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Cannabis Use and Psychosis: Theme Introduction

Giovanni Martinotti[1,*], Giuseppe Di Iorio[1], Gianna Sepede[1], Domenico De Berardis[1], Luisa De Risio[2] and Massimo Di Giannantonio[1]

[1]*Department of Neuroscience and Imaging, "G. d' Annunzio" University, Chieti, Italy;* [2]*Institute of Psychiatry and Psychology, Catholic University of Rome, Rome, Italy*

Abstract: Cannabis is among the most widely used illicit substances. Epidemiological and neuroscientific evidence, though poorly integrated, have established a strong association between cannabis use and increased risk of psychosis. Chronic cannabis use, especially of new synthetic varieties, may trigger psychosis and precipitate schizophrenia in vulnerable individuals. However, the specific pathways by which cannabis affects brain function are unclear. It seems likely that a complex genetic-environmental interaction may underlie the link between cannabis exposure and psychosis onset, with multiple genetic variations and several environmental factors (i.e., trauma or maltreatment during childhood) involved. Also, the possible role of basic symptoms in cannabis users is still not fully acknowledged. Basic symptoms may possibly be a marker for the development of full schizophrenia in cannabis users and their recognition may play a role in prevention strategies. Moreover, the differential impact of different types of cannabis has been generally overlooked and little is known about possible pharmacological treatment approaches (with antipsychotics, cannabis agonists, cannabis antagonists) for cannabis users at risk of psychosis. The aim of the present review is to open this issue with a broad introduction on the clinical and pathophysiological link between cannabis abuse and psychosis onset.

Keywords: Cannabis, psychosis, schizophrenia, risk factors, basic symptoms.

INTRODUCTION

The relationship between cannabis use and onset of psychosis has been extensively investigated in both epidemiological and neuroscientific studies. Epidemiological studies focus on the association between cannabis use and development of psychosis, whereas neuroscientific studies explore the effects of cannabis on neurochemical functioning. These two lines of research have been poorly integrated, with little interdisciplinary cross-fertilisation. Moreover, the differential impact on psychosis induction of the different types of cannabis, including new synthetic varieties, has been generally overlooked. Likewise, scarce literature on possible pharmacological treatment approaches for cannabis users at risk of psychosis is currently available. We tried to gather these strands of evidence in order to provide a broader picture. The aim of the present review is to open this issue with a broad introduction on the clinical and pathophysiological link between cannabis abuse and psychosis onset.

EPIDEMIOLOGY AND RISK FACTORS

Cannabis is among the most widely used illicit substances. Recent evidence points to an increasingly higher prevalence of cannabis use, abuse and dependence [1, 2], as well as an earlier age at onset [3].

The association between cannabis use (CU) and risk of psychosis has been established worldwide [4-6]. Retrospective and cross-sectional epidemiological studies report an increased rate of CU among psychotics compared to the general population [7]. The high rate of CU among schizophrenic patients has long been considered an attempt at self-medication, intended to facilitate subjects' coping with psychotic experiences or to reduce antipsychotic drugs' side-effects on cognitive functions. However, this hypothesis does not explain why CU often precedes the clinical onset of psychotic disorders. A more complex integrated model, which considers the interaction between cannabis exposure and other pre-existing genetic or environmental vulnerability factors for psychosis, has, therefore, been proposed [8].

*Address correspondence to this author at the Department of Neuroscience and Imaging, Institute of Psychiatry, "G. d' Annunzio" University, Chieti, Italy; Mobile: +393.3556.27362; E-mail: giovanni.martinotti@gmail.com

CANNABIS AS A PRECIPITATOR OF SCHIZOPHRENIA

Tennant *et al.* [9], in their study on the consequences of prolonged hashish use among American servicemen in Germany between 1968 and 1971, first hypothesized that heavy, chronic cannabis use may precipitate schizophrenia. They reported 112 cases of "persistent schizophrenic reactions following prolonged hashish use" and provided evidence for a four-fold increase in the incidence of schizophrenia among these subjects.

Several longitudinal studies have explored the relationship between CU and the development of schizophrenia. Andréasson *et al.* [10] conducted a 15 years follow-up study on a large cohort of Sweden conscripts and demonstrated a strong association between cannabis exposure at conscription and subsequent development of schizophrenia. The role of cannabis as a risk factor for schizophrenia remained significant even after controlling for potential confounding variables, such as other psychiatric disorders and a negative socioeconomic status. Also, the increase in the relative risk for schizophrenia was proportional to degree of cannabis consumption, as evidenced by the 6-times higher relative risk in cannabis users compared to non-users. Other studies have confirmed these results [11, 12], suggesting that the increased risk of psychosis in cannabis users is dose-dependent. In a retrospective study, Allebeck and colleagues [13] found that most schizophrenics with comorbid CU had a record of heavy cannabis consumption at least one year before the onset of psychotic symptoms. Furthermore, as described in Fergusson *et al.*'s (2003) longitudinal study [14], even when the diagnostic criteria for schizophrenia are not fulfilled, cannabis use is nonetheless associated with the development of psychotic symptoms. The association between degree of cannabis dependence and psychotic symptoms remains strong even when taking into account pre-existing symptoms and other background factors.

A strong stimulation of the endocannabinoid system during adolescence may lead to subtle changes in brain function, resulting in a higher risk of developing schizophrenia in adulthood [15, 16]. The risk was higher when CU began early in adolescence (at age 15 rather than 18) [17] and lasted more than six years [18]. Hence, preventing or ending CU in adolescence may be crucial in reducing the harmful impact of cannabis on the developing brain. The psychosis-inducing effects of cannabis may be enhanced by environ-

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mental factors, such as trauma or maltreatment during childhood [19, 20]. Trauma exposure during sensitive development periods may affect brain structure, neurocognition, emotion regulation and social interaction, thus significantly increasing the risk of developing a psychotic syndrome [21, 22]. Moreover, genetics seems to play a key role in modulating the effects of cannabis on brain functioning. A greater familial risk for schizophrenia was observed in patients with acute psychotic symptoms and comorbid CU [23]. Basic symptoms, defined as self-experienced subclinical disturbances, were more severe in cannabis users with a family history of psychiatric disorders [24]. Variations in genes involved in endocannabinoid systems have been found in subjects with an increased risk of developing psychosis after cannabis exposure [25], whereas COMT genotypes seem to modulate the association between cannabis and age at onset of psychotic disorders [26]. Therefore, a complex genetic-environmental interaction may underlie the link between CU and psychosis, with multiple genetic variations and several environmental factors involved [27].

Other investigators have argued that heavy cannabis use may produce an acute functional psychosis, meaning a psychotic disorder that resembles schizophrenia rather than an organic syndrome caused by drug intoxication. In Thacore and Shukla's case-control study [28], for instance, subjects with a putatively functional cannabis psychosis were compared with controls diagnosed as having paranoid schizophrenia. The 25 cases of cannabis psychosis presented with a paranoid psychosis resembling schizophrenia, in which "a clear temporal relationship between the prolonged use of cannabis and the development of psychosis has been observed on more than two occasions" (p384). Rottanburg *et al*. [29] provide one of the most convincing research studies in favour of the hypothesis that cannabis can produce an acute functional psychosis. They conducted a case-control study in which psychotic patients with cannabinoids in their urines were compared with psychotic patients without cannabinoids in their urines.

The results showed that, compared to controls, psychotic patients with cannabinoids in their urine displayed more symptoms of hypomania and agitation and less auditory hallucinations, flattening of affect, incoherent speech and hysteria. Also, symptoms notably improved by the end of a week, while no change was observed in controls even though they received comparable amounts of antipsychotic drugs. The authors concluded that "heavy cannabis intake is associated with a rapidly resolving psychotic illness characterised by marked hypomanic features". All considered, the case for cannabis use as facilitator of a functional paranoid disorder is much less compelling than that for cannabis as triggerer of a toxic psychosis [30]. The research designs for studies supporting this hypothesis have more often included control groups, though [31].

CANNABIS AS AN EXACERBATOR OF SCHIZOPHRENIA

In Regier *et al.*'s study [32], the possibility that a psychotic patient develop a Cannabis Use Disorder was six times higher than controls. However, literature findings on CU impact on psychotic disorders' clinical features are controversial. Cleghorn *et al*. [33] compared symptom profiles of schizophrenic patients with substance abuse history of varying severity (none, moderate and severe), with cannabis as the most heavily used drug. Comparisons with a subset of patients receiving neuroleptic drugs revealed that drug abusers had a higher prevalence of hallucinations, delusions and positive symptoms. Schizophrenics with comorbid CU often show a sudden onset of disease [13] and more acute relapses [34]. More severe positive symptoms were observed in psychotic patients with CU disorder compared to patients without substance use disorders [7] and positive symptoms improved after CU discontinuation [35].

On the other hand, CU is reported to significantly reduce unpleasant affects among psychotic subjects [36]. To this respect, illicit drug use can be considered as a form of self-medication, intended to help the patient deal with some of the unpleasant symptoms of schizophrenia (such as depression, anxiety, lethargy and anhedonia) as well as with neuroleptic drugs' side effects [37, 38]. Some support for this hypothesis emerges from the work of Dixon *et al.* [39], who surveyed 83 patients with schizophrenia or schizophreniform psychoses on the effects of various illicit drugs on their mood and symptoms. Patients reported that cannabis use reduced anxiety and depression and increased a sense of calm, though they experienced some increase in suspiciousness and mixed effects on hallucinations and energy. Kuepper and colleagues [40] suggested that sporadic CU may provoke transient and subthreshold psychotic symptoms, whereas only prolonged CU may yield persistent psychosis. This hypothesis is supported by longitudinal studies [17]. In early onset first-episode psychotic patients, a significant association between CU and worse functional outcome, in terms of symptomatologic remission and service disengagement, was limited to those subjects with prolonged and severe CU [41]. These studies provide a basis upon which to draw conclusions about the effects of cannabis on schizophrenic symptoms. Overall they suggest that cannabis plays a key role in triggering psychotic symptoms in subjects who are vulnerable to the illness.

BASIC SYMPTOMS AND USE OF CANNABIS

In psychosis, prodrome is an area of potential early intervention. However, previous research, which has mostly been retrospective, has highlighted the varying and usually nonspecific nature of prodromal phenomena, raising the issue of false positives [42, 43]. The wide range of prodrome duration further contributes to the difficulties encountered in predicting if and when a person will make the transition from an at-risk mental state to a psychotic episode, regardless of whether or not the subject is using cannabis and/or other substances.

Prospective studies have shown that the development of schizophrenia may be correctly predicted by the earlier presence of subjective experiences (SEs) [44 - 46], that may be experienced by patients long before signs of full-fledged schizophrenia become apparent [47] . Huber, who monitored a cohort of schizophrenic patients over several decades [48], used the term "basic symptoms", originating from Bleuler's concept of latent schizophrenia, to refer to the self-perception of cognitive disorders in schizophrenia. Basic symptoms can only be directly identified by the affected subject, whereas Bleuler's fundamental symptoms are externally observed by others on the basis of behaviour. Huber's theory states that: (1) cognitive disturbances are present in the development of basic symptoms; (2) basic symptoms represent a direct neuropathological expression; (3) basic symptoms are subjectively accessible outside of the acute phase and (4) they predict future development of Schneiderian symptoms along a continuum of psychopathological evolution [49]. Perceptual disturbances seem to be the basis of delusions, while cognitive disturbances are thought to lead to acoustic hallucinations. Physical and mental exhaustion along with decreased resiliency and efficiency may represent the basis for negative symptoms. Patients can have intrusive ideas that impinge on cognitive processes or experience blurred vision or hypersensitivity to visual and acoustic stimuli. Thus, basic symptoms, especially cognitive ones, seem to be a good tool to distinguish (pre-)psychotic conditions from other disorders [50]. To this regard, the relationship between cannabis use and the presence of basic symptoms can be of some interest, with significant implications on prevention strategies. The study carried out by Martinotti *et al.* [24] evaluated, in a sample of healthy university students, the presence and level of SEs and their relation to cannabis use. The Frankfurt Complaint Questionnaire, the most frequently used procedure in Europe to measure basic symptoms [51], was used for its capacity to rate a wide range of dysfunctions of perception, speech, thought, motor responses and memory. In this study, SE intensity was not found to be influenced by cannabis use, regardless of whether the use was daily and protracted over more than 1 year. The results of

this study, though limited by the "light" cannabis use in the sample and the lack of control for possible drugs other than cannabis [52], differ from those of previous studies [53 - 59], in which schizotypal and borderline personality traits, that resemble the characteristics of basic symptoms, were found to be associated with cannabis use. These studies focused on the recognition of schizotypy in non-clinical samples as an index of propensity to psychosis, reporting that cannabis users have higher schizotypy scores than non-users [57], [60 - 62]. Moreover, in another study [63], both vulnerability to psychosis and cannabis use were independently associated with unusual perceptual experiences.

These contrasting findings may be explained by the peculiar difference between personality dimensions, such as the schizotypal trait, and subjective experiences (SEs). While the first can be considered traits, the latter refer to the subject's state. SEs are the early clinical manifestation of schizophrenia and the direct clinical expression of a psychopathological and phenomenological dimension [64]. According to Mass *et al.* [65], vulnerability to schizophrenia is a relatively permanent, enduring trait, while SEs are defined as reversible states. As opposed to the schizotypy questionnaire, the FCQ is therefore an episode marker. Moreover, by definition, the FCQ evaluates self-experiences of cognitive deficiencies, notably anhedonia, whereas schizotypy scales predominantly focused on positive symptoms. In light of this, it is possible that cannabis users, experiencing reinforcing effects, may report higher scores on schizotypy scales, while negative symptoms, with SEs as their precursor, may be underestimated. The role of basic symptoms in cannabis users is still not fully recognized and further studies with larger samples and with a prospective design are required to fully determine the importance in prevention strategies. However, to date, we can assert that cannabis does not directly trigger the development of subjective experiences. On the other hand, the presence of basic symptoms in cannabis users at risk for psychosis may possibly be a marker for the development of full schizophrenia. Therefore, the use of the FCQ could aid in differentiating cannabis users without a specific pre-psychotic feature from those at risk for a full psychosis.

NEUROBIOLOGICAL MECHANISMS OF Δ9-THC-INDUCED PSYCHOSIS

Cannabinoids have two specific receptor subtypes, which have been cloned. The human cannabinoid receptor 1 (CB1) was cloned in 1990 [66], whereas CB2 was first identified in 1993 [67]. CB1 receptors are present in many brain regions (including the cortex, hippocampus, nucleus accumbens, basal ganglia, hypothalamus, amygdala, cerebellum) and in the retina, though the highest CB1 receptor concentration is in cerebellar, basal ganglia and hippocampal brain regions [68]. CB1 receptors are mainly expressed at central and peripheral neurons' terminals, where they usually mediate neurotransmitter release inhibition [69]. CB2 receptors are predominantly located in immune cells, both within and outside the central nervous system; the main functions of these receptors include modulation of cytokine release and of immune cell migration [70]. In the brain, CB2 receptors are expressed by microglia, blood vessels and some neurons, but the role of neuronal CB2 receptors is currently unknown [71]. Another two serpentine receptors, named GPR55 and GPR119, are presumed to be cannabinoid receptors but are classified among orphan receptors because no specific binding ligand exists [72].

Two endogenous cannabinoid receptor ligands, anandamide (AEA, arachidonylethanolamide) and 2-arachidonylglycerol (2-AG) (known as endocannabinoids), have been discovered [73]. Both these compounds are arachidonic acid derivates that activate cannabinoid receptors centrally and peripherally [74]. Endocannabinoids may represent the first members of a new class of neuromodulators, not stored in cell vesicles but rather synthesized by the cell upon request, in response to an increase in intracellular calcium levels [75]. AEA was found to bind both CB1 and CB2 receptors, although its CB1 receptor binding activity is 24-times greater than that of 2-AG [76] (the endocannabinoid system will be systematically reviewed by Parolaro *et al.* in this issue).

Δ9-tetrahydrocannabinol (Δ9-THC) exerts its central effects primarily via the CB1 receptor and its endogenous ligands, AEA and 2-AG [77]. This system interacts with many brain neurotransmitters directly or indirectly implicated in psychosis development and maintenance, including dopamine, serotonin, GABA, glutamate and acetylcholine [78, 79]. Though cannabinoid receptors are not directly expressed by dopaminergic neurons [80], Cheer *et al.* [81] have demonstrated that WIN55,212-2, a potent CB1 receptor agonist, increases dopamine neurotransmission in the nucleus accumbens (NAc). *In vivo* studies have shown that, when administered at doses that elevate NAc dopamine levels, cannabinoids also excite dopaminergic neurons in the ventral tegmental area (VTA) through CB1 receptors [82]. Moreover, mounting evidence hints at AEA dysfunction in schizophrenia [25], [83]. In fact, dopamine D2 receptor hyperactivity is associated with increased AEA release in rodents [84] and, in humans, a negative correlation between CSF AEA levels and the positive symptoms of schizophrenia was observed, suggesting that the acute phase of psychosis could reflect a failure of AEA compensatory mechanisms [85].

With respect to the dopamine hypothesis on cannabis-induced psychosis, it has been suggested that cannabis possibly plays a causal role in individuals who are genetically vulnerable to its effects, as most young cannabis users do not actually develop psychosis) [86]. Hopfer *et al.* [87] identified a specific CB1 receptor haplotype that predisposes to the development of cannabis dependence symptoms. Also, cannabis users carrying the Val-Val genotype of the catechol-O-methyltransferase (COMT) Val158Met gene polymorphism have a greater risk of developing psychosis [26], [88, 89]. In fact, a valine to methionine substitution at the single nucleotide polymorphism (SNP) rs4680 (Val158Met) within COMT results in reduced enzymatic activity and thus slower degradation of dopamine in the frontal lobe, with evidence of a dose-response effect based on the number of methionine alleles present [90]. Though further studies have not yet confirmed these findings, cannabis smokers carrying the Val-Val genotype of COMT may present enhanced vulnerability for psychosis [91, 92].

In conclusion, several evidences suggest that cannabis influences the dopamine system, which has long been known to play a key role in psychosis development and maintenance, and may therefore predispose to psychosis in the presence of genetic vulnerability [83].

HIGH-POTENCY CANNABIS AND THE RISK OF PSYCHOSIS

Despite the reinforcing effects of cannabis and the transient cognitive impairment usually described, most individuals who try cannabis do not develop psychosis or a cannabis use disorder. This raises the question of what factors determine vulnerability to the harmful effects of cannabis. One of the critical factors may be the type of cannabis consumed. The principal constituents of cannabis are Δ9-tetrahydro-cannabinol (Δ9-THC) and cannabidiol. When administered intravenously, Δ9-THC produces psychotic-like and anxiogenic effects [93, 94], whereas cannabidiol seems to have antipsychotic properties and does not induce hallucinations and delusions [95].

Until recently, resin (hash) was the most readily available type of cannabis (approximately 70% of the street market), followed by traditional imported herbal cannabis and sinsemilla (skunk). Cannabis resin and herbal cannabis contain similar quantities of Δ9-THC (2-4%), while its concentration in skunk is between 12% and 18%; cannabidiol in resin is present in a similar proportion to Δ9-THC, whereas it is virtually absent in herbal cannabis and skunk [96].

Hydroponically grown varieties like "Super Skunk" and "Big Bud" and cross-bred strains contain higher levels of Δ9-THC and are increasingly more popular throughout Europe [97], as a result of the drug scenario change that has occurred in the past two decades [98, 99].

It is not surprising that the higher concentration of Δ9-THC in skunk is more likely to have detrimental effects on mental health. Smith [100] suggested that such high-potency cannabis might be especially harmful to mental health and a recent study has clearly demonstrated that patients with first-episode psychosis preferentially recur to high potency cannabis preparations, such as skunk [101].

An experimental study on healthy subjects exploring the acute effects of higher levels of Δ9-THC intravenous administration found that the resulting psychotic symptoms were dose-dependent [94]. Furthermore, a positron emission tomography study has shown that inhalation of Δ9-THC acutely increases striatal dopamine, which is thought to underlie psychotic symptoms [102].

The relative lack of cannabidiol in skunk may also be relevant, as there is some evidence that cannabidiol has antipsychotic properties. Cannabidiol has no affinity for CB1 and CB2 receptors but acts as an indirect antagonist of cannabinoid agonists, tempering the psychotomimetic effects of Δ9-THC [103]. Furthermore, Curran *et al.* [104] measured cannabinoid traces in the hair of three groups of healthy volunteers and found that those with Δ9-THC only had higher levels of schizophrenia-like symptoms compared to the "Δ9-THC plus cannabidiol" and "no cannabidiol" groups.

Given the opposing neuropharmacological actions of Δ9-THC and cannabidiol (see the paper by Bhatthaccharrya *et al.* published in the present issue), Morgan *et al.* hypothesized that cannabidiol may protect users against cognitive impairment and psychotic-like effects [103]. These authors did not, however, confirm this hypothesis in a subsequent study and postulated that the potentially protective effects of low doses of cannabidiol (present in street cannabis) may possibly occur over time rather than acutely [105]. Indeed, chronic neuroprotective-like effects have been observed in long term cannabis users [106]. Cannabidiol's protective role has also been investigated in a study conducted in an area where hash (that has high levels of cannabidiol) is the most frequently sold cannabis variety. The presence and degree of basic symptoms did not differ between cannabis users and non-users [24]. Recently, Morgan *et al.* [107] explored whether cannabidiol may also guard against memory impairment and reduced psychological well-being. 120 current cannabis smokers, 66 daily users and 54 recreational users were assigned to groups according to the presence versus absence of cannabidiol and high versus low levels of THC, as measured with hair analysis. Hair positivity to cannabidiol was associated with better recognition memory and, in recreational users only (who had the highest THC levels), with fewer psychotic-like symptoms. Higher THC levels correlated with increased depressive and anxious symptoms and, only in daily users, with poorer prose recall and source memory.

In light of the data exposed, it seems that the potency and type of cannabis consumed are relevant variables when assessing the extent to which cannabis induces psychosis. As is the case for sinsemilla (skunk), certain cannabis varieties may be associated with a higher risk of psychosis. On the other hand, cannabidiol may represent a protective ingredient that counterbalances psychotomimetic effects. Its role merits further studies in order to be fully understood.

SYNTHETIC CANNABINOIDS

A new generation of synthetic cannabinoids, readily available on the web and in smart shops under the brand names of "Spice," "Spice Gold," "Spice Diamond," "Arctic Spice," "Silver," "Aroma," or "Dream", has recently come on the market (see for review Fattore and Fratta, 2011) [108]. These synthetic cannabinoids are advertised as meditation potpourris, bath additives or air fresheners and are often referred to as "herbal highs" or "legal highs" because of their legal status and alleged natural herbal make-up. They produce psychoactive reinforcement, are highly attractive, perceived as safe drugs and not easily detectable in urine and blood samples.

"Spice" products rarely contain THC and do not contain the phytocannabinoids cannabidiol but synthetic cannabinoid drugs instead. These belong to four chemically distinct groups: JWH compounds, CP-compounds, HU-compounds and benzoylindoles. JWH compounds are the most numerous and, although their chemical structure differs greatly from that of THC, they have a higher affinity for CB1 and/or CB2 receptors and are more potent [109]. *In vitro* experiments have suggested that this higher potency might be explained by the fact that, while THC acts as a partial agonist on the CB1 receptor, JWH-018 acts as a full and potent agonist [110]. Moreover, compared to THC, JWH-018 possesses approximately a four-fold higher affinity for the cannabinoid CB1 receptor and a 10-fold higher affinity for the CB2 receptor [111, 112]. Spice blends better satisfy users' expectations, in that their psychoactive effects are perceived to be even stronger than cannabis [113]. Regrettably, Spice products are believed to be only the tip of an iceberg, merely the first of a much larger number of synthetic substances with cannabis-like effects mediated by agonistic activity at the CB1 (and/or CB2) receptor. More than 50 compounds with cannabimimetic properties are still to be identified. Some Spice users have reported effects similar to or even stronger than those obtained by smoking cannabis, such as physical relaxation, changes in perception and mild euphoria.

Few data are available on the psychological and other risks of synthetic cannabinoids; despite limited clinical observations, in the Internet fora a growing number of users have reported experiencing psychotic symptoms after smoking Spice. A first case report described the effects of Spice on a 25-year-old man with a history of cannabis-induced recurrent psychotic episodes [114]. Spice triggered both acute exacerbation of cannabis-induced recurrent psychotic episodes and the emergence of new symptoms, such as recurrent paranoid hallucinations. The absence of cannabidiol, presumed to have antipsychotic properties [95], [115], could have contributed to acute symptom reactivation after Spice abuse. This suggests that these new substances might be even more powerful in inducing psychosis. In line with this, in psychotic patients, relapses following Spice use have been reported by forensic services [116]. More recently, psychotic relapse after smoking Spice was confirmed in 15 psychotic New Zealand patients, all familiar with a locally available JWH-018-containing product called "Aroma" [117].

Very limited information is available on the safety of Spice ingredients in humans and the occurrence of serious health damage in abusers is highly probable, as is the likelihood of prompting the development of psychotic symptoms and full psychotic episodes.

POSSIBLE TREATMENTS IN SUBJECTS EXPERIENCING EARLY PSYCHOSIS AND USING CANNABIS

The psychological and psychopharmacological options for treating cannabis use in psychosis are extensively reviewed in Baker *et al.* in this issue and we only provide here a short summary. Cannon and colleagues [118] have demonstrated that prediction algorithms for transition to psychosis can be improved by adding certain features underestimated so far, including substance abuse history. The Cannabis and Psychosis (CAP) intervention project has been proposed [119]. It is composed of an individualized, phase-linked intervention aimed at reducing the negative impact of cannabis use on youth with first-episode psychosis. Edwards and colleagues at the Early Psychosis Prevention and Intervention Centre have developed cognitive-behavioral interventions targeting substance use and persistent psychotic symptoms [120, 121]. One in-

tervention focuses on reducing problematic cannabis use in individuals with first-episode psychosis and comprises psychoeducation, motivational interviewing, goal setting and discussion about goal achievement and relapse prevention. A randomized, controlled trial comparing the cannabis and psychosis intervention program with psychoeducation alone was conducted and preliminary results suggest that cannabis use in both groups decreased, with no clear advantages for the cannabis and psychosis intervention program [119]. A randomized, controlled trial evaluating the relative and combined effects of clozapine and systematic treatment of persistently psychotic individuals, with and without substance abuse, is currently being conducted at the Early Psychosis Prevention and Intervention Centre [121]. The PRIME (Prevention through Risk Identification, Management and Education) study [122] uncovered no significant differences between cannabis users and non-users in term of psychosis transition.

A recent review [123] suggests that medication intake must be increased in cases of schizophrenia/cannabis dependence comorbidity. In particular, antidepressants seem either not highly effective or with unfavourable side-effect profiles or high toxicity. Second generation antipsychotics are more effective in treating schizophrenia and comorbid substance abuse (see the paper by Lazary *et al.* included in the present issue). Some evidence suggests that clozapine, olanzapine and risperidone are among the best. Clozapine appears to be the most effective in reducing cannabis, along with alcohol and cocaine, abuse among schizophrenics [124]. As for other antipsychotics, the role of quetiapine and aripiprazole could be of some interest, given their efficacy in other forms of addiction [125 - 127]. Highly structured therapy programs that integrate intensive outpatient treatment, case management services and behavioral therapies (such as contingency management) are the most effective in treating severe comorbid conditions. A systematic review conducted by Wisdom *et al.* [128] shows that many subjects (approximately half) became abstinent or significantly reduced their alcohol and drug use after a first episode of psychosis. This percentage could further improve if knowledge on this issue were to grow.

Cannabidiol and Rimonabant (SR141716) are two exogenous cannabinoids that antagonize the effect of Δ9-THC. Cannabidiol, as previously described, is the second most abundant constituent of Cannabis sativa and has weak partial antagonistic properties at the CB1 receptor. Cannabidiol inhibits the reuptake and hydrolysis of anandamide, the most important endogenous CB1 receptor agonist, and exhibits neuroprotective antioxidant activity. Rimonabant is a potent and selective CB1 receptor antagonist. Since both cannabidiol and rimonabant can reverse many of the biochemical, physiological and behavioural effects of CB1 receptor agonists, it has been proposed that they have antipsychotic properties. Various experimental studies on animals, healthy volunteers and schizophrenic patients support this hypothesis [129]. A 12-week, double-blind, placebo-controlled, randomized trial [130] evaluated the safety and efficacy of dronabinol, a synthetic form of Δ9-THC, in treating 156 cannabis-dependent adults. This is the first trial testing an agonist substitution strategy in the treatment of cannabis dependence. At the end of the maintenance phase, treatment retention was significantly higher for dronabinol (77%) compared to placebo (61%) (P=.02) and withdrawal symptoms were significantly lower for dronabinol (P=.02). During the study, no psychotic symptoms occurred at any time. Dronabinol's positive effect also emerged in Schwarcz and colleagues' [131] case series on severe, chronic, treatment-refractory schizophrenics with history of marijuana abuse. Dronabinol did not merely yield non-specific calming, but reduced core psychotic symptoms in 3 of the 4 responders and no clinically significant adverse effects were observed. These results complement the recent finding that the cannabinoid blocker rimonabant does not improve schizophrenic symptoms and suggest that the role of cannabinoids in psychosis may be more complex than previously thought. Kelly and colleagues [124] conducted a 16-week, double-blind, placebo-controlled study on rimonabant (20 mg/d) in overweight schizophrenics or schizoaffective disorder patients clinically stable on second-generation antipsychotics. Rimonabant was associated with a greater reduction in Brief Psychiatric Rating Scale total score versus placebo. In this small sample, rimonabant did not cause significant weight loss, metabolic effects or adverse psychiatric effects, supporting the idea that the endocannabinoid system is a promising pharmacological target in schizophrenia and obesity.

CONCLUSIONS

Over the past two decades, a high prevalence of cannabis use has been reported among individuals suffering from schizophrenia. Although the association between cannabis and psychosis is nowadays undebatable, the specific etiopathological pathway underlying this association is still unknown and likely to be confounded by external factors. From an epidemiological standpoint, the evidence for a causal link is striking. On the other hand, current neuroscientific research has shed lights on the brain mechanisms underlying the acute and chronic effects of cannabis and on the neurobiological changes underlying the onset of psychosis. The present issue will discuss these points in detail, thanks to the contribution of worldwide experts in the field.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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