

Cannabis-induced psychosis: clinical characteristics and its differentiation from schizophrenia with and without cannabis use

Psicosis inducida por cannabis: características clínicas y su diferenciación con la esquizofrenia con y sin consumo de cannabis asociado

DAVID RENTERO*, FRANCISCO ARIAS*, SERGIO SÁNCHEZ-ROMERO**,
GABRIEL RUBIO*,***, ROBERTO RODRÍGUEZ-JIMÉNEZ*,***,****.

* Servicio de Psiquiatría. Instituto de Investigación Sanitaria Hospital Universitario 12 de Octubre (imas12), Madrid. España.

** Servicio de Psiquiatría. Hospital Universitario Fundación Alcorcón. España.

*** Universidad Complutense de Madrid (UCM), Madrid. España.

**** Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid. España.

Abstract

Cannabis use is considered an established risk factor for psychosis development. Differentiating between cannabis-induced disorders and schizophrenia is useful for prognostic and therapeutic purposes. Three inpatients groups were differentiated: cannabis-induced psychosis (CIP) ($n = 69$; mean age = 27.4, $SD = 6.5$; 82.6% males), schizophrenia with cannabis abuse or dependence (SZ + CB) ($n = 57$; mean age = 31.9, $SD = 10.1$; 94.7% males) and schizophrenia without cannabis abuse or dependence (SZ) ($n = 181$; mean age = 41.8, $SD = 13.3$; 54.1% males). The *Psychiatric Research Interview for Substance and Mental Disorders* (PRISM-IV) scale was used to differentiate induced psychosis. The CIP group presented lower mean scores on the negative PANSS subscale ($M = 12.9$, $SD = 5.9$; $F = 32.24$, $p < 0.001$), fewer auditory hallucinations (60.3%; $\chi^2 = 6.60$, $p = 0.037$) and greater presence of mania (26.1% vs. 12.3%; $\chi^2 = 32.58$, $p < 0.001$) than the SZ + CB group. There were few clinical differences between patients with schizophrenia, regardless of previous cannabis use. The age of first admission due to psychosis was lower in both psychotic inpatients groups with cannabis use ($M = 26.1$, $SD = 6.4$ in CIP and $M = 25.3$, $SD = 6.2$ in SZ + CB; $\chi^2 = 20.02$, $p < 0.001$). A clinical pattern characteristic of cannabis-induced psychosis was not observed, but the precipitating role of cannabis in the appearance of psychotic symptoms was demonstrated, given the lower age of first admission due to psychosis in cannabis user groups.

Keywords: Psychosis; Schizophrenia; Cannabis; Induced psychosis.

Resumen

El consumo de cannabis se considera un factor de riesgo establecido para el desarrollo de psicosis. Diferenciar los trastornos inducidos por cannabis de la esquizofrenia resulta útil desde el punto de vista pronóstico y terapéutico. Se diferenciaron tres grupos de pacientes hospitalizados: psicosis inducida por cannabis (PIC) ($n = 69$; Media de edad = 27,4, $DE = 6,5$; 82,6 % varones), esquizofrenia con abuso o dependencia de cannabis (EZ + CB) ($n = 57$; Media de edad = 31,9, $DE = 10,1$; 94,7% varones) y esquizofrenia sin abuso o dependencia de cannabis (EZ) ($n = 181$; Media de edad = 41,8, $DE = 13,3$; 54,1% varones). Se utilizó la escala *Psychiatric Research Interview for Substance and Mental Disorders* (PRISM-IV) para la diferenciación de cuadros inducidos. El grupo PIC presentó puntuaciones inferiores en la subescala PANSS negativa ($M = 12,9$, $DE = 5,9$; $F = 32,24$; $p < 0,001$), menos alucinaciones auditivas (60,3%; $\chi^2 = 6,60$; $p = 0,037$) y mayor presencia de manía (26,1% vs. 12,3%; $\chi^2 = 32,58$; $p < 0,001$) en comparación con el grupo EZ + CB. Hubo pocas diferencias clínicas entre los pacientes con esquizofrenia, independientemente del consumo de cannabis. La edad del primer ingreso por psicosis fue menor en ambos grupos de psicóticos consumidores ($M = 26,1$, $DE = 6,4$ en PIC y $M = 25,3$, $DE = 6,2$ en EZ + CB; $\chi^2 = 20,02$; $p < 0,001$). No se observó un patrón clínico característico de las psicosis inducidas por cannabis, aunque sí se demostró el papel precipitante del cannabis en la aparición de psicosis, dada la menor edad de ingreso en los consumidores.

Palabras clave: Psicosis; Esquizofrenia; Cannabis; Psicosis inducidas.

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Send correspondence to:

David Rentero Martín. Servicio de Psiquiatría, Hospital Universitario 12 de octubre. Avda. de Córdoba s/n, 28041, Madrid, España.
E-mail: davidrente7@hotmail.com.

Cannabis use is frequent among patients with psychotic disorders. Over 25% of patients with schizophrenia have concomitant cannabis dependence (Koskinen, Löhönen, Koponen, Isohanni & Miettunen, 2010), although polydrug use of other substances is also common (Volkow, 2009).

In recent decades, several cohort studies have been conducted to investigate the relationship between cannabis use and schizophrenia. After an initial study by Andréasson, Allebeck, Engström and Rydberg (1987), other cohort studies have been carried out, producing consistent data. In general, most authors consider that cannabis use may be a risk factor for the development of schizophrenia in vulnerable subjects, especially when it occurs at an early age and in large quantities (Konings, Henquet, Mahara-jh, Hutchinson & Van Os, 2008; Marconi, Di Forti, Lewis, Murray & Vassos, 2016). It has also been observed that this risk is greater than with other drugs and that cannabis is the only drug which has been shown to bring forward the age of onset of psychosis (Large, Sharma, Compton, Slade & Nielssen, 2011). However, other authors have suggested that, although cannabis use precedes the onset of psychotic symptoms, subjects who are vulnerable to the development of psychosis would already have greater susceptibility to cannabis dependence (Power et al., 2014).

Several studies in healthy volunteers have shown that cannabis produces not only positive symptoms but also negative and cognitive symptoms (García-Álvarez, Gomar, García-Portilla & Bobes, 2019), thus mimicking the typical characteristics of schizophrenia (D'Souza et al., 2004). Cannabis-induced psychosis involves a psychotic state which subsides within a month with antipsychotic treatment and abstinence. The new findings suggest that a large number of patients with cannabis-induced psychosis will subsequently develop chronic psychotic conditions in about 50% of cases (Starzer, Nordentoft & Hjorthøj, 2018). The argument that cannabis plays a causal role is supported by the findings that the use of cannabis of greater potency, as measured by the amount of tetrahydrocannabinol (THC), presents a higher risk of producing psychosis (Pierre, Gandal & Son, 2016). There are also recent studies showing that the use of synthetic cannabinoids is involved in the appearance of transient psychotic symptoms (Monte et al., 2017), induced psychosis (Barratt, Cacic & Lenton, 2013), first psychotic episodes (FPE) (Khan, Pace, Truong, Gordon & Moukaddam, 2016) and psychotic relapses in patients with schizophrenia (Celofiga, Koprivsek & Klavz, 2014).

Given that schizophrenia is a neurodevelopmental disease and the existing evidence that the endocannabinoid system modulates this brain process (cell proliferation, neurogenesis, neuronal migration, axonal projections), cannabis use, especially at an early age, could interfere in neurodevelopment, constituting a plausible biological ex-

planation (Lubman, Cheetham & Yücel, 2015). Keshavan (1999) proposed the integration of three neurobiological models on the pathogenesis of schizophrenia: the early development model, the late development model and the neurodegenerative model. Premorbid vulnerability to schizophrenia is likely caused by an interaction of multiple genetic and environmental factors affecting early brain development. The onset of the disorder in adolescence may be determined by the processes of late brain maturation, as well as by the exclusive stress of adolescence and the impact of repeated exposure to neurochemical or environmental stressors, such as drug use (Keshavan, Gilbert & Diwadkar, 2006).

Some authors suggest that the pathogenic mechanisms behind the appearance of psychotic conditions in patients with cannabis use are different to those involved in the appearance of psychosis in non-users. The action of THC on the cannabinoid system, whether intact or already previously damaged, may produce neurobiological changes other than schizophrenia in non-users, which could lead to different clinical manifestations (Murray et al., 2017). On the other hand, CB2 cannabinoid receptors and neuroinflammatory mechanisms may also be relevant and could play a differential role between users and non-users (Minichino et al., 2019; Suárez-Pinilla, López-Gil & Crespo-Facorro, 2014). Other authors posit that, although psychosis develops by different mechanisms, a common final impairment occurs in the NMDA system, which is intimately regulated by CB1 cannabinoid receptors (Sánchez-Blázquez, Rodríguez-Muñoz & Garzón, 2014).

It is disputed whether cannabis use modifies the clinical presentation of psychosis and whether it constitutes a different clinical entity. An attempt has been made to establish a clinical method to differentiate between the psychotic conditions appearing in cannabis users and non-users which could guide the diagnosis. The data are rather contradictory. Cannabis use has been linked to greater severity of positive symptoms and lesser severity of negative symptoms (Pencer & Addington, 2003). In hospitalized patients, the presence of more neurotic symptoms and more depressive symptoms was observed in induced psychoses (Rubio et al., 2012; Thompson et al., 2016). Other authors report more hostility and anxiety symptoms in drug-induced psychosis versus primary psychoses (Fraser, Hides, Philips, Proctor & Lubman, 2012) or a higher frequency of mania and behavioral disorders, although positive symptoms subsided more quickly and negative symptoms were less prominent (Dawe, Geppert, Occhipinti & Kingswell, 2011). Conversely, some authors observed no clinical differences or differences in family history in cases of already existing schizophrenia when analyzing whether or not they had a history of previous cannabis use (O'Connell, Sunwoo, McGorry & O'Donoghue, 2019). Hence it seems that there may be some clinical differences in induced psychoses, but once

schizophrenia is established there are few differences depending on whether cannabis is used or not, so it is important to take such differences into account (Mauri, Di Pace, Reggiori, Paletta & Colasanti, 2017).

In general, the studies carried out to date are quite contradictory, probably due to the heterogeneity of the inclusion and exclusion criteria applied. Specifically, the exclusion of abuse or dependence on substances other than cannabis has not been taken into account in the research reviewed to date, something which could interfere with results. In addition, there are no studies directly comparing patients with cannabis-induced psychosis, patients with schizophrenia with cannabis abuse or dependence, and patients with schizophrenia without assessing abuse of or dependence on this substance.

The objective of this study was to analyze the possible existence of sociodemographic, clinical, developmental and prognostic differences between three groups of hospitalized patients: patients with cannabis-induced psychosis, schizophrenia with a history of cannabis abuse or dependence, and schizophrenia without a history of such abuse or dependence. In each group, we studied: 1) sociodemographic characteristics, family history and medical history; 2) clinical characteristics; 3) comorbid substance use; 4) age of first admission for psychotic symptoms by sex.

Method

Participants

A total of 331 patients were recruited with the following inclusion criteria: a) patients aged over 18; and b) diagnosed with schizophrenia or other unspecified psychotic disorders according to DSM-IV-TR criteria (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, text rev.*) (American Psychiatric Association, 2000). Exclusion criteria were: a) presence of psychosis in the context of affective disorders; b) history of moderate-severe head trauma; c) prior diagnosis of mental retardation; and d) a history of

abuse or dependence on drugs other than cannabis and tobacco.

Intentional sampling was conducted and patients were classified into those with psychotic disorder and history of cannabis abuse or dependence and those diagnosed with schizophrenia without drug abuse or dependence except tobacco (SZ). Patients with psychosis and cannabis abuse or dependence were subdivided into schizophrenia with cannabis abuse or dependence (SZ + CB) and cannabis-induced psychosis (CIP). During the assessments, some patients dropped out of the study (see Figure 1) before their classification into groups as well as afterwards, declining consent for the study during admission.

As shown in Table 1, the mean age of the sample was 36.7 years ($SD = 13.1$), with a higher percentage of men (68.1%). The majority of patients were single (71%) and lived with their family of origin (59%). In the comparison between the three groups, baseline age was not distributed equally among the three groups ($p < 0.001$). SZ group patients were older than those in the other groups in a statistically significant way ($p < 0.001$). Among cannabis-using patients, the SZ + CB group were older, although this difference did not reach statistical significance. Regarding sex, the proportion of men in the SZ group was statistically significantly smaller ($p < 0.001$). When comparing both groups of consumers, the SZ + CB group presented a higher percentage of men (94.7%) which was statistically significant ($p = 0.036$). In terms of the remaining variables, SZ group patients lived more frequently with their own family, had a higher educational level and a lower family history of SUD. In addition, they had a higher frequency of medical pathology (mainly arterial hypertension and diabetes), higher BMI (Body Mass Index) and a lower frequency of attention deficit hyperactivity disorder history.

Informed written consent was obtained from each participant once they had received a full description of the study. If patients were unable to make decisions, a family member was informed. The research protocol was ap-

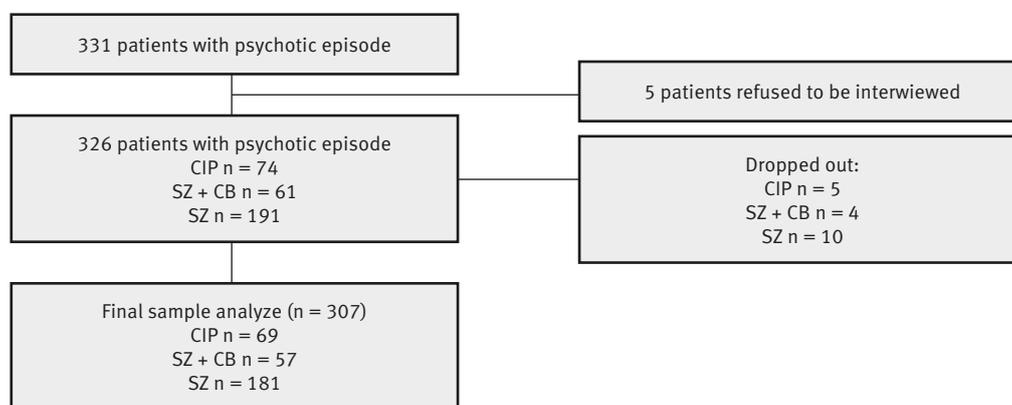


Figure 1. Sample selection process.

CIP: cannabis-induced psychosis; SZ: patients with schizophrenia; CB: patients with cannabis abuse or dependence.

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Table 1. Sociodemographic characteristics, family history and medical history.

	Total (n = 307)	CIP (n = 69)	SZ+CB (n = 57)	SZ (n = 181)	Test value
Age (years) ^a Mean (SD)	36.7 (13.1)	27.4 (6.5)	31.9 (10.1)	41.8 (13.3)	$\chi^2 = 76.61$ $p < 0.001^{***}$
Sex					
Male	209 (68.1%)	57 (82.6%) R.C = 2.9	54 (94.7%) R.C = 4.8	98 (54.1%) R.C = -6.3	$\chi^2 = 41.51$ $p < 0.001^{***}$
Female	98 (31.9%)	12 (17.4%) R.C = -2.9	3 (5.3%) R.C = -4.8	83 (45.9%) R.C = 6.3	
Marital status					
Single	218 (71%)	57 (82.6%)	45 (78.9%)	116 (64.1%)	$\chi^2 = 11.23$ $p = 0.024^*$ T appr = 2.84
Married	56 (18.2%)	8 (11.6%)	6 (10.5%)	42 (23.2%)	
Other	33 (10.7%)	4 (5.8%)	6 (10.5%)	23 (12.7%)	
Living arrangements					
Family of origin	181 (59%)	52 (75.4%)	42 (73.7%)	87 (48.1%)	$\chi^2 = 23.7$ $p = 0.003^{**}$ T appr = 3.64
Own family	64 (20.8%)	9 (13%)	7 (12.3%)	48 (26.5%)	
Other	62 (20.2%)	8 (11.6%)	8 (14%)	46 (25.5%)	
Educational level					
Primary	192 (62.5%)	36 (52.2%)	40 (70.2%)	121 (66.9%)	$\chi^2 = 17.01$ $p = 0.009^{**}$ T appr = -1.33
Secondary	80 (26.1%)	27 (39.1%)	15 (26.3%)	38 (21%)	
University	30 (9.8%)	6 (8.7%)	2 (3.5%)	22 (12.2%)	
Employment					
Unemployed	88 (28.7%)	35 (50.7%)	17 (29.8%)	36 (19.9%)	$\chi^2 = 60.00$ $p < 0.001^{***}$ T appr = 2.43
Working	78 (25.4%)	19 (27.5%)	12 (21.1%)	47 (26%)	
PWD	83 (27%)	1 (1.4%)	12 (21.1%)	70 (38.7%)	
Other	58 (18.9%)	14 (20.2%)	16 (28.1%)	28 (15.5%)	
Infantile hyperactivity	46 (15%)	25 (36.2%)	16 (28.6%)	5 (3.4%)	$\chi^2 = 42.84$ $p < 0.001^{***}$
Family history					
Substance dependence	50 (16.3%)	19 (27.5%)	11 (19.3%)	20 (11%)	$\chi^2 = 10.42$ $p = 0.005^{**}$
Psychotics	67 (21.8%)	12 (17.4%)	15 (26.3%)	40 (22.1%)	$\chi^2 = 1.47$ $p = 0.47$
Medical comorbidity	79 (26.1%)	11 (17.3%)	10 (15.6%)	58 (32.2%)	$\chi^2 = 27.84$ $p = 0.26$
Basal BMI Mean (SD)	26.6 (6.0)	23.4 (3.6)	25.1 (3.8)	28.3 (6.7)	$F = 10.09$ $p < 0.001^{***}$

Note. SD = standard deviation. χ^2 = chi-square. PWD = permanent work disability. BMI = body mass index. F = ANOVA value. T appr = approximate T, using the typical asymptotic error based on the null hypothesis. CR = corrected residuals. (aKruskal-Wallis). *significant values $p < 0.05$; ** very significant values $p < 0.01$; *** highly significant values $p < 0.001$.

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Instruments

PANSS scale (Positive and Negative Syndrome Scale). The Positive and Negative Syndromes Scale developed by Kay, Fiszbein and Opler (1987) and adapted to Spanish by Peralta and Cuesta (1994) is one of the most frequently

used instruments to assess symptoms in patients with schizophrenia. It is a hetero-applied scale which is completed through a semi-structured interview of about 45 minutes. In its original version, the PANSS scale comprises 30 items grouped into three factors: positive syndrome (consisting of 7 items), negative syndrome (also made up of 7 items) and general psychopathology (consisting of 16 items). The scores for each item range from 1 (absent),

2 (normal limit), 3 (mild), 4 (moderate), 5 (moderate/severe), 6 (severe) and 7 (extremely severe). The main psychometric properties of the PANSS scale are currently well documented (Kay, Opler & Lindenmayer, 1989; Kay & Sevy, 1990). Wallwork, Fortgang, Hashimoto, Weinberger and Dickinson (2012) proposed a five-scale model of the scale, commonly labeled as “positive”, “negative”, “cognitive”, “depression” and “excitability”. In a Spanish study, the internal consistency for the five-factor model ranged from 0.59 (excitability factor) to 0.90 (negative factor). Although the internal consistency of the excitability factor was below the widely accepted limit of 0.70, it was close to 0.60, an acceptable limit for short scales (Rodríguez-Jiménez et al., 2013).

In addition to the total scores of the PANSS scale, this study used the classical subscales (positive, negative and general psychopathology). The negative subscale requires a special mention as it was used to quantify and compare the negative symptoms of the three groups of patients studied.

PRISM-IV Scale (Psychiatric Research Interview for Substance and Mental Disorders for DSM-IV) (Hasin et al., 1996). This is a semi-structured interview with which many DSM-IV disorders can be reliably diagnosed and which is highly valid in people who abuse substances, including substance dependence, major primary and substance-induced depressive disorder, primary psychotic and substance-induced disorder, and some primary anxiety disorders, dissociative personality disorder and borderline personality disorder. For this study, the Spanish version was used (Torrens, Serrano, Astals, Pérez-Domínguez & Martín-Santos, 2004), which has proven to be a better structured and more accurate interview for the diagnosis of drug-induced psychosis than the version in SCID-1 Spanish (Structured Clinical Interview for DSM-IV) (First, Spitzer, Gibbon & Williams, 2002).

In addition to previous diagnoses, the presence of hetero-aggressive behaviors and the prevalence of dysphoric, depressive or manic humor, as well as the presence of suicidal behavior were collected with this scale.

The reliability of the scale for patients who abuse substances is at least as good as that shown by other interviews with general samples (Hasin et al., 1996).

Substance use questionnaire. For the assessment of substance use, a series of ad hoc questions were formulated regarding alcohol consumption and drug use, specifically cannabis, cocaine, designer drugs and opiates. For alcohol use, information was collected on whether the participant was a non-drinker, drinker or former drinker. Likewise, information was also collected on other substances such as cannabis/marijuana/hashish, cocaine, designer drugs/methamphetamines/ecstasy/LSD and opioids. For each of these, information on the age of onset in years, how long it was used in months, and the days of use in the previous month were requested. These questions were formulated in line with previous research (Dumas et al., 2002) and pre-

viously validated scales (Soto-Brandt et al., 2014). Patients with criteria of abuse or dependence other than cannabis or nicotine were excluded from this study.

Addiction Severity Index (ASI) (McLellan et al., 1992). This is a semi-structured interview of between 45 to 60 minutes in length, administered by a trained clinician or interviewer, plus a further 10-20 minutes for scoring. It focuses on seven areas which may be affected by drug use: physical health, employment and financial support, illegal or criminal activity, family and social relationships, psychiatric symptoms and use of drugs and alcohol. For each area, the severity of symptoms and the treatment applied in the previous 30 days and lifetime are assessed.

The psychometric properties of the ASI scale have been demonstrated in different studies (Butler, Redondo, Fernandez & Villapiano, 2009; Carise et al., 2001).

Study Procedure

The recruitment of patients was carried out between January 1, 2005 and December 31, 2011 in a tertiary hospital in the southern area of the Community of Madrid (Alcorcón Foundation University Hospital). This hospital serves an urban area of about 200,000 inhabitants and a rural area of approximately 50,000 inhabitants; it is the only reference hospital for this population.

Patients were recruited consecutively as they attended the short hospitalization unit (SHU) of the hospital with a psychotic episode. The clinical assessments of the study were carried out during admission through standardized data collection by a psychiatric specialist at the SHU, who was the only interviewer in the study.

Some patients who maintained contact with mental health services in the area were monitored until 2013, either through the hospital or in outpatient clinics. This follow-up was performed to assess relapses and readmissions. The sample follow-up was on average 51 months ($SD = 2.1$), median 52 (4-84 months). In the CIP group, 43 patients were followed up ($M = 40.2$ months, $SD = 30.4$), in the SZ + CB group the follow-up was with 33 patients with a mean of 58.2 months ($SD = 31.9$), and in the SZ group 102 patients were followed with a mean of 59.3 months ($SD = 31.3$) (non-statistically significant differences with respect to the SZ + CB group).

Data analysis

All analyses were performed comparing SZ patients to SZ + CB patients and patients with CIP. Comparisons were made between the three groups using chi-square test (χ^2) or Fisher's exact test (F) for categorical data and ANOVA variance analysis or Kruskal-Wallis test for continuous data, depending on whether assumptions of normality and sample size were met. The Bonferroni test was used for post-hoc analysis and multiple comparison between the three clinical groups. The Kolmogorov-Smirnov test was used to

check normality. Inter-group effect size was calculated using Cohen's d (d). All tests were bilateral with a $p < 0.05$. The analyses were performed with SPSS 20.0 (*Statistical Package for the Social Sciences*, 2011).

Results

Clinical differences

As Table 2 shows, the SZ group had a higher age of first admission for psychosis compared to the other groups. In the post-hoc analysis, this difference was found both with the CIP group ($t = -3.44$; $p = 0.001$; $d = 0.48$) and with the SZ + CB group ($t = -3.67$; $p < 0.001$; $d = 0.56$).

There were no differences between the groups regarding the total scores on the positive PANSS subscale. However, when comparing the different items of the subscale, there were differences in the excitability ($p < 0.001$) and hostility items ($p = 0.001$). In the post-hoc study, it was found that these differences occurred mainly between CIP and SZ groups. In direct comparison, the CIP group had a higher score in excitability with respect to the SZ group ($t = 4.64$; $p < 0.001$; $d = -0.76$) but not to the SZ + CB group ($p = 0.70$). As regards hostility, the CIP group again scored higher than the SZ group ($t = 3.52$; $p = 0.001$; $d = -0.56$) as did the SZ + CB group with respect to the SZ group ($t = 2.43$; $p = 0.01$; $d = -0.008$). Conversely, the SZ + CB group had a higher score on the negative PANSS subscale, a difference which did not occur with the SZ group ($p = 0.54$) but with the CIP group ($t = -8.14$; $p < 0.001$; $d = 1.22$).

Finally, in the SZ group dysphoric mood was less frequent ($\chi^2 = 12.92$; $p = 0.02$; $d = 0.13$), as was hetero-aggressive behavior ($\chi^2 = 23.75$; $p < 0.001$; $d = 0.25$). The SZ and SZ + CB groups had a higher frequency of auditory hallucinations ($\chi^2 = 6.60$; $p = 0.037$; $d = 0.08$), a lower frequency of expansive mood ($\chi^2 = 30.46$; $p < 0.001$; $d = 0.1$), and greater disorganization with respect to the CIP group ($\chi^2 = 4.34$; $p = 0.11$; $d = 0.14$).

Differences in follow-up

Table 3 reflects the following results: in the SZ and SZ + CB group there was less interepisodic remission and more relapse during follow-up with respect to the CIP group. In the post-hoc analysis, the difference in relapse occurred between the SZ + CB group and the CIP group ($t = -2.92$; $p = 0.05$; $d = 0.59$). In both subgroups of patients with schizophrenia, there were no differences in development nor in the percentage of relapses. There were no differences in follow-up time either.

Differences in drug use

With respect to drug use (see Table 4), there were more alcohol users in the SZ + CB group, but the age of habitual drinking was higher. They also smoked more. There were no differences regarding cannabis use compared to

the CIP group. On the ASI scale, there was greater severity in the area of drug use with induced cases ($M = 6.5$; $SD = 1.3$ vs. $M = 5.2$; $SD = 1.8$; $F = 6.7$, $p < 0.001$; $d = -0.78$) and greater severity in the medical area in the SZ + CB group ($M = 1.1$; $SD = 0.5$ vs. $M = 1.6$; $SD = 1.3$; $F = 27.7$, $p = 0.002$; $d = 0.55$).

In the SZ group there were fewer users of tobacco, alcohol and cocaine compared to the SZ + CB group. On the ASI scale there was greater severity in the SZ + CB group in alcohol ($M = 2.2$; $SD = 1.5$ vs. $M = 1.4$; $SD = 1.1$; $F = 8.6$, $p < 0.001$; $d = -0.7$), drugs ($M = 5.2$; $SD = 1.9$ vs. $M = 1.8$; $SD = 1.4$; $F = 7.8$, $p < 0.001$; $d = -2.22$), and employment ($M = 5.4$; $SD = 1.8$ vs. $M = 4.3$; $SD = 1.9$; $F = 6.6$, $p < 0.001$; $d = -0.58$).

Age of first admission adjusted by sex

Since the age of hospital admission may be influenced by sex, a stratified analysis was performed. Statistical significance was maintained in men ($F = 5.08$; $p = 0.007$), with means of 25.9 ($SD = 5.6$) in the CIP group, 25.2 ($SD = 5.9$) in SZ + CB, and 28.7 ($SD = 8.5$) in SZ. The post-hoc study showed a difference between the CIP and SZ groups ($t = -2.23$; $p = 0.04$; $d = 0.37$) and between the SZ + CB and SZ groups ($t = -2.94$; $p = 0.01$; $d = 0.45$), but not between both groups of users. Statistical significance was not found in women, probably due to poor representation in the SZ + CB group ($n = 3$).

Discussion

Most recent studies examine the demographic and clinical differences between two groups of patients: schizophrenia patients who use cannabis versus those who do not, and do not consider whether induced psychosis or established schizophrenia is involved. As to studies addressing the concept of induced psychosis, most include patients with a diagnosis of substance-induced psychosis and those with a diagnosis of schizophrenia and substance abuse (Caton, Samet & Hasin, 2000; Dawe et al., 2011; Fraser et al., 2012) regardless of whether the psychosis was induced by cannabis or other drugs. Only two studies also consider a third cohort of patients: those with a schizophrenia diagnosis who had no abuse or dependence on other substances (Dragogna et al., 2014; Weibell et al., 2013). Of these, only Dragogna et al. (2014) specifically speak of cannabis as a substance of abuse and of cannabis-induced psychosis. In addition, due to the sample inclusion criteria, research to date has been heterogeneous with respect to the selected sample, including FPE with or without cannabis use, schizophrenia with or without a history of cannabis, or comparing chronic patients with acute episodes in terms of cannabis use or the results of a toxicological analysis.

The concept used by some authors of "cannabis psychosis" implies the presence of a specific psychopathology of a potentially different psychotic subtype. In a review

Table 2. *Clinical characteristics.*

	Total (n = 307)	CIP (n = 69)	SZ+CB (n = 57)	SZ (n =181)	Test value
Age of first admission, mean (SD)	28.9 (9.8)	26.1 (6.4)	25.3 (6.2)	31.1 (11.2)	$F = 11.56$ $p < 0.001^{***}$
Number of previous admissions, mean (SD)	2.6 (3.7)	0.6 (1)	2.2 (2.2)	3.5 (4.4)	$F = 16.56$ $p < 0.001^{***}$
Positive PANSS mean (SD)	23.3 (7.1)	24.3 (5.6)	23.3 (7.2)	22.9 (7.6)	$F = 0.81$ $p = 0.445$
Negative PANSS mean (SD)	20.4 (8.9)	12.9 (5.9)	22.1 (8.9)	23 (8.3)	$F = 32.24$ $p < 0.001^{***}$
Disorganization (thought and behavior)	69 (22.5%)	10 (14.5%)	17 (29.8%)	42 (23.2%)	$\chi^2 = 4.34$ $p = 0.114$
Suicide					
Ideation	28 (9.1%)	5 (7.2%)	8 (14%)	15 (8.3%)	
Gestures	23 (7.5%)	5 (7.2%)	2 (3.5%)	16 (8.8%)	$\chi^2 = 4.53$ $p = 0.605$
Attempts	22 (7.2%)	4 (5.8%)	3 (5.3%)	15 (8.3%)	
Delirium					
Paranoid	275 (89.6%)	65 (94.2%)	50 (87.7%)	160 (88.4%)	$\chi^2 = 2.06$ $p = 0.357$
Reference	189 (61.9%)	48 (69.6%)	34 (59.6%)	107 (59.1%)	$\chi^2 = 2.41$ $p = 0.299$
Megalomaniac	66 (21.5%)	16 (23.2%)	15 (26.3%)	35 (19.3%)	$\chi^2 = 1.40$ $p = 0.496$
Mystical	74 (24.1%)	17 (24.6%)	12 (21.1%)	45 (24.9%)	$\chi^2 = 4.68$ $p = 0.321$
Somatic	23 (7.5%)	4 (5.8%)	3 (5.3%)	16 (8.8%)	$\chi^2 = 1.16$ $p = 0.557$
Other	95 (30.9%)	16 (23.2%)	15 (26.3%)	64 (35.4%)	$\chi^2 = 4.16$ $p = 0.125$
Hallucinations					
Auditory	222 (72.3%)	41 (60.3%) R.C = -2.3	43 (75.4%) R.C = 0.2	138 (76.2%) R.C = 1.7	$\chi^2 = 6.60$ $p = 0.037^*$
Visual	20 (6.5%)	6 (8.7%)	2 (3.5%)	12 (6.6%)	$\chi^2 = 1.38$ $p = 0.5$
Somatic	46 (15%)	10 (14.5%)	4 (7%)	32 (17.7%)	$\chi^2 = 3.88$ $p = 0.143$
Other	13 (4.2%)	3 (4.3%)	1 (1.8%)	9 (5%)	$\chi^2 = 1.11$ $p = 0.574$
Predominant mood state					
Dysphoria	77 (25.1%)	23 (33.3%) R.C = 2.1	22 (38.6%) R.C = 2.3	32 (17.7%) R.C = 3.8	
Depressive	65 (21.2%)	9 (13%) R.C = -1.9	12 (21.1%) R.C = 0.0	44 (24.3%) R.C = 1.6	$\chi^2 = 30.46$ $p < 0.001^{***}$
Mania	41 (13.4%)	18 (26.1%) R.C = 3.1	7 (12.3%) R.C = 0.2	16 (8.8%) R.C = -2.8	
Hetero-aggression					
Mild	37 (12.1%)	8 (11.6%)	7 (12.3%)	22 (12.2%)	
Moderate	89 (29%)	28 (40.6%)	20 (35.1%)	41 (22.7%)	$\chi^2 = 23.18$ $p < 0.001^{***}$
Severe	17 (5.5%)	4 (5.8%)	8 (14%)	5 (2.8%)	

Note. SD = standard deviation. χ^2 = chi-square. F = ANOVA value. CR = corrected residuals.

* significant values $p < 0.05$; ** very significant values $p < 0.01$; *** highly significant values $p < 0.001$.

Table 3. Follow-up characteristics.

	Total (n = 205)	CIP (n = 43)	SZ+CB (n = 33)	SZ (n = 102)	Test value
Interepisodic remission	117 (57.1%)	43 (100%)	17 (51.5%)	57 (55.8%)	$\chi^2 = 49.32$ $p < 0.001^{***}$
Relapse	112 (54.6%)	13 (29.5%) R.C = -3.2	25 (64.1%) R.C = 1.8	74 (54.4%) R.C = 1.2	$\chi^2 = 11.41$ $p = 0.003^{**}$

Note. χ^2 = chi-square. CR = corrected residuals.

* significant values $p < 0.05$; ** very significant values $p < 0.01$; *** highly significant values $p < 0.001$.

Table 4. Substance use.

	CIP (n = 69)	SZ+CB (n = 57)	SZ (n = 181)	Test value
Cannabis: age of habitual use, mean (SD)	18 (5)	16.4 (3.4)		$F = 1.99$ $p = 0.107$
Cannabis: maximum joints/day, mean (SD)	7.7 (6.2)	7.2 (5.3)		$F = 0.82$ $p = 0.697$
Tobacco: lifetime	65 (94.2%)	53 (93%)	102 (56.4%)	$\chi^2 = 50.9$ $p < 0.001^{***}$
Tobacco: cigarettes/day, mean (SD)	19.1 (11.8)	24.1 (13.9)	25.7 (16.2)	$F = 3.07$ $p = 0.049^*$
Alcohol without use/dependence data	22 (34.9%)	26 (50%)	28 (16.5%)	$\chi^2 = 25.71$ $p < 0.001^{***}$
Alcohol age of habitual use, mean (SD)	15.6 (1.9)	16.8 (3.5)	18.8 (3.1)	$F = 2.85$ $p = 0.073$
Alcohol maximum SDUs, mean (SD)	2.2 (6.4)	3.4 (4.7)	0.6 (1.6)	$F = 7.93$ $p < 0.001^{***}$
Alcohol days/week, mean (SD)	2.1 (2.4)	3.2 (2.7)	1.1 (2.1)	$F = 10.7$ $p < 0.001^{***}$
Cocaine without use/dependence data	7 (10.9%)	11 (20.8%)	0 (0%)	$\chi^2 = 33.52$ $p < 0.001^{***}$
Substance use remission	38 (55.1%)	35 (61.4%)		$\chi^2 = 86.64$ $p < 0.001^{***}$

Note. SD = standard deviation. χ^2 = chi-square. F = ANOVA value. SDU = standard drink units.

* significant values $p < 0.05$; ** very significant values $p < 0.01$; *** highly significant values $p < 0.001$.

of the literature with eight selected studies, seven of these observed at least one statistically significant clinical difference. The authors thus conclude that it is not that there is no “cannabis psychosis”, only that from the psychopathological point of view it is not qualitatively different from other forms of psychosis (Baldacchino et al., 2012). The data in the present article supports this conclusion, finding no relevant clinical differences that would help establish an entity distinct from other psychoses.

The sociodemographic differences observed are as expected. Cannabis users are more often male and young (Kavanagh et al., 2004). Data on sex, marital status, employment status are similar to other studies (Dawe et al., 2011).

No differences were observed between the groups regarding family history of psychosis, which supports the role of family vulnerability to the development of psychosis that can be precipitated by cannabis use, and thus highlights the importance of preventing cannabis use in subjects at high risk of developing psychosis. Similarly, oth-

er authors have supported the idea that individuals with cannabis-induced psychosis are genetically similar to those with schizophrenic disorders (Wilson, Szigeti, Kearney & Clarke, 2018), and high rates of family history of psychosis have been described in patients with schizophrenia and cannabis use (Bersani, Orlandi, Kotzalidis & Pancheri, 2002). This supports a possible interaction between cannabis use and genetic vulnerability to psychosis in increasing the risk of psychosis in these patients. However, differences regarding family history of substance use disorders were found.

Fewer negative symptoms were observed in the induced conditions, but there were no differences between the two groups of patients with schizophrenia. One of the findings reported more consistently in the literature is the presence of fewer negative symptoms in cannabis and drug users in general (Baldacchino et al., 2012). In any case, it is not normally considered whether or not they are induced or schizophrenic, nor is the progress of the clinical picture.

The data in the present study suggest that there are indeed fewer negative symptoms in induced disorders, as other authors have pointed out (Caton et al., 2005), but when considering the presence of schizophrenia, this difference disappears. Similarly, in studies which only consider the presence of schizophrenia this difference depending on use was also not observed (Boydell et al., 2007).

During the acute phase of psychosis, there was no difference in the total score on the positive PANSS subscale across the three groups of patients, as reported by other authors (Boydell et al., 2007; Stone et al., 2014). However, a higher score was observed in the items of excitability and hostility in those induced compared to the other groups, as described by other authors (Baeza et al., 2009). Our study further observed that differences also existed in hostility between both groups of patients with schizophrenia.

One of the clinical characteristics seen as related to induced psychosis, the lower frequency of auditory hallucinations (Caton et al., 2005; Drake et al., 2011), was also observed in our study. Patients with disorganization were also less frequent in the induced condition. However, there were no differences in disorganization in schizophrenia with or without cannabis use. The presence of hetero-aggressive behaviors occurred more frequently in both groups of users, which has also been described in other psychotic patients with addictions (Fraser et al., 2012), so it can be seen as related to the presence of drug use. In a sample of patients with schizophrenia and cannabis use, there was greater hostility than in non-users (Caspari, 1999).

Regarding the predominant mood during the acute phase, more dysphoria was observed in the SZ + CB group and more manic symptoms in the induced cases. Another characteristic which has been suggested in induced cases is the presence of an expansive mood. Other studies have found that cannabis users had more overt symptoms (McGuire et al., 1994; Núñez & Gurpegui, 2002; Rottamburg, Ben-Arie, Robins, Teggin & Elk, 1982; Stone et al., 2014;), which was also the case in our study. One explanation is that psychotic symptoms with an expansive mood in non-users would tend to be labelled as affective psychosis or schizoaffective disorder. Other authors noted that patients with induced psychosis experience more severe manic symptoms and disruptive behavior upon arrival at the hospital than those with a primary psychotic disorder (Dawe et al., 2011). A recent study divided cannabis-induced disorders into two subtypes, cannabis-induced psychosis and cannabis-induced affective disorder (Shah, Chand, Bandawar, Benegal & Murthy, 2017), claiming that such differentiation at the time of diagnosis may be valuable in predicting the course of the disease and in deciding on a plan of treatment. However, the majority of patients with cannabis-induced psychosis which developed into psychotic disorders had high percentages of affective symptoms.

Several authors have pointed out that there are few clinical differences between patients with psychosis, regardless of cannabis use (McGuire et al., 1994). The cross-sectional assessment of the clinical picture does not permit differentiation between psychosis in cannabis users and other psychotic conditions. The few clinical differences do not allow an adequate differential diagnosis to be established exclusively through psychopathological assessment. Induced psychoses may be the initial stage of schizophrenia, since over 50% of these develop into the disease (Arendt, Rosenberg, Foldager, Perto & Munk-Jørgensen, 2005; Caton et al., 2007; Mauri et al., 2017; Sara, Burgess, Malhi, Whiteford & Hall, 2014; Starzer, et al., 2018) and once schizophrenia is established, the picture seems indistinguishable from schizophrenia in non-users (Boydell et al., 2007). Therefore, taking whether or not they are induced psychoses into consideration in clinical studies may partly explain the observed discrepancies.

Another aspect to consider is the presence of other comorbid addictive disorders, since polydrug use is common. Thus, by excluding the effects of drug abuse or dependence on patients with schizophrenia and cannabis dependence, the impact of cannabis use can be much better analyzed (Dubertret, Bidard, Adès & Gorwood, 2006). Therefore, one of the strengths of this study is the exclusion of abuse or dependence criteria involving drugs other than cannabis.

The age of first admission was lower in the two groups of users, in line with multiple studies (Dawe et al., 2011; Van Dijk, Koeter, Hijman, Kahn & Van den Brink, 2012) which suggest that cannabis use is at least one precipitating factor of psychosis. In a meta-analysis, it was pointed out that it was the only drug capable of bringing forward the age of onset of psychosis (Large et al., 2011). Given its effect on this variable, the sample was stratified by sex. In men, the youngest age of first admission was confirmed in the user groups. It has been reported that cannabis is associated with early onset of symptoms compared to other drugs, especially among women (Allegrì et al., 2013), and the differences in the age of onset according to sex is lower in cannabis users, although other authors observe an advance independent of sex (Dekker et al., 2012).

No differences were observed in follow-up between the SZ + CB and SZ groups. Users usually have more relapses and poor treatment adherence (Zammit et al., 2008). In several studies, cannabis use was not associated with psychopathological differences, but relapses were significantly higher among users (Caspari, 1999; Van Dijk et al., 2012). Given the small number of patients followed up in the SZ + CB group, these differences may not have been detectable in this study.

This study has several strengths: it compares the socio-demographic, clinical, follow-up and prognostic characteristics across three groups of patients (CIP, SZ + CB, SZ),

thus making it possible to differentiate between subjects with induced psychosis and patients with chronic psychotic disorders. Although there are few psychopathological differences between cannabis-induced psychosis and schizophrenia with cannabis use, it is fundamental to differentiate between them in the different studies and in clinical practice given that in the case of the former the prognosis is more favorable and antipsychotic treatment can be seen as a short-term treatment, with an emphasis on the treatment of drug abuse or dependence. Thus, cessation of cannabis use can in some cases lead to complete remission of the condition, without a chronic psychotic disorder setting in, which, moreover, seems indistinguishable from schizophrenia once established. In addition, the study used standardized assessments based on drug use, sociodemographic aspects and psychopathology, as well as operational diagnostic criteria for clinical diagnoses. Finally, the sample size allowed us to analyze exclusively the presence of cannabis abuse or dependence criteria, thereby eliminating the confounding effect of abuse or dependence on other drugs, although not their sporadic use.

However, the findings must be interpreted taking into account certain methodological limitations. This study only included patients who had contact with psychiatry services, excluding all patients who did not, such as those attending addiction services. In addition, substance use data were based mainly on what the patients themselves reported. Induced psychoses were not compared with primary FPEs to try to differentiate which differential characteristics of induced psychoses may be due to cannabis use and which to the fact of being initial episodes, such as the presence of negative symptoms. Furthermore, there are no data on continuing use during follow-up, and patients dropped out during this period.

In conclusion, the clinical differences of the CIP group were few compared to the other groups: there was a greater presence of affective disorders of the overt type, a lower percentage of auditory hallucinations and negative symptomatology and, finally, more aggressive behaviors. However, these clinical differences disappear once schizophrenia establishes itself. In addition, patients with cannabis dependence have an earlier age of onset of psychosis, suggesting at least a precipitating role of this substance in the onset of psychotic disorders. Future studies should consider differentiating between induced psychosis and schizophrenia with cannabis abuse or dependence.

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FA set the objectives, designed the literature search, wrote the first draft of the article, and consecutive drafts were reviewed by DR, SS, RR and GR. FA contributed to the complete design of the study and the interpretation of the data. FA and DR contributed in defining the data analysis

procedures and carrying out the statistical analysis. FA and SS participated in data collection. All authors reviewed the draft and approved the final version.

Conflict of interests

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