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New insight in psychotic cannabis withdrawal: case series and brief overview

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Summary. Background. Cannabis is the most used recreational drug worldwide. Its use can increase the risk of developing psychotic disorders and exacerbate their course. However, little is known about the relationship between psychosis and withdrawal and the literature is still scarce. **Case presentation.** In this study, based on an analysis of 4 patients referred to our mental health department and evaluated between 2019 and 2023, we describe psychotic features emerged after abrupt cannabis withdrawal and we attempt to explore its characteristics. **Conclusion.** Although it is difficult to show specific mechanisms underlying the psychopathological alterations in cannabis withdrawal induced psychosis, it is clear that this serious clinical picture could be a risk factor for precipitating psychosis especially in a vulnerable group of patients. Clinicians should be aware of the possibility of a higher risk of psychotic onset associated not only with chronic cannabis use but also with its abrupt cessation.

Key words. Cannabis, cannabis use disorder, psychosis, schizophrenia, withdrawal.

Riassunto. Introduzione. La cannabis è la sostanza d'abuso ricreativa più utilizzata al mondo. Il suo uso può aumentare il rischio di sviluppare disturbi psicotici e peggiorarne il decorso. Tuttavia, si sa poco della relazione tra psicosi e astinenza, e la letteratura è ancora scarsa. **Presentazione dei casi.** In questo studio, basato sull'analisi di 4 pazienti segnalati al nostro Dipartimento di salute mentale e valutati tra il 2019 e il 2023, descriviamo le caratteristiche psicotiche emerse dopo un'interruzione improvvisa dell'uso di cannabis e tentiamo di esplorarne le caratteristiche. **Conclusione.** Sebbene sia difficile mostrare meccanismi specifici alla base delle alterazioni psicopatologiche indotte dalla psicosi da astinenza da cannabis, è chiaro che questo grave quadro clinico potrebbe rappresentare un fattore di rischio per l'insorgenza della psicosi, specialmente in un gruppo vulnerabile di pazienti. I clinici dovrebbero essere consapevoli della possibilità di un rischio maggiore di insorgenza psicotica associata non solo all'uso cronico di cannabis, ma anche alla sua cessazione improvvisa.

Parole chiave. Astinenza, cannabis, disturbo da uso di cannabis, psicosi, schizofrenia.

Introduction

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) estimates that around 75.5 million Europeans have consumed cannabis at least once (one-time prevalence), which accounts for more than one in five individuals aged 15-64. There are significant variations between countries, with prevalence rates ranging from 1.5% to 38.6%. However, about half of the countries report estimates between 10% and 30%[1].

Regarding intensive or long-term cannabis use patterns, it is important for clinical implications and public health policies. Daily or near-daily cannabis consumption (on 20 or more days over the past 30) may indicate intensive use. Based on limited data from a field trial in 13 European countries, it is estimated that more than 1% of the entire European adult population, or about 4 million people, use cannabis on a daily or near-daily basis. Most of these individuals (about 3 million) are aged between 15 and 34 years, representing around 2-2.5% of all European citizens in this age group.

A study[2] monitoring young people aged 14-24 for ten years revealed that repeated cannabis use can persist for long periods, with a substantial proportion of users who had used cannabis repeatedly at the beginning of the study continuing to do so over time. On the other hand, occasional use of cannabis at the beginning of the study did not appear to be linked to subsequent problematic and long-term consumption patterns.

The long-term effects of cannabis use include the development of Cannabis Use Disorders (CUD), characterized by physical and psychological dependence on the substance, leading to cravings and withdrawal symptoms upon cessation[3]. Cannabis withdrawal can cause irritability, anxiety, insomnia, appetite loss, and other physical discomforts, leading to functional impairment in daily activities[4]. Heavy

cannabis use may also result in amotivational syndrome, where individuals experience reduced social activities, detachment, apathy, memory problems, and attention deficits[5]. Depersonalization disorder may also occur, leading to feelings of detachment from reality, altered body image, and visual distortions[6]. Moreover, long-term cannabis use can lead to cognitive disorders, such as impaired memory, attention, and executive functions. The recovery of neurocognitive functions after cessation of cannabis use is still under debate, with some studies suggesting a few days or months, while others indicate up to 25 days for cognitive dysfunctions to subside during withdrawal[7]. More research is needed to fully understand these effects.

Finally, one of the most severe and invalidating manifestations of long-term cannabis exposure are psychiatric manifestations such as psychosis[8,9].

However, while much attention has focused on cannabis-induced psychosis, little is known about psychotic symptoms during cannabis withdrawal[10,11].

In this study, based on an analysis of four patients referred to our mental health department and evaluated between 2019 and 2022 (tables 1 and 2), we describe a first psychotic episode that emerged after abrupt cannabis withdrawal and attempt to explore its characteristics. The onset of symptoms coincided with the Italian government's mandatory home confinement during the Covid-19 pandemic. The lockdown compelled patients to abruptly discontinue chronic cannabis use. This cessation persisted beyond the lockdown period, with patients either maintaining abstinence or resuming cannabis use at a reduced frequency and intensity compared to their previous habits. However, psychotic symptoms, though significantly less pronounced and sporadic, continued to manifest.

Table 2. Psychometric assessment.

Variables	Patient 1	Patient 2	Patient 3	Patient 4
PANSS T0	45	50	48	47
PANSS T1	30	28	32	30
GAF T0	60	55	58	57
GAF T1	75	70	78	74
DES T0	12	15	13	14
DES T1	8	9	7	8
CWS T0	24	22	23	25
CWS T1	12	11	13	14

"T0" indicates the baseline measurement, and "T1" indicates the measurement after treatment or intervention.

Legend: PANSS= Positive And Negative Symptoms Scale; GAF= Global Assessment Functioning; DES= Dissociative Experiences Scale; CWS= Cannabis Withdrawal Scale.

Clinical cases

Case one

A 28-year-old male patient came to our emergency department after the onset of disorganised and aggressive behaviour. The patient presented a florid acute psychotic symptomatology characterised by auditory hallucinations (denigrating voices), and delusional thinking of a persecutory type (he thought the doctors were conspiring against him to hospitalise him and change his DNA). The patient often criticised his symptoms, was aware of them and therefore experienced a strong state of anxiety.

This symptomatology began about three days after the patient stopped using cannabinoids, which he had been using for 10 years, with a frequency of 1 to 5 daily doses. He reported sporadic use of metham-

Table 1. Demographical and clinical characteristics of the sample.

Variables	Patient 1	Patient 2	Patient 3	Patient 4
Age	28	21	42	24
Gender	Male	Male	Male	Female
Last cannabis intake (days)	3	2	2	3
Frequency of daily use	3	1	4	2
Other substances	Coc, Meth	Coc, Her	Coc, Her	None
Antipsychotic medications	Olan	Car	Risp, Arip	Arip
Daily number of cigarettes	13	20	8	3
Duration of dependence (years)	10	10	16	9

Legend: Coc = cocaine; Meth = methaphemtanine; Her = heroine; risp = risperidone; Arip = aripiprazole; Olan = olanzapine; Car = cariprazine.

phetamine and cocaine and synthetic cannabinoids (Spyce); he occasionally abused alcohol. The patient also had contact with the local psychiatric service for the onset of anxiety symptoms and insomnia four years ago. He lived at home alone and worked as a bricklayer. Blood and urine tests were normal except cannabis positivity in urine. Neuroradiological examinations and an ECG were performed during hospitalisation, which were normal. During the two-week hospital stay the patient took lorazepam 12 mg first intravenously and then by mouth. The benzodiazepine dose was reduced to 6 mg daily for maintenance. In addition, the patient took Olanzapine 20 mg daily, later reduced to 10 mg. After discharge, the patient was sent to the territorial addiction service for continuation of pharmacological treatment and monitoring withdrawal symptoms. Psychotic symptoms resolved after approximately two weeks, and the patient resumed daily activities. During follow-up, the patient reported occasional subthreshold psychotic phenomena, such as delusional interpretations, which were not triggered by cannabis use.

Case two

A 21-year-old male patient who came to our emergency department accompanied by the police following a fight with other people. The patient was clearly altered, confused in time and space, very aggressive towards everyone and disorganised in his behaviour. On objective examination a strong auditory and visual hallucinatory state was manifest: he saw strange monstrous objects approaching to devour him and heard confused voices whispering and shouting incomprehensible phrases. He was severely distressed, irritable and anxious and called for help while displaying aggressive behaviour. Admitted to the psychiatric ward, the patient first took midazolam and then lorazepam i.v. After the benzodiazepines reduced the agitated state, on the third day of admission the patient started cariprazine treatment up to 3 mg daily with good response and reduction of psychotic symptoms. Medically, the patient presented with hypertension which normalised after a few days, blood tests were normal. Cannabis positivity was present in the urine. The patient denied using other substances. He ceased cannabis use (which he had been consuming at least two to three times daily over the past two years) approximately two days prior and admitted to heavy use of synthetic cannabinoids (spice) at least 4-5 times in the past month. He had no prior contact with psychiatric services. After three weeks of treatment, he was discharged on a maintenance regimen of lorazepam 5 mg daily and cariprazine 1.5 mg daily and referred to a specialized facility for substance use rehabilitation. Psychotic symptoms disappeared, but occasional flashbacks and dissociative states persisted, despite the minimal use of cannabinoids.

Case three

He is a 42-year-old man, unemployed, with a past legal problems and followed by the territorial service for pathological gambling addiction and cannabis use disorder. He was brought by the police to our emergency department after he tried to strangle his mother. For about a week, the patient has been experiencing strange and bizarre behaviour. He has become suspicious, believes his mother is not telling him the truth, follows her, spies on her, interrogates her, and forces her to confess non-existent facts. The use of cannabis began at the age of 16, first for recreational use during the weekends at the discotheque and later more intensively up to two intakes per day. The patient reported subsequent use in the last year of synthetic cannabinoids at least once or twice a week. Once admitted, the patient was sedated with midazolam and valium with moderate benefit and then started taking risperidone 6 mg, changed to aripiprazole 30 mg daily due to the appearance of side effects (muscle rigidity). Medically, the patient was hepatitis c positive, and carrier of thalessemic trait. The urine was positive for cannabis. The patient had stopped using cannabis about a week ago. He reported sporadic use of cocaine and heroin in the past. He had previously been in contact with a psychiatrist for the occurrence of subthreshold psychotic symptoms (suspiciousness, ideas of reference, bizarre ideas, passivity experiences), which had been treated with partial benefit using low doses of antipsychotic medication.

After three 10-day admissions, the patient was discharged and entrusted to the care of the community service. Although the psychotic symptoms were greatly reduced, the patient still presented moderate persecutory ideation. Two additional episodes of auditory and visual hallucinations occurred after discharge, not triggered by THC use. These episodes lasted a few days and did not necessitate admission to the psychiatric ward.

Case four

24-year-old female university student. No psychiatric history or family problems. She comes to our observation complaining that her face has lengthened, and her nose is no longer in its usual place. For the past few days, she has led a withdrawn life, locking herself in her room for fear of others staring at her all the time and laughing at her. She has taken cannabis since the age of 15 years daily, stopping it about 3 weeks ago. The patient also reported recreational use of synthetic cannabinoid K2 during disco parties.

On psychopathological examination, ideations of reference emerged. The dominant symptomatologic picture was presence of somatic delusions of body transformation and tactile hallucinations (tingling sensation in the upper and lower limbs). Admitted to our ward for a week, she had no changes in routine tests, CT scan, serological tests for hepatitis B and HIV. Urinary tests were positive for THC, but not for other substances of abuse. ECG was normal. The patient also had an EEG with no particular alterations. During her hospitalisation she took antipsychotic therapy with aripiprazole 15 mg a day, which reduced the baseline symptoms; unfortunately, the bodily transformation delirium remained, although not as intense as before her hospitalisation. After discharge the patient was followed by a private psychiatrist maintaining aripirpazole at 15 mg daily and flurazepam 15 mg at night for sleep. In addition, the patient undertook a course of cognitve behavioural therapy with good results. At present she has resumed her academic activity; from time to time subthreshold reference ideations emerge, but they do not alter her daily relationships.

Assessment

All patients underwent psychopathological evaluation tests during the initial days of admission and upon discharge, and all met the criteria for cannabis dependence and withdrawal according to the DSM-5.

- PANSS, a 30-item questionnaire, divided into 3 subscales (i.e., positive, negative, and psychopathology) measuring positive and negative symptoms and the general severity of the illness.
- GAF scale, which is a clinician-rated scale to measure the level of psychological, social and occupational functioning on a continuum from 0 to 100.
- DES-II, a self-report questionnaire that measures dissociative experiences, such as derealization, depersonalization, absorption and amnesia. The DES comprises 28 items based on the assumption of a 'dissociative continuum' ranging from a mild alteration to severe dissociation.
- 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, and it is not specific for certain substances. NC/SC use was assessed with the Cannabis Use Disorders Identification Test-Revised (CUDIT-R), an 8-item measure set to screen for CUD. It was developed from the original 10-item, a direct modification of the Alcohol Use Disorders Identification Test (AUDIT). The type of cannabis used was detected through clinical interviews.

Cannabis withdrawal severity was assessed using the Cannabis Withdrawal Scale CWS, a 19-item self-report measure scored using an 11-point scale (0= not at all; 5= moderately; 10= extremely), referencing the previous 24-h period. This test was translated into Italian by the interviewer.

All patients smoked an average of 15-20 cigarettes per day. As this was a clinical observation derived from daily clinical practice, no exclusion criteria were established, provided the patient was not suffering from severe neurological, autoimmune, or oncological diseases.

All patients presented in this study were informed and consented to the presentation that is published here.

Discussion

It was only after 1990 that the diagnosis of Cannabis Withdrawal Syndrome (CWS) began to have a dignity of its own and was subsequently recognised in the DSM-5. The massive spread of cannabis throughout the world, together with the emergence of new synthetic cannabinoids, has highlighted numerous psychopathological problems, both acute and chronic, ranging from addiction to cognitive problems, to the development of severe psychotic pictures.

Considering these populations and also non-treatment-seeking cannabis-dependent individuals, larger retrospective clinical trials[12] demonstrated that discontinuation of regular cannabis use is frequently followed by waxing and waning behavioral, mood and physical symptoms such weakness, sweating, restlessness, dysphoria, sleeping problems, anxiety, and craving, which are subsequently positively associated with relapse to cannabis use[13]. In most instances, cannabis withdrawal is not severe and does not have a high risk of severe adverse outcomes. Medical or psychiatric comorbidities increase the risk of severity and the requirement for additional management.

In this study, we described the occurrence of psychotic symptoms during cannabis withdrawal following its abrupt discontinuation, with symptoms persisting thereafter. These patients began heavy use of cannabinoids starting in their early to late adolescence. The correlation between cannabis and psychosis has often been highlighted, especially in THC's ability to trigger a psychotic onset[14,15].

While most studies focused on the clinic features and management of cannabis withdrawal, especially agitation, aggressive behaviour, anxiety, and medical comorbidity, very little has been written about psychotic symptoms arising during withdrawal[16,17]. To our knowledge, only two case report describe this clinical occurrence[10,11]; Marin and colleagues[11] de-

scribe the occurrence of brief psychotic episodes in cannabis abstinence during the national lockdown secondary to the Covid 19 pandemic, hypothesising the strong emotional distress induced by the forced confinement as a possible trigger for the psychotic development; another study addressed the antipsychotic action of brexpiprazole in the treatment of cannabis psychosis withdrawal[18] .

Looking back on our work, some distinctive features detected should be emphasised. According to DSM-5 psychotic symptoms may be present during withdrawal of any substance. These symptoms should not be independent or substance-induced and should finish with the end of withdrawal. Persistence of psychotic symptoms after a prolonged period (at least one month), once the withdrawal phase has ceased, could point to a primary psychosis. On the other hand, the diagnosis of psychosis during cannabis withdrawal is difficult to define and often presents heterogeneous pictures. In our patients, this may be characterised by positive hallucinatory delusional symptoms, delusions of bodily transformation with tactile hallucinations, significant dissociative states, and altered consciousness. Apart from the first case, where the psychotic picture disappeared within two weeks, the other patients exhibit psychotic symptoms that persist even after the end of the abstinent state with minor severity. This could lead to the speculation that these patients already had a preexisting psychotic vulnerability, triggered by the sudden cannabis cessation. Moreover, the persistence of dissociative symptoms is another feature already observed in a previous study[19]. An essential factor to be taken into consideration is the possible use of synthetic cannabinoids: these compounds due to higher ratio of THC, have a stronger association with the risk of developing psychotic disorders than Low-Potency Cannabis (LPC), where CBD is in high concentrations. Synthetic Cannabinoids (SCs), a heterogeneous group of psychoactive drugs often classified as “Spice” or with other brand names, have emerged in the drug market; these have quickly become the largest and most widespread class of New Psychoactive Substances (NPS) utilized[20]. They are new drugs, or psychotropic substances, not controlled by the Conventions on Narcotics or the Convention on Psychotropic Substances, yet they can still pose a risk to public health[21]. While the second patient admitted to using a synthetic cannabinoid, the probability that the others may also have used it cannot be ruled out, since synthetic cannabinoids with high concentrations of THC are now widespread and are taken without the person’s consent. From a clinical point of view, a common element for all patients is awareness of their symptoms. Patients in these phases experience a critical self that is able to define and delineate psychotic symptoms and aberrant experiences.

From a neurobiological point of view, the development of psychosis during cannabis withdrawal is challenging to understand. It is possible to hypothesise that dopaminergic rebound after abrupt cannabis withdrawal, associated with downregulation of the CB1 receptor located in the midbrain contiguously to dopamine neurons may induce the onset of psychosis. On the other hand, the low availability of CB1 receptors is the basis of withdrawal[22].

Regarding therapy, there is currently no antipsychotic treatment of choice. Many studies focused attention on the pharmacological management of withdrawal syndromes, especially the most striking ones such as anxiety, insomnia and aggressive behaviour. Nothing has been written on psychotic symptoms, except for a previous case report on the action of brexpiprazole. Certainly, the patient’s anamnestic, clinical and physical conditions will help the choice of the best antipsychotic drug to prescribe at that time. Our patients have been taking antipsychotics in mild dosages and treatment is still ongoing due to the persistence of subthreshold psychotic symptoms.

Nonetheless, several limitations and biases should be noted. The small sample size limits the generalizability of our findings and might not capture the full variability within the population. Potential confounding factors, such as other psychiatric conditions and substance use, could also influence our results, making it challenging to attribute psychotic symptoms solely to cannabis withdrawal.

Generalizability is another concern, as our study population might not represent all individuals experiencing cannabis withdrawal, especially those from diverse backgrounds. Additionally, relying on self-reported data introduces biases, and the timing of evaluations might not fully capture the fluctuating nature of withdrawal symptoms.

Conclusions

Cannabis is one of the most commonly used illicit drugs, depending on the jurisdiction either legally or illegally, and a substantial percentage of users will develop a CUD. The CWS is one of the main characteristics of CUD and can cause distressing and disabling symptoms.

Investigating cannabis withdrawal symptoms is of paramount clinical importance. Cannabis withdrawal is a valid clinical syndrome that emerges following abrupt cessation of frequent cannabis use. The primary symptoms are behavioral and affective in nature, including irritability, anger, anxiety, sleep disturbances, decreased appetite, restlessness, and depressed mood. Physical symptoms such as abdominal pain, tremors, sweating, fever, chills, or headaches are less common. This syndrome causes

significant discomfort and functional impairment, which can maintain regular cannabis use and reduce the likelihood of successful cessation attempts. Recognition of the cannabis withdrawal syndrome in the DSM-5 highlights its clinical significance, aiding in diagnostic accuracy and informing the development of behavioral and pharmacological interventions. Furthermore, the validation of this syndrome has important public health implications, given the increasing treatment admissions for cannabis use and the declining perception of the risks associated with cannabis use.

From a clinical perspective, understanding the mechanisms underlying psychosis during cannabis withdrawal is crucial for developing effective treatment strategies. Clinicians need to be aware of the potential for psychotic symptoms during withdrawal and consider this in their management plans. This awareness can improve patient outcomes by facilitating early identification and intervention, thus preventing severe psychotic episodes and enhancing the overall treatment process.

Future research should focus on large clinical populations to further elucidate the neurobiological mechanisms of cannabis withdrawal-induced psychosis. Studies should aim to achieve a consensus on the definition, clinical status, and assessment of this nosological entity. Additionally, research should explore the potential genetic and environmental factors that may predispose individuals to this condition. These insights will be critical for developing targeted prevention programs and therapeutic interventions. Engaging both clinicians and researchers in these efforts will be essential to ensure that the findings translate into improved clinical practices and policies, ultimately reducing the burden of cannabis-related psychosis and improving patient care.

Conflict of interests: the authors have no conflict of interests to declare.

Ethics approval and consent to participate: written informed consent was obtained from the clinical case subject after a detailed explanation of the objectives and protocol of the study, as well as the approval of the local IRB.

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