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Cannabis Induced Schizophrenia-Like Psychosis: A Comparative Study between Cannabis and Cocaine Use Disorder

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Abstract

Introduction: Psychosis can be defined as a combination of psychopathological symptoms including delusions and/or hallucinations without insight. Psychotic disorders may configure a primary psychiatric illness or represent the result of a functional/structural brain damage induced by substance use, neurological diseases or other medical conditions. They are multifactorial disorders in which genetic, environmental and gene-environment interaction factors contribute to the manifestation of symptoms. Among the environmental factors, psychotropic substances represent the most important removable facilitators of psychosis.

Methods: In our study, we compared the prevalence of substance induced schizophrenia-like psychosis between a sample of patients affected by cannabis use disorder and a sample of patients affected by cocaine use disorder analyzing retrospectively the data of outpatients without personal or family history of psychiatric illnesses.

Results: Our analysis have shown a prevalence of schizophrenia-like psychosis of 4.6% and 3.5% in patients affected by cannabis use disorder and cocaine use disorder, respectively, with no statistical significant differences between groups.

Conclusion: No differences between samples was found in the prevalence of schizophrenia-like psychosis after five or more years of chronic substance use.

Keywords: Cannabis • Δ^9-THC • Induced psychosis • Schizophrenia

Introduction

Psychosis can be defined as a combination of psychopathological symptoms including delusions and/or hallucinations without insight [1,2]. Psychosis is a common feature in many psychiatric, neurodevelopmental, neurologic, and medical diseases. In schizophrenia spectrum and other psychotic disorders, psychosis represents the hallmark feature, however, it can be a co-occurring aspect in other psychiatric diseases including mood, alcohol use, and substance use disorders [3,4]. Symptoms of psychosis can also be present in many medical and neurologic diseases, in the onset phase or during their evolution. Generally, the appearance of psychotic symptoms in these illnesses complicates the diagnosis and treatment [3,4]. In the general population, the lifetime prevalence of psychotic disorders is approximately 3% [3]. The incidence of a first-time episode of psychosis is about 50 in 100000 while it is approximately 15 in 100000 for schizophrenia. Psychosis is uncommon in children and the peak age of onset is for young people in the mid-20s for males and late-20s for females [3-5]. Clinical evidences suggest as an early onset of psychosis correlates with poorer outcomes as well as an early and relevant treatment correlates with better results [3,5]. Psychotic disorders may configure a primary psychiatric illness or represent the result of a functional/structural brain damage induced by substance use, neurological diseases or other medical conditions [6]. Primary psychoses are considered neurodevelopmental disorders and believed to develop in utero. Although the etiopathogenesis is still poorly understood, we know that a series of genetic, epigenetic and environmental factors can contribute to the development of the full-blown illness [7]. In particular, schizophrenia and psychotic disorders are considered highly heritable psychiatric diseases since numerous genome-wide association studies have found various genetic risk variants associated to the development of psychotic symptoms [8]. The genetic risk variants appear to be able to mediate the effects of environmental risk factors within a polygenic risk scores system [9,10]. Among the environmental factors, psychotropic substances represent the most important removable facilitators of psychosis [11]. Drug use continue to be a public health challenge worldwide. As reported in the latest World Drug Report, the estimated number of users grew from 240 million in 2011 to 296 million in 2021 representing the 5.8% of the global population aged 15-64. Overall, 1 in every 17 people aged 15-64 in the world had used a drug in the past 12 months. Cannabis continues to be the most used drug, with an estimated 219 million users in 2021 representing the 4.3% of the global population aged 15-64. Cocaine, amphetamines, ecstasy-type substances, and opioid, were used in 2021 by 22, 36, 20, and 60 million people aged 15-64, respectively [12]. Correlation between substance use and onset of psychosis is heavily sustained by clinical and epidemiological studies [13-15]. Psychotomimetic effects of drugs can induce transient psychotic symptoms during intoxication/ withdrawal, but also chronic psychosis completely resembling a primary psychosis [16]. Overall, we can theoretically identify three conditions describing the association between substance use and psychosis: First, substance-induced acute psychosis, a condition in which delusions and/or hallucinations appear during or soon after intoxication; Second, psychotic disorders with comorbid substance use, a condition in which both disorders develop simultaneously and independently in the same patient; Third, substance induced chronic psychosis, a condition in which psychopathological manifestations are determined by the pharmacological/toxicological effects of drugs [17]. The different psychotropic substances may show a different propensity in

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causing acute and chronic psychotic symptoms. Amphetamines, methamphetamines, and arylcyclohexylamines are well known for their ability to induce transient and chronic psychotic symptoms [18,19]. These substances have been used for decades to create animal models for studying schizophrenia [20,21]. Similarly, cocaine is a stimulant well known for its ability to cause transient psychotic symptoms and induce chronic psychosis [22]. The most frequent psychotic symptoms are paranoid delusions and auditory/visual hallucinations. The risk of developing psychotic symptoms is related to the dose, frequency of use, age of onset, and comorbid psychiatric illnesses such as ADHD, borderline and antisocial personality disorder [22-24]. Furthermore, in recent years, the emergence of new psychoactive substances within the recreational drug market has greatly complicated the impact of drugs on the development of psychopathology [25]. Indeed, numerous substances belonging to the synthetic cannabinoids, synthetic cathinones, piperazines, phenethylamines, aminoindanes, and other families have been associated to transient and long lasting psychotic symptoms worldwide [26]. However, cannabis remains the most consistently replicated environmental risk factor for psychosis [27]. Cannabis shows the higher rates of transition from substance-induced psychosis to schizophrenia with a mean of 36% if compared to other substances highlighting a mean of 25% [16,28]. The search for the correct link between psychotic symptoms and substance use might seem like a simple clinical elugubration, contrariwise, it represents a very important diagnostic element for a correct medical evaluation and, above all, for choosing the most effective treatment. Patients who develop acute psychosis after taking drugs have high risk of developing a chronic psychosis over time. In fact, up to 32.2% of substance induced psychosis may convert to either schizophrenia or bipolar disorder and the highest conversion rate was found for cannabis-induced psychosis, with 47.4% [29]. Half the cases of conversion to schizophrenia occur within 3.1 years after developing a substance-induced psychosis, and half the cases of conversion to bipolar disorder occur within 4.4 years [29]. Conversion risk appears to be associated with various factors such as: Genetic and psychological vulnerability, age of onset of drug use, frequency of use, type of substance, potency, and polydrug use [30]. Although some studies highlight symptomatological differences between primary and induced psychosis, it is always very difficult to distinguish between these two types of psychosis [31]. However, some authors found that, compared to primary psychosis, patients affected by drug-induced psychosis display weaker family history of psychotic disorders, greater degree of insight, fewer positive and negative symptoms, more depressive symptoms, and more anxiety [31]. Patients affected by drug associated psychosis generally show more impulsivity/aggressiveness, more severe psychomotor agitation, higher risk of self harm, and poorer therapeutic response [30,31]. Although there is still scepticism, even in a part of the scientific community, psychotogenic effects induced by cannabis have been confirmed by a large amount of studies, nevertheless, discrepancies exist in term of consistency and magnitude of this data. Andréasson et al., in the first longitudinal case-control study performed in a cohort of 45570 Swedish military conscripts, investigated during over 15 years the association between level of cannabis consumption and development of schizophrenia. They found that, in strong consumers, cannabis was an independent risk factor for schizophrenia [32]. Zammit et al., in a self repor historical cohort study performed on 50,087 Swedish men conscripted, found that cannabis was associated with an increased risk of developing schizophrenia in a dose dependent manner. Additionally, they found that the association was not explained by use of other psychoactive drugs or personality traits [33]. Semple et al., in a systematic review and meta-analysis of 11 cohort and case control studies published between January 1966 and January 2004, found that cannabis was an independent risk factor for psychosis and psychotic symptoms in a dose dependent manner in particular, in young people [34]. Moore et al., in a systematic review of 35 studies, found that cannabis increased the risk of any psychotic outcome, particularly in strong users [35]. Le Bec et al., in a systematic review of seven studies including 50,275 people, found that cannabis was an independent risk factor for the development of psychotic disorders [36]. Kuepper et al., in a population based cohort study conducted in Germany on 1923 persons from the general population, aged 14-24 at baseline, found that cannabis use was a risk factor for the development of psychotic symptoms [37]. In a systematic review of 18 studies and a meta-analysis of 10 for a total of 66 816 persons, Marconi et al., found a consistent increase in the risk of schizophrenia and other psychosis outcomes among the most severe cannabis users compared to the nonusers [27]. In a longitudinal population-based study, van Os et al. found that cannabis use was an independent risk factor for the emergence of psychosis in psychosis-free persons and that people with an established vulnerability to psychotic disorder were particularly sensitive to its effects [38]. Epidemiological evidences strongly support the hypothesis that regular or heavy cannabis use increases the risk of developing chronic psychotic disorders, however, there is still uncertainty when observational studies are relied on for evidence of causation [39]. In order to further investigate the impact of cannabis consumption on the development of schizophrenia-like psychosis, we compared the prevalence of substance induced psychosis between a sample of patients affected by Cannabis Use Disorder (CaUD) and a sample of patients affected by Cocaine Use Disorder (CoUD) analyzing retrospectively the data of outpatients without personal or family history of psychiatric diseases.

Materials and Methods

Our retrospective observational study was carried out in the Addiction Treatment Unit of Alba, Italy, between June 2015 and May 2016. We compared the prevalence of substance-induced schizophrenia-like psychosis between a group of outpatients affected by CaUD and a group affected by CoUD. Both groups were made up including patients without a personal or family history of psychiatric illnesses. Clinical and socio-demographic information was extracted from the medical records available in our database. All disorders were assessed based on the DSM IV criteria using the Mini-International Neuropsychiatric Interview (MINI) Plus 5.0.0 [40]. Inclusion criteria were: 1) at least 18 years of age; 2) A diagnosis of CaUD o CoUD; 3) A history of substance use disorder for at least 5 years; 4) A diagnosis of substance induced psychosis/schizophrenia. Exclusion criteria were: 1) Less then 18 years; 2) A diagnosis of poly-substance use disorder; 3) A diagnosis of substance induced acute psychosis; 4) A diagnosis of substance induced mood disorders; 5) A family history of psychotic disorders; 6) A diagnosis of psychotic disorder earlier to the diagnosis of CaUD/CoUD. The study was conducted in accordance to the Declaration of Helsinki. All patients signed a written informed consent and the study protocol was approved by the Local Ethics Committee with the code ASLCN2/SerD. The data has been analyzed using the Social Science Statistics (www.socscistatistics.com/). Results were tabulated as mean, absolute numbers or percentage. The clinical and sociodemographic characteristics of groups were analysed. Categorical variables were examined using the chi square test while the continuous variables were examined using the t-test and the ManneWhitney's U test for normally and non-normally distributed data, respectively. Normal and non-normal distribution of variables was evaluated using the Kolmogorov-Smirnov test. Considering cannabis as a factor of exposure, we used the Odds Ratio to determine the comparative risk of developing psychosis. A p-value of 0.05 was fixed as level of significance.

Results

On the whole, 906 patients were selected in our study. In the Group 1 (CaUD) were included 478 patients (432 males and 46 females) with a mean age of 30.1 years. In the Group 2 (CoUD) were placed 428 patients (390 males and 38 females) with a mean age of 40.7 years. Sociodemographic and clinical characteristics were reported in Table 1. No difference between groups was found in the gender composition, years of study, and people employed percentage. A significant group difference was found in the mean age ($p<0.01$): Patients in the Group 1 were significantly younger than patients in the Group 2. In the Group 1, the number of students was significantly higher than in the Group 2 ($p<0.01$). Still in the Group 1, the age of onset of drug use was significantly lower than in the Group 2 ($p<0.01$). Contrariwise,

in the Group 2 there was a significant higher number of patients with a stable relationship (p<0.01). Our analysis of schizophrenia-like psychosis prevalence between group 1 (4.6%) and group 2 (3.5%) found no difference between groups. Finally, the Odds Ratio showed a score of 1.33, compatible with a weak association.

Table 1. Sociodemographic and clinical characteristics.

	Group 1	Group 2	P
Sample	478	428	
Males	432	390	NS*
Females	46	38	NS*
Mean age	30.1	40.7	<0.01
Married/cohabitant	41	81	<0.01
Education in years	9.3	8.4	NS*
Employed	170	189	NS*
Student	143	6	<0.01
Onset drug use in years	14.2	19.4	<0.01
Psychotic patients	22 (4.6%)	15 (3.5%)	NS*

Note: *NS: Not Significant.

Discussion

In the last decades, there has been an increasing interest in the relationship between cannabis consumption and psychosis. The reasons for this interest can be traced back to the great availability of cannabis, especially among younge people, as well as the growing power of cannabis that can be purchased on the market [12]. Since 2009, the average Delta-9-Tetrahydrocannabinol (Δ^9-THC) content of cannabis raised by almost 40% in the Europe and USA, whereas the Cannabidiol (CBD) content decreased [12]. Clinical evidences have shown that increased Δ^9-THC content and decreased CBD percentage may be associated to a rised risk of developing psychotic symptoms [41-43]. In line with this observation, studies who have evaluated the synthetic cannabinoids effects have highlighted how psychosis and psychosis-like conditions seem to occur relatively often following their use [44]. Presumably, the high frequency of synthetic cannabinoids induced psychotic symptoms may be related to the high potency and absence of CBD [44]. The data analysis of our samples displayed some differences between groups in socio-demographic and clinical parameters. Patients included in the group 1 were significantly younger than patients placed in the group 2 (p<0.01). Our result is in line with the global epidemiological data confirming cannabis as the first substance generally experienced by young people [45-47]. Over the years, the age of first cannabis use has decreased occurring before the age of 14 [48,49]. Neurofunctional and neuroimaging studies of the human brain across different ages have shown that brain maturation is generally not complete until the mid-twenties [50]. Consequently, adolescent brain is especially vulnerable to damage from exposure to exogenous toxins and substances, including cannabis [50]. During adolescence, the prefrontal cortex is redundant in the number of synapses. The Pruning phase allows the brain to cut inefficient connections and consolidate those that remain. The pruning process is followed by myelination, the final stage of development. Both stages constitute a critical period and are susceptible to disruption from outside factors [50]. Alterations in the synapsis maturation and myelination have been associated with numerous neurologic, behavioural, and psychiatric disorders [50,51]. Human endocannabinoid system performs neuromodulatory function playing a key role in regulating the balance between progenitor neural cell proliferation and programmed neural cell death, synaptic connectivity, and neuronal migration in the developing brain [50,51]. Δ^9-THC can bind the cannabinoid receptors CB1 and CB2 in substitution of the endcannabinoids depolarizeing cells and making them less likely to release either excitatory or inhibitory neurotransmitters into the synapse. This disturbance of neurotransmitter balance can alter the normal neurotransmitter system development, likely producing neurobehavioral disorders [50,51]. Our study have also shown that in the group of patients affected by CaUD there is a higher percentage of students if compared to the group of patients affected by CoUD. This finding is compatible with the fact that cannabis is used by young people who are therefore of school age [45-47]. Numerous evidences have highlighted as strong and long-term cannabis users develop cognitive deficits and smaller hippocampal volume in midlife [52]. Longitudinal studies have clearly shown that adolescents regular cannabis users have worse academic performance, problem behaviours, and higher risk of school dropout if compared to abstinents or mild cannabis users [53]. An earlier age of onset cannabis use has been associated with poorer verbal learning, memory, planning performance, decreased mental flexibility, and increased perseveration over time [54]. Cannabis use has been related to cognitive alterations during acute and chronic intoxication. Generally, cognitive performances return to normality state after some days/weeks after cessation. However, in some cases of prolonged and heavy cannabis use, compromissions in verbal memory, attention, and some executive functions may persist long after cannabis use cessation [55]. Cognitive impairment is recognized as a core feature of schizophrenia, and a clinically relevant cognitive compromission is observed in the majority of patients affected by this neurodevelopmental disorder [56]. Cannabis use in schizophrenia can lead to worsened illness prognoses, worsened clinical outcome, longer psychotic episodes, more frequent relapses, more frequent re-hospitalizations, poorer social functioning, poorer compliance, and increased treatment needs [56]. However, the data extrapolated from the scientific literature regarding the correlation between cannabis use and cognitive functions in schizophrenic patients have shown a paradoxical effect: Cannabis-using schizophrenic patients have similar or better overall cognitive performance compared to schizophrenic patients who do not use cannabis. These effects appear to be only evident in lifetime cannabis users, but not in current (or within last 6 months) smokers [57]. To explain this apparent paradox, various hypotheses have been formulated. First, cannabis could contain substances capable of protecting the brain from the neurodegenerative effect induced by the schizophrenic process. In this regard, the cannabidiol may exert a neuroprotective effect even in psychotic patients by balancing the induced neurotoxicity of Δ^9-THC [58,59]. Not surprisingly, the effect would be evident far from the intoxication phase which could induce a false evidence of cognitive impairment [56]. Second, cannabis-using schizophrenic patients could represent a different phenotype with superior cognitive skills, regardless from the effect induced by cannabis consumption [56,57]. However, the data are scarce and controversial and conflict with the evidence of a worse prognosis of the disease in schizophrenic patients who use cannabis [56,57,60,61]. Third, cannabis consumption of sufficient magnitude, or in individuals particularly vulnerable to its effects, especially during the neurodevelopmental processes, could induce transient cognitive alterations that mimic the typical cognitive vulnerability endophenotype seen in shizophrenic patients which precedes and is associated to the development of psychotic symptoms. This hypothesis could confirm cannabis as an environmental factor that, in particular conditions of genetic vulnerability, could promote a different neuropathological path to schizophrenia [62]. However, since cognitive dysfunctions are induced by cannabis, patients who discontinue consumption may continue to have the psychotic symptoms promoted by Δ^9-THC, but improve in cognitive functioning compared to schizophrenic patients who do not smoke [63,64]. However, it should be emphasized that, in the long term, the prognosis for schizophrenia patients who use cannabis is worse than for those who do not use [56,57,65]. In the Group 1, the age of onset of drug use was significantly lower than in the Group 2. This result is in line with literature data showing an earlier onset of schizophrenia in patients who use cannabis [66,67]. Considering schizophrenia as a neurodevelopmental disorder, cannabis could determine or accelerate the neurobiological alterations underlying the psychotic process by acting with its neurotoxic effect in a very delicate phase of brain maturation, in particular, the pruning of exuberant synapses and myelination of axons in the prefrontal cortex [68]. Our results have shown that in the Group 2, patients had a greater tendency to maintain stable relationships if compared

to patients included in the Group 1 [69]. This finding could be due to various sociodemographic and clinical factors. First, in the Group 1, patients were younger and therefore had a lower propensity to maintain stable relationships. Secondly, Group 1 patients were more frequently students and, consequently, with less economic stability to maintain a stable relationship. Third, heavy marijuana use causes a decrease of dopaminergic transmission in the striatum of the brain, resulting in a brain significantly less sensitive to dopamine and with a decreased reactivity to stimuli and challenges [70,71]. The consequent decline in motivation can heavily impact social and work functioning, including the ability to manage an interpersonal relationship. Regular cannabis users are less likely than others to have a stable relationship, more likely to engage in a conflicting interpersonal relationship, more likely to experience a low couple satisfaction [70-72]. Finally, when we compared the prevalence of schizophrenia- like psychosis between group 1 (4.6%) and group 2 (3.6%), we found no difference between groups. The Odds Ratio carried out considering the cannabis as the exposure factor of one group compared to the other showed a value of 1.33 (95% confidence interval 0.68-2.59). This result is statistically significant, however, the value is to be considered very low and consequently, not clinically significant. Substantially, the Odds Ratio also confirms that, in our study, the two substances have the same ability to induce chronic psychosis in long-time users. Overall, our results appear to be in line with the literature data showing cannabis as the substance most frequently associated to the development of induced psychosis. The incidence of cannabis-induced psychosis is around 2.7 per 100,000 person-years, with a conversion rate to a schizophrenia-spectrum disorders ranging between one-third and one-half [73]. The age-old question remains to answer the question: Cannabis-induced psychosis or psychosis comorbid with cannabis use? Although observational epidemiology and experimental studies are broadly consistent in indicating a link between heavy cannabis use and risk of psychosis, some authors highlight various critical issues [39]. The first inconsistency concerns the lack of increase in the prvalence of schizophrenia despite the significant increase in the spread of cannabis, particularly among young and very young people, in the last decades. In this regard, we must consider the possibility of underestimation of the data due to the masking effect on positive psychotic symptoms produced by the amotivational syndrome affecting heavy cannabis smokers [74]. Especially in a non-specialist setting, cognitive flattening could make the identification of psychotic symptoms and behavioral alterations attributable to induced psychosis more complex. In light of this possibility, it would be useful to re-evaluate the clinical picture of patients with cannabis dependence referred to addiction treatment Centers, considering the confounding effect induced by the amotivational syndrome. Another critical issue concern the impossibility of verifying with certainty the absence of prodromal or subclinical symptoms before starting cannabis consumption in patients affected by psychosis. In this case, clinical vulnerability would have existed before the onset of cannabis use resulting in an inverse association between cannabis and psychosis. In support of this hypothesis, a recent meta-analysis by Pasman and colleagues showed significant causality between schizophrenia and risk of developing cannabis abuse, but low evidence of causality to the contrary [75]. However, it should be considered that in the aforementioned meta-analysis, the authors did not consider frequency and potency of cannabis use, two variables considered very important in inducing psychotic symptoms [16,41-43]. Given the lack of knowledge of the neurobiological mechanisms underlying the Δ^9-THC induced psychotic symptoms, some authors object that cannabis contains dozens of other substances other than contaminants such as tobacco, heavy metals and pesticides. In particular, some studies have shown that tobacco smoking (10 or more cigarettes per day) and inhaling nitric oxide from the urban air pollution increased risk of developing psychosis [76,77]. Although this information may increase attention on the identification of environmental factors that with varying potency can contribute to the development of psychosis, it does not detract from the role of Δ^9-THC in inducing psychotic symptoms. In fact, it is well known that both edible cannabis and the intravenous administration of Δ^9-THC can cause the onset of psychotic symptoms [78,79].

Conclusion

Despite the extensive scientific literature, it is not yet possible to draw definitive conclusions on the correlation between cannabis use and psychosis. Schizophrenia and psychotic disorders are very complex syndromes in which multiple genetic, environmental and gene-environment interaction cofactors play an important and still not well understood role. The effect of frequent, long-term, high-potency cannabis use on the risk of inducing psychotic symptoms appears supported by consistent evidence. Otherwise, the impact of infrequent and low- Δ^9-THC cannabis use on the onset of psychosis requires further investigation. However, cannabis use is so widespread in the population, especially among young people, that it would be inappropriate for the scientific community not to keep the phenomenon under close observation. While we are waiting for scientific research able to clarify the neurobiological mechanisms underlying the development of psychotic disorders, with the possibility of discovering that there is not just one etiopathogenic mechanism, but many possible models including that promoted by cannabis consumption, we could imagine a clinical model that considers psychotic symptoms and cannabis use as part of the same complex syndrome. Clinical and epidemiological data clearly highlight how the two disorders negatively influence each other Cannabis promotes the onset of psychotic symptoms, worsens response to therapies and reduces adherence to treatment programs, while schizophrenia favors the development of cannabis use disorder, compromises retention in treatment and accentuates cognitive impairment. This model would allow to the healthcare staff to structure more complete and personalized programs with the awareness that to best treat both disorders, both diseases must be treated simultaneously. To the best of our knowledge, our study is the first to directly compare the prevalence of induced psychosis between two samples of patients with CaUD and CoUD. Furthermore, although the anamnestic data of lack of family history of psychotic disorders and absence of evident psychotic symptoms before the onset of substance use, do not represent sufficient criteria to define with certainty the lack of genetic risk, they are certainly sufficient to define the patients enrolled at low risk. Our results show a substantially comparabloe risk in promoting induced psychosis between the two substances. OR would even seem to be in favor of cannabis, but the score, although statistically significant, is too low to have clinical significance. The numerous factors of individual vulnerability, relatively small size of the two samples and monocentricity of the study do not allow us to draw definitive conclusions. However, the data emerged in our study are in line to that present in the international literature and goes in the direction of considering cannabis at least as dangerous as other popular psychotropic substances that are widespread in the population such as cocaine, amphetamines, and methamphetamines. In conclusion, despite the numerous critical issues to be clarified, the data currently available highlights how cannabis and psychotic disorders negatively influence each other: Cannabis can favor, especially in vulnerable subjects, the development of acute and chronic psychotic symptoms and psychotic disorders increase the risk of developing a CaUD. Considering the ever-increasing diffusion of cannabis with a high Δ^9-THC content and given the change in the legal status in many countries, it is clear that an ever-growing number of people will be exposed to consumption and, consequently, to the consequences related to the CaUD Addiction, cognitive impairment, and risk of developing psychotic disorders. A close collaboration between centers for the treatment of addiction and mental health will be necessary in order to develop effective prevention strategies, identify vulnerable people, and treat both disorders early according to the single model of disease.

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Conflicts of interest

The authors declare no conflicts of interest.

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