et al., 2017; Starzer et al., 2018), so the results of the present study are in line with the literature.

When comparing the groups "stable diagnosis" and "changing diagnosis", greater family history of psychotic disorder and addiction were found in those whose diagnosis change, which matches previous studies (Singal et al., 2015). Various explanations have been put forward for this diagnostic change from SIPD to NSIPD. On the one hand, it may be that certain individuals are particularly vulnerable to the sympathomimetic effects of substances (Singal et al., 2015) and end up developing a chronic psychotic disorder; on the other, it could be due to underdiagnosis of NSIPD in patients with both psychosis and substance use disorder; or that substance use disorder is a marker of emerging psychotic disorder which has not yet manifested with psychotic symptoms (Singal et al., 2015). The patients with SIPD whose diagnosis changed in the last six years of follow-up had worse progression with more readmissions and visits to the emergency room than the group that remained stable; this had already been indicated as factors of worse prognosis (Caton et al., 2007; Chaudhury et al., 2016). On the other hand, no statistically significant differences were found in terms of substance use between the group that changed diagnosis and the one remaining stable, which is probably due to the decrease in the sample for analysis since the substance use data in the years of follow-up were not duly recorded in the medical records. Based previous research, it could have been expected that patients with a change in diagnosis, with a worse progression with more visits to the emergency department and hospitalizations, would present greater substance use (Abdel-Baki et al., 2017; Latt et al., 2011).

This study is not without limitations. First, the comparison of patients with episodes of substance-induced psychosis and patients diagnosed with schizophrenia is a limiting factor when establishing differences in symptomatology at admission, given that it is predominantly negative among individuals diagnosed with schizophrenia and could be due to the progression of the disease itself. Future lines of research could consider the study of patients with first episodes. A second limitation is be the missing data in both groups as a result of incomplete data collection regarding some variables in the medical records, such as substance use or change of diagnosis, when monitored by outpatient psychiatrists in an unstructured manner. This should lead us to reflect on the extent to which important parameters such as such substance use are explored and noted in check-ups of patients with chronic disorders, especially those individuals who have had episodes of induced psychotic disorders. Third, given that the sample of cases is from a specific health area and involved hospitalized patients, and despite the fact that recruitment was carried out consecutively, the results cannot be extrapolated to other clinical contexts and health areas.

Despite the limitations, a strength of this study is the structured baseline assessment to establish differences between the groups of induced and non-induced psychosis since, to our knowledge, little research has focused on this point. In addition, the follow-up time is longer than that of other studies aimed at assessing diagnostic stability in induced psychotic disorders. Finally, attempts were made to assess substance use in order to determine its influence on diagnostic stability, despite the large volume of missing data, which serves as a pointer for future research. In terms of clinical recommendations, substance use should be explored at each check-up visit and correspondingly noted as part of clinical history, and changes in diagnosis should be indicated when they occur, especially in cases of SIPD. For future research, it would be interesting to study first psychotic episodes, both induced and non-induced, gathering data systematically on baseline use and progression, and the time of diagnosis change, which allows the assessment of the influence of such use on diagnostic stability and the search for predictors of chronification. Finally, these findings underscore the need for periodic reassessment of clinical diagnoses to ensure that patients receive appropriate interventions.

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Conflicts of interest

The authors declare no conflicts of interest.

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