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First episode psychosis with and without the use of cannabis and synthetic cannabinoids: Psychopathology, global functioning and suicidal ideation and antipsychotic effectiveness

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ABSTRACT

Background: Natural Cannabis (NC) and Synthetic Cannabinoids (SCs) use can increase the risk of developing psychotic disorders and exacerbate their course.
Aims: To examine the differences between psychoses not associated with cannabis use and those associated with NC and SCs use, evaluating psychotic symptoms, global functioning, dissociative symptoms and suicidal ideation.
Methods: The sample of 61 patients with First Episode Psychosis (FEP) was divided into 3 groups: non-Cannabis users (non-users, N = 20); NC users (THC-users, N = 21); SCs users (SPICE-users, N = 20). Each group was assessed at FEP and after 3 and 9 months through specific psychopathological scales.
Results: THC-users, and even more SPICE-users, displayed much more severe positive symptoms than non-users. Negative symptoms were higher among non-users. After 9 months the non-users had recovered significantly better than SPICE-users in their global functioning. Dissociative symptoms were significantly greater in substance users. Finally, suicidal ideation was higher in SPICE-users than in both THC-users and non-users.
Discussion: The psychoses induced by NC and SCs showed different symptomatic pictures and outcomes from each other and when compared to the psychoses not associated with the use of substances; such knowledge could be relevant in identifying a specific drug treatment.

1. Introduction

Nowadays, abundant literature supports the existence of a strong link between cannabis use and psychosis (Henquet et al., 2005; Marconi et al., 2016; Moore et al., 2007). Cannabis is the most commonly used illicit psychoactive substance; its widespread consumption is second only to alcohol and tobacco (United Nations, 2022). THC, the main psychoactive component of Natural Cannabis (NC), is a partial agonist of the cannabinoid receptors CB1 and CB2 and it is believed to be responsible for the risk of developing psychotic symptoms (Iseger and Bossong, 2015). Approximately 8–12% of regular cannabis users also develop Cannabis Use Disorder (CUD) (Moss et al., 2012; Perkonigg et al., 2008), defined by the DSM-5 as "a problematic pattern of cannabis use leading to clinically significant impairment or distress" (American Psychiatric Association, 2013).

Furthermore, in recent times, a multitude of Synthetic Cannabinoids (SCs), a heterogeneous group of psychoactive drugs often classified as "Spice" or with other brand names (e.g., Kronic, Northern Lights, K2 and Kaos), have emerged in the drug market; these have quickly become the largest and most widespread class of New Psychoactive Substances (NPS) utilized (Martinotti et al., 2017a). They are new drugs, or psychotropic substances, not controlled by the Conventions on Narcotics or

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the Convention on Psychotropic Substances, yet they can still pose a risk to public health (Martinotti et al., 2021b). Internet has become an important marketplace for NPS, nonetheless they are also easily found in convenience stores and "head stores" (Chiappini et al., 2022). Furthermore, they are cheap and difficult to detect in routine drug screenings (Auwärter, 2009). Most SCs act as full agonists at CB1 and are therefore much more powerful than THC (ElSohly et al., 2014) with a 4–5 times higher affinity and a 40–660 times higher potency (van Amsterdam et al., 2015). In some cases, SCs may also contain other psychoactive molecules with different pharmacodynamic properties than cannabinoids.

In addition to the role of cannabinoid receptors, a dysregulation of the dopaminergic system appears to be involved in the genesis of NC and SCs induced psychosis (D'Souza et al., 2009).CB1R and dopamine D2 receptors are expressed together in many brain regions, where convergent signal transduction occurs. The effect of CB1R activation in increasing mesolimbic dopaminergic activity may be one explanation for the activity of THC in promoting positive psychotic symptoms. Finally, cannabinoids appear to interact with the GABAergic and glutamatergic systems (D'Souza et al., 2009). Interactions of the CB1R and GABAergic systems, due to elevated CB1R expression on GABAergic interneurons, may in fact explain the psychotomimetic effects of THC. Also, cannabinoids reduce glutamatergic synaptic transmission in hippocampus, prefrontal cortex, nucleus accumbens and amygdala. This effect could be compared to that of compounds such as phencyclidine and ketamine, which induce NMDA receptor hypofunction thus providing a mechanism by which cannabinoids could induce psychosis (Martinotti et al., 2021a).

In most first episode psychosis (FEP) studies, cannabis-related disorders are highly prevalent (Schimmelmann et al., 2012). The link between cannabis use and the development of schizophrenia has been amply demonstrated. Epidemiological evidence suggests that the use of cannabis increases the risk of developing psychotic disorders (di Forti et al., 2019; di Forti et al., 2009), anticipates the age of onset and exacerbates their course (Ringen et al., 2016a; Seddon et al., 2016a). Recent evidence shows that cannabis users have a two (Henquet et al., 2005; Moore et al., 2007) to four (Marconi et al., 2016) times greater risk of developing a psychotic disorder than non-users. Approximately one in every four individuals with schizophrenia has a concurrent diagnosis of CUD (Lowe et al., 2019).

Numerous studies have already characterized cannabis associated psychosis. First of all, FEP can occur earlier in those who use cannabis than in those who do not (Bhavsar, 2015; Mané et al., 2015). From a psychopathological perspective, most evidence suggests that FEP patients using cannabis experience more positive than negative symptoms when compared to those not utilizing cannabis (Quattrone et al., 2020a; Ricci et al., 2021b, 2021a; Ringen et al., 2016a; Seddon et al., 2016a). Moreover, cannabis-associated psychosis may be characterized by a greater number of days of hospitalization (Baudin et al., 2016), a lower response to therapy (Patel et al., 2016), lower pharmacological compliance (Schoeler et al., 2017) and a higher relapse rate (Hasan et al., 2020). Patients with a psychosis associated with CUD have also a worse global functioning, measured through the Global Assessment of Functioning (GAF) scale, when compared with psychotic subjects who have never used cannabis (Ringen et al., 2016a; Seddon et al., 2016a).

Furthermore, data show SC use to be associated with a higher risk of developing psychosis, acute psychosis, persistent psychotic disorder and the relapse/worsening of a pre-existing psychosis (Castaneto et al., 2014; Cohen and Weinstein, 2018; Karila et al., 2016; Papanti et al., 2013; Spaderna et al., 2013; Tait et al., 2016). Increasing cases of acute psychosis after the use of SCs, labelled as "Spiceophrenia" (Papanti et al., 2013), have been reported and a higher incidence of psychosis has been found in psychiatric patients who have used SCs rather than NC (71.4% vs 61.5%) (Welter et al., 2017). The psychotic symptomatology associated with the use of SCs is characterized by perceptual alterations, delusions, paranoia, catatonia, depersonalization, dissociation and auditory and/or visual hallucinations. Also, greater positive symptoms, and fewer negative symptoms, were found in these forms of psychosis (Akram et al., 2019; Altintas et al., 2016; Welter et al., 2017).

Dissociative symptoms may also occur in psychotic disorders. As of today, the dissociative dimension in psychosis and the relationship between cannabis use and dissociative symptoms has been scarcely investigated (Sideli et al., 2020). Recent studies reveal that FEP associated with cannabis use shows higher levels of dissociative experiences (Ricci et al., 2021b). Dissociative symptoms also appear to be higher in SCs users than in NC users; the former also display worse long-term outcomes (Martinotti et al., 2017b; Murray et al., 2016a). Furthermore, it was observed how an acute consumption of SCs causes a dissociative effect expressed as alterations in the internal and external perception of oneself and symptoms such as amnesia, derealization and depersonalization (Theunissen et al., 2019).

Dissociative symptoms/experiences can also contribute to the risk of self-harm, suicidal ideation and suicide attempts (Calati et al., 2017); cannabis is also able to increase the magnitude of impulsivity. In particular, self-injurious behaviors are triggered by SCs. Data on the correlation between cannabis use and suicide risk in patients with schizophrenia, or other schizophrenia spectrum disorders, are still controversial, but several studies show that there is a positive correlation, particularly in regard to FEP (Ricci et al., 2022).

Finally, if a lot is already known about the relationship between cannabis and psychosis, little or nothing is known about the differences between psychoses associated with the use of NC and those associated with the use of SCs. The different mechanism of action of these two substances suggests that they can cause psychotic pictures with peculiar characteristics.

The main objective of our study was to investigate the differences between psychoses not associated with cannabis use and those associated with the use of NC and SCs, in terms of (a) psychotic symptoms (b), global functioning (c), dissociative symptoms and (d) suicidal ideation, evaluated through the PANSS, the GAF scale, the DES-II and the Scale for Suicidal Ideation (SSI). This comparison was made at baseline and at three and nine months after a specific antipsychotic treatment was administered. The secondary objectives of the study were: (a) to evaluate a possible correlation between dissociative symptomatology and suicidal ideation; (b) to evaluate the role of a comorbid use of other substances.

2. Materials and methods

2.1. Participants

All subjects included in the study had experienced a FEP; they were recruited throughout various psychiatric inpatient facilities in the Italian regions of Lazio, Val d'Aosta and Piemonte between 2013 and 2022. Specifically, the term FEP refers to the first time a patient displays positive psychotic symptoms of delusions and/or hallucinations or marked disorganized behavior.

The inclusion criteria were (1) age, between 16 and 50 years; (2) diagnosis of schizophrenia spectrum disorder or other psychotic disorders (performed at baseline and confirmed at six months), with or without concurrent cannabis/SCs use disorder (depending on the study group to which they belong), according to the diagnostic criteria of the DSM-5; (3) frequent (at least 2-3 times a week) anamnestically clearly prevalent use of NC and SCs for individuals with NC/SCs use disorder; (4) no lifetime use of NC/SCs for individuals without NC/SCs use disorder and (5) home residence in the recruitment area.

The exclusion criteria were (1) previous contact with mental health services for psychosis; (2) prior treatment with antipsychotic medications; (3) a diagnosis of intellectual disability (intelligence quotient below 70); (4) any lifetime history of significant medical illness; (5) non-sporadic use (greater than once or twice a month) of substances other than cannabis (cocaine, heroin, 3,4-methylenedioxymethamphetamine

[MDMA], and ketamine); (6) alcohol use disorder.

After receiving a complete description of the study, 85 participants gave informed written consent and were recruited over a period of nine years, to form three groups of similar size and comparable by gender and age. During the follow up, 24 patients, approximately 3 per year, were lost with an attrition rate of approximately 28.2 %.

All patients received antipsychotic treatments with different drugs, in line with clinical guidelines (Gaebel et al., 2011) and on the basis of each patient's individual case history, in a real-world setting. Each subject was prospectively evaluated after three months (T1) and nine months (T2), which allowed to assess the first effects of treatment and abstention from the use of NC and SCs (T1) and the condition after a period of relative stabilization (T2).

Substance use was assessed by a thorough medical history and by the Drug Abuse Screening Test-10 (DAST-10), a valid and reliable screening tool for drug use and drug use-related problems. It's a brief self-report questionnaire, the abbreviated form of the original DAST-28 and the longer DAST-20 (Skinner, 1982), and it is not specific for certain substances. NC/SCs use was assessed with the Cannabis Use Disorders Identification Test-Revised (CUDIT-R) (Adamson et al., 2010), an 8-item measure set to screen for CUD. It was developed from the original 10-item CUDIT (Adamson and Sellman, 2003), a direct modification of the Alcohol Use Disorders Identification Test (AUDIT). The type of cannabis used was detected through clinical interviews (Saunders et al., 1993) with patients and family members, who also went to investigate activities, habits (for example buying substances on the internet) and trips made. All these elements can give indications about the type of substance with which the patient has found himself having to deal the most.

The sample was divided in 3 groups, based on whether or not cannabis was used, and eventually which type:

- A group of non-Cannabis users (non-users).
- A group of cannabis-users who used Natural Cannabis (THC-users).
- A group of subjects who used Synthetic Cannabinoids (SPICE-users).

2.2. Measurements

The following psychopathological scales were administered at T0, T1 and T2:

- The PANSS (Kay et al., 1987), a 30-item questionnaire, divided into 3 subscales (i.e., positive, negative, and general psychopathology) measuring positive and negative symptoms and the general severity of the illness (Kay et al., 1987).
- The GAF scale (Jones et al., 1995), which is a clinician-rated scale to measure the level of psychological, social and occupational functioning on a continuum from 0 to 100 (Pedersen et al., 2018).
- The DES-II (Carlson et al., 2018), a self-report questionnaire that measures dissociative experiences, such as derealization, depersonalization, absorption and amnesia (Saggino et al., 2020).The DES (Bernstein and Putnam, 1986)comprises 28 items based on the assumption of a 'dissociative continuum' ranging from a mild alteration to severe dissociation.
- The SSI (Beck et al., 1979), a 19-item scale to measure the intensity, pervasiveness and characteristics of suicidal ideation in adults. It also aims at assessing the risk of later possible suicide attempts in individuals who have thoughts, plan or wish to commit suicide.

2.3. Statistical analysis

Statistical analyses were performed using IBM SPSS windows version 22. Shapiro–Wilk test and an estimation of the values of asymmetry and excess coefficients were used to determine whether the data were normally distributed across the whole group and the sub-groups. Parametric tests were used as data were found to be normally distributed. Groups were compared using one way ANOVA test, Tukey post-hoc test, Chi-square test and Fisher's exact test, as needed. ANOVA test was used for continuous variables, whereas Chi-square test and Fisher's exact test were used for categorical variables. Correlations were calculated using Pearson's r. The quantitative parameters were presented as mean ± standard deviation (SD) and the qualitative parameters as number and percentage per class. The significance level was set for $p < 0.05$.

2.4. Ethics

All participants provided written informed consent after receiving explanations of the study. The study was conducted according to the principles outlined in the Declaration of Helsinki (World Medical Association, 2013). The study was approved by the SS. Annunziata Hospital – University G. d'Annunzio Ethical Committee (reference code: CHPN189, 26 January 2012).

3. Results

3.1. Demographical and clinical characteristics of the sample

A total of 61 patients completed all of the follow-up assessments and were included in the analysis, with a mean age of 23.98 years (SD ± 4.61). Of these, about one third of the sample ($n = 20$) was part of the non-user group, roughly another third ($n = 21$) were NC-user and the remaining subjects ($n = 20$) were SPICE-users. The three groups were comparable in terms of age ($p = 0.079$) and gender ($p = 0.373$). The

Table 1
Demographical and clinical characteristics of the sample.

Variables	Non-users ($n = 20$)	THC-users ($n = 21$)	SPICE-users ($n = 20$)	Total ($n = 61$)	Statistic (F/Chi-square)	p
Age, years (SD)	25.10 (4.30)	24.71 (5.31)	22.10 (3.67)	23.98 (4.61)	2.650	0.079
Sex, female, n (%)	10 (50)	13 (62)	8 (40)	31 (51)	1.975	0.373
Marital status, n (%)						
Single	15 (75)	17 (81)	18 (90)	50 (82)		0.502
In a relationship/ married	5 (25)	4 (19)	2 (10)	11 (18)		
Age of onset of cannabis use, years (SD)	-	18.38 (2.8)	19.55 (2.67)	18.95 (2.76)	1.870	0.179
Use of other substances, n (%)	7 (35)	12 (57)	8 (40)	27 (44)	2.255	0.324
Use of cocaine, n (%)	5 (25)	6 (29)	6 (30)	17 (28)		1.000
Use of heroin, n (%)	4 (20)	7 (33)	1 (5)	12 (20)		0.071
Use of MDMA, n (%)	1 (5)	5 (24)	5 (25)	11 (18)		0.195
Use of ketamine, n (%)	3 (15)	4 (19)	4 (20)	11 (18)		1.000
Antipsychotic medication						
1st generation	2 (10)	4 (19)	4 (20)	10 (16)		0.977
2nd generation -pines	2 (10)	2 (9)	2 (10)	6 (10)		
2nd generation -dones	5 (25)	6 (29)	4 (20)	15 (25)		
Partial agonists	11 (55)	9 (43)	10 (50)	30 (49)		

Data are reported as mean (SD) or as n (%), as appropriate. Statistics: one-way ANOVA, Chi-square test and Fisher Exact test.

participants' characteristics at baseline are detailed in Table 1.

3.2. Psychometric scores

Psychometric scores at baseline (T0), T1 and T2 were compared between the three groups. PANSS positive was higher among SPICE-users in the three evaluations with respect to non-users and at T1 and T2 with respect to THC-users. PANSS negative was higher among non-users in the three evaluations with respect to THC-users and SPICE-users. There was no difference between the three groups regarding PANSS general scores.

The score of the GAF scale was greater in the non-users compared to SPICE-users.

The scores of DES-II were higher at T0, T1 e T2 in THC-users with respect to non-users and among SPICE-users with respect to non-users.

Finally, SSI scores were greater in SPICE-users than both THC-users and non-users.

We then proceeded to evaluate how the scores of the various scales varied between the last evaluation and the one made at baseline throughout all three groups, to then compare those variations between groups: significant differences were found for PANSS positive ($F = 6.931$; $p = 0.002$), the GAF scale ($F = 4.813$; $p = 0.012$) and the DES-II ($F = 6.876$; $p = 0.002$).

For positive PANSS, this variation was less in SPICE-users than both THC-users and non-users. For the GAF scale it was higher in non-users than in SPICE-users and for the DES-II in the same group than in THC-users.

The complete data are reported in Table 2.

3.3. Correlation between dissociative symptomatology and suicidal ideation

There was no correlation between the degree of dissociation, as measured with the DES-II and suicidal ideation, as measured with SSI, as shown in Table 3.

3.4. Use of other substances

No correlations were found between the use of substances other than NC and SCs and the outcome of the psychotic pathology within the time frames taken into consideration (see Table 4). By outcome we mean an improvement or worsening in the scores of the scales.

4. Discussion

This paper offers a first attempt at comparing users of natural (THC-users) and synthetic cannabis (SPICE-users) in terms of psychotic symptoms at onset. Other points of novelty are represented by the specific evaluation of suicidality in such populations and the possible therapeutic response of different groups of antipsychotic treatments in real-life scenarios.

Moreover, we tried to evaluate the role of SCs in relation to the specific symptom of dissociation, an area already investigated by our group in previous studies performed among cannabis users (Ricci et al., 2021a, 2021b).

In line with the existing literature, more severe positive symptoms were found in THC-users, and even more in SPICE-users (Quattrone et al., 2020b; Ringen et al., 2016a; Seddon et al., 2016a), than in non-users (Escelsior et al., 2021; Kolla and Mishra, 2018; Ricci et al., 2021b; Welter et al., 2017). However, it should be noted that at 9 months these symptoms were less reduced among SPICE-users than among the other two groups. This is a relevant result, since it demonstrates that SCs may trigger positive symptoms (D'Souza et al., 2009; ElSohly et al., 2014; Riegel and Lupica, 2004; van Amsterdam et al., 2015) and that the modifications that they induce may be very persistent.

Table 2
Psychometric assessment between groups and within groups at different timepoints.

	Non-users (n = 20)	THC-users (n = 21)	SPICE-users (n = 20)	Statistic (F)	p	Tukey Post-Hoc
PANSS - positive						
T0	23.60 (4.41)	24.57 (4.48)	27.50 (3.10)	5.030	0.010	SPICE-users > Non-users
T1	21.45 (4.33)	22.10 (4.25)	26.10 (3.54)	7.733	0.001	SPICE-users > Non-users SPICE-users > THC-users
T2	18.35 (3.62)	19.90 (4.27)	25.60 (4.02)	18.446	0.000	SPICE-users > Non-users SPICE-users > THC-users
Difference T2-T0	-5.25 (4.45)	-4.67 (2.06)	-1.90 (2.02)	6.931	0.002	SPICE-users < Non-users SPICE-users < THC-users
P	<0.001	<0.001	<0.001			
PANSS - negative						
T0	20.30 (3.56)	17.43 (2.80)	15.55 (2.16)	13.657	0.000	Non-users > THC-users Non-users > SPICE-users
T1	19.45 (3.09)	16.52 (2.89)	14.15 (2.68)	16.868	0.000	Non-users > THC-users > SPICE-users
T2	18.45 (3.52)	15.14 (2.71)	12.85 (3.22)	15.910	0.000	Non-users > THC-users Non-users > SPICE-users
Difference T2-T0	-1.85 (1.95)	-2.29 (2.24)	-2.70 (2.08)	0.822	0.445	-
p	<0.001	<0.001	<0.001			
PANSS - general						
T0	52.35 (4.08)	52.62 (3.37)	53.40 (6.57)	0.254	0.777	-
T1	48.45 (3.94)	49.29 (3.84)	50.05 (6.98)	0.491	0.615	-
T2	45.75 (5.15)	45.52 (4.32)	47.10 (7.03)	0.469	0.628	-
Difference T2-T0	-6.60 (4.21)	-7.10 (3.16)	-6.30 (3.70)	0.241	0.786	-
p	<0.001	<0.001	<0.001			
GAF scale						
T0				0.613	0.545	-

(continued on next page)

Table 2 (*continued*)

	Non-users (*n* = 20)	THC-users (*n* = 21)	SPICE-users (*n* = 20)	Statistic (F)	p	Tukey Post-Hoc
	49.45 (5.56)	50.86 (4.63)	50.80 (3.21)			
T1	52.90 (5.78)	53.14 (4.15)	53.15 (3.00)	0.021	0.980	-
T2	58.65 (3.27)	56.71 (5.29)	55.30 (3.34)	3.366	0.041	Non users > SPICE-users
Difference T2-T0	9.20 (5.77)	5.86 (4.40)	4.50 (4.55)	4.813	0.012	Non users > SPICE-users
p	<0.001	<0.001	<0.001			
DES-II						
T0	24.55 (4.48)	34.19 (8.48)	34.50 (9.76)	10.306	0.000	THC-users > Non-users SPICE-users > Non-users
T1	20.90 (5.41)	32.62 (8.56)	33.20 (10.01)	14.330	0.000	THC-users > Non-users SPICE-users > Non-users
T2	18.45 (5.72)	31.86 (8.42)	30.35 (9.38)	17.055	0.000	THC-users > Non-users SPICE-users > Non-users
Difference T2-T0	-6.10 (3.23)	-2.33 (3.37)	-4.15 (3.15)	6.876	0.002	Non users > THC-users
p	<0.001	0.005	<0.001			
SSI						
T0	2.45 (1.47)	3.29 (1.71)	4.95 (2.19)	9.891	0.000	SPICE-users > Non-users SPICE-users > THC-users
T1	2.30 (1.38)	2.57 (1.03)	4.35 (1.95)	11.128	0.000	SPICE-users > Non-users SPICE-users > THC-users
T2	2.35 (1.46)	2.43 (1.12)	4.15 (2.06)	8.267	0.001	SPICE-users > Non-users SPICE-users > THC-users
Difference T2-T0	-0.10 (1.02)	-0.86 (1.35)	-0.80 (1.20)	2.492	0.092	-
p	0.666	0.009	0.008			

Data are reported as mean (SD). Statistics: one-way ANOVA, Tukey post-hoc test and paired sample t-test.

Table 3
Correlations between dissociation (DES-II) and suicidal ideation (SSI).

		DES-II T0	DES-II T1	DES-II T2
SSI T0	r	0.182	0.192	0.180
	p	0.161	0.138	0.164
SSI T1	r	0.184	0.174	0.148
	p	0.155	0.179	0.256
SSI T2	r	0.123	0.109	0.095
	p	0.345	0.401	0.467

Statistic: Pearson's r coefficient.

Table 4
Correlations between the use of other substances and symptomatology (PANSS) over time.

		Use of other substances (yes)
Δ PANSS positive	r	-0.023
	p	0.859
Δ PANSS negative	r	0.168
	p	0.197
Δ PANSS general	r	0.092
	p	0.479
Δ GAF	r	-0.119
	p	0.361
Δ DES2	r	0.201
	p	0.121
Δ SSI	r	-0.110
	p	0.399

Δ = difference T2 – T0. Statistic: Pearson's r coefficient.

The data relating to negative symptoms, which are greater in non-users than in THC-users and SPICE-users, have been previously noted in the literature (Akram et al., 2019; Altintas et al., 2016; Ricci et al., 2021b; Welter et al., 2017). In our opinion, two hypotheses could explain them: the possibility that the greater persistent positive symptoms can mask the negative ones and the greater dopaminergic activating effect of SCs compared to NC (Riegel and Lupica, 2004).

As for the global functioning, the interesting fact is that if at the beginning it changed in similar ways for all three groups, after 9 months the non-users had recovered significantly better than the SPICE-users, consistently with other findings in the literature (Akram et al., 2019; Ricci et al., 2021a, 2021b; Ringen et al., 2016a; Seddon et al., 2016a).

Dissociative symptoms in the three samples were significantly greater in substance users than in non-users, in line with our previous studies (Ricci et al., 2021a, 2021b). However, in this case as well, during the last evaluation the group in which such symptoms remained significantly less reduced was the THC-users. This data should be evaluated with caution, but could be evidence of a different mechanism underlying the genesis of positive and dissociative symptoms, with a greater ability of natural cannabis to induce the latter.

At each evaluation, suicidal ideation was found to be higher in SPICE-users than in both THC-users and non-users, showing no correlation with the degree of dissociation. Hence, the latter does not appear to be the cause of the former (Calati et al., 2017). It could be indirectly due to a greater degree of impulsivity induced by SCs, as well as to a greater persistence of positive symptoms and impaired overall functioning (Escelsior et al., 2021; Kolla and Mishra, 2018; Martinotti et al., 2020).

The entire symptomatic picture presented by the three groups of patients was not influenced by the concomitant use of other substances, underlining the crucial role of THC and Spices in the induction and maintenance of psychosis (Bassir Nia et al., 2016; Murray et al., 2016b; Ringen et al., 2016b; Seddon et al., 2016b).

4.1. Limitations

Several limitations can be reported in our study: i) the study included

a low number of participants for a disorder that is very heterogenous in its clinical manifestations; ii) a period of nine months cannot be considered sufficient to draw conclusions regarding clinical outcomes; iii) the pharmacological treatment included a wide variety of antipsychotic treatments; iv) the knowledge of which type of substances were used was obtained through clinical interviews with patients and family members; v) finally, the DES questionnaire, used to evaluate the dissociative experience, is a self-report measure, hence, it might have been under- or over-estimated, or possibly, misunderstood and related to a psychotic symptomatology.

5. Conclusions

Despite the numerous limitations and the need to further and better structure the research on the subject, our study lays the grounds for a better understanding of the specific mechanism of action of NC and SCs in inducing psychotic disorders with specific symptom characteristics at onset and over time. The development of such knowledge could be relevant to identify a targeted drug treatment.

CRediT authorship contribution statement

Valerio Ricci: Conceptualization, Methodology, Investigation. **Franca Ceci:** Project administration, Methodology, Writing – original draft. **Francesco Di Carlo:** Methodology, Formal analysis, Writing – original draft. **Ilenia Di Muzio:** Writing – original draft. **Laura Ciavoni:** Writing – original draft. **Monica Santangelo:** Writing – original draft. **Gabriele Di Salvo:** Investigation. **Mauro Pettorruso:** Supervision, Writing – review & editing. **Giovanni Martinotti:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Giuseppe Maina:** Supervision, Writing – review & editing.

Declaration of Competing Interest

Giovanni Martinotti has been a consultant and/or a speaker and/or has received research grants from Angelini, Doc Generici, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Servier, and Recordati.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed

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