

Cannabis and Schizophrenia Spectrum Disorders: A Review of Clinical Studies

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ABSTRACT

Cannabis is the most widely used illegitimate substance in the world, and the number of users has increased by 10% over the last decade worldwide. Therefore, it is important to review the evidence on psychoactive properties of cannabis and its possible association with schizophrenia spectrum disorders (SSD). We searched MEDLINE with the key words *cannabis* and *schizophrenia*. The search was limited to articles published in English over the last 10 years (1999-2009). Bibliographies of cited literature were also searched. Data sources included reviews published in core clinical journals, cohort studies, interventional studies, case-control studies, cross-sectional analyses and epidemiological data. Results are discussed under 2 topics. Firstly, evidence related to biochemical functioning of cannabinoids and their relationship to endocannabinoid system is discussed briefly. Secondly, the evidence from clinical studies on cannabis, psychosis proneness and SSD are discussed in detail. The discussion is structured to fit in the evidence from results section to 3 plausible hypotheses on cannabis use and SSD. The evidence for and against each hypothesis is discussed. Despite new evidence, the exact relationship between cannabis and SSD is unclear. There is no firm evidence that cannabis causes SSD. The evidence for the argument that schizophrenic patients are attracted to cannabis is also not strong. The most plausible explanation is that cannabis use and psychosis proneness may have synergistic effects in a vulnerable minority.

Key words: *Cannabis, schizophrenia spectrum disorders*

INTRODUCTION

There has been a recent surge in research activity on cannabis and its impact on psychopathology.^[1] Many opinions and interpretations are exchanged on the evidence of several clinical studies, biochemical and genetic analyses looking into the purported 'cannabis-induced psychosis' and its link to schizophrenia spectrum disorders (SSD).

The plant *Cannabis sativa* grows in temperate and tropical climates. Its seeds, flowering tops, leaves and stalks contain a cocktail of chemicals termed *cannabinoids* that causes psychoactive manifestations following ingestion or inhalation of smoke.^[2] Though the special significance of this plant was first recorded

in allopathic medical literature at the turn of the last century, the oriental physicians have been using it as a medicinal plant for many millennia.^[3] Dried leaves and flowering tops (grass, marijuana, joint, weed, ganja, hashish), resinous extracts from flowering tops and cannabis oil (hash oil) are different formulations with psychoactive chemicals that are used for medicinal and recreational purposes.^[4]

Cannabis is considered to be the most widely used illegal drug in the world, and it was estimated that 4% of the world's adult population (160 million) were using cannabis in 2005. This was a 10% increase compared to the estimates in the mid 90s.^[5] The available data on cannabis usage is mostly from the developed nations. The burden of cannabis abuse in developing nations is

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still not well quantified. There is a wide range in the percentage of cannabis users in various countries, which may partly be due to the legal restrictions each country imposes. It is interesting to note that in many developed regions the percentage of adults reporting cannabis use is above the global average with the only exception being Africa (Oceania-16%, North America-11%, Africa-8% and western Europe-7%).^[6]

With the rising trend in cannabis use and with the more liberal attitude towards its use in some countries, it is important to revisit and review the evidence on psychoactive properties of this drug and its possible association with SSD.

We searched MEDLINE with the key words *cannabis* and *schizophrenia* using the software Endnote XI.01 to filter articles. The search was limited to articles published in English over the last 10 years (1999-2009). Bibliographies of cited literature were also searched. Relevant publications and epidemiological data were downloaded from websites of international agencies such as United Nations Office on Drugs and Crime (UNODC) and World Health Organization (WHO). All abstracts were read independently by the two authors, and relevant papers were identified for review of the full papers. The coding was done by two reviewers independently, blinded to each other. Data sources included reviews published in core clinical journals, cohort studies, interventional studies, case-control studies, cross-sectional analyses and epidemiological data. The inter-reviewer agreement for data included in the final synthesis was 100%.

RESULTS

Cannabinoids, endocannabinoid system and symptomatology from a biological perspective

The term *cannabinoids* is used for a number of chemicals found in the extracts of *Cannabis sativa*. The main active component is Δ^9 tetrahydrocannabinol (THC), which has been shown to induce acute transient psychotic reactions in previously well individuals when administered as an isolated compound.^[7] Still, there are other components in this chemical mixture, such as cannabidiol (CBD) and cannabigerol, which may also play a role in modulating the effects of THC.^[8]

Intravenous administration of THC in a double-blind placebo-controlled study in healthy individuals has demonstrated positive symptoms (suspiciousness, paranoid thinking, grandiosity) and negative symptoms (blunted affect, reduced rapport, reduced spontaneity in speech, etc.) of schizophrenia with cognitive deficits.^[9] A repetition of the study with the same doses of THC in patients with schizophrenia (clinically stable) elicited

a similar spectrum of symptoms, although the patients seemed more sensitive to the chemical than did the healthy volunteers.^[10]

Cannabinoids mediate their effects on the central nervous system via the cannabinoid receptors. There are 2 receptors: CB1R and CB2R. THC has a partial agonist activity on CB1R.^[11] CB2R is found in macrophages and other immune cells.^[2] The cannabinoids work through the centrally located CB1R, which shows an aggregation in substantia nigra, putamen, hippocampus, cerebellum and cerebral cortex (especially in frontal cortex).^[11] Understandably, there must be endogenous substances that act on these receptors as neither THC nor CBD occurs naturally in the human body. Anandamide and 2-arachidonylglycerol (2-AG) are two such compounds characterized and given the collective term *endocannabinoids*.^[12] It has been shown that the anandamide levels in cerebrospinal fluid (CSF) of schizophrenia patients are significantly elevated, suggesting a role of the endocannabinoid system in the pathogenesis of schizophrenia.^[13] A second study has shown that the CSF anandamide levels were significantly high in low-frequency cannabis-using schizophrenic patients when compared with high-frequency cannabis-using patients and healthy cannabis users. The CSF anandamide levels were negatively correlated with psychotic symptoms in all users. The authors concluded that chronic cannabis use down-regulates anandamide-mediated signaling in schizophrenics but not in healthy users.^[14]

The symptomatology with cannabinoids is explained with hypotheses relating to the modulation of release of neurotransmitters dopamine, gamma amino-butyric acid (GABA) and glutamate via CB1R in mesolimbic and mesocortical systems.^[11] For example, it has been shown that THC induces dopamine release from striatum, and such a surge in dopamine levels positively correlates with severity of psychotic symptoms in schizophrenic patients.^[15] However, this area in neurobiology is still up to speculation and testing of hypotheses. For example, Stolks *et al.*^[16] in testing a dose of oral THC (equivalent to that of a cigar) in healthy recreational cannabis users have failed to demonstrate a rise in dopamine levels in striatum despite eliciting psychomimetic symptoms, thus challenging the dopamine release hypothesis.

While THC is purported to have psychomimetic and anxiety-enhancing effects, another cannabinoid, cannabidiol (CBD), is attributed to have anxiolytic and antipsychotic properties which may partially offset harmful effects of THC.^[17-19] The relative concentrations of THC and CBD vary in different preparations of cannabis. A study by Morgan *et al.*^[20] has shown that psychosis proneness and delusional thinking

were significantly more in cannabis users compared to non-users. The cannabis users were also divided into 2 groups: THC only and THC + CBD (by analysis of hair samples). The THC only group had significantly worse scores compared to the other group. This provides evidence that different chemicals in cannabis can have divergent and contrasting effects on human brain, which may explain individual differences in response to cannabis.

Cannabinoids and schizophrenia; evidence from clinical studies

The first landmark longitudinal study demonstrating a link between cannabis abuse and schizophrenia was published in 1987 by Andreasson *et al.*^[21] They showed (in a 15-year follow-up of 45,570 Swedish conscripts) that the risk of schizophrenia was considerably high among heavy cannabis users (Relative risk, 6.0). An analysis of a smaller subsample of this study has reconfirmed the findings and showed that the association between cannabis and schizophrenia persisted even when allowing for other substance abuse and past psychiatric illness.^[22] The risk of developing schizophrenia was dose dependent, with those using cannabis more than 50 times having a higher risk.^[23] Another retrospective analysis of medical records over 12 years in Stockholm, Sweden, suggests a similar association between schizophrenia and cannabis abuse.^[24]

A nationwide population-based cohort in Denmark was analyzed retrospectively for association between familial predisposition to schizophrenia spectrum disorders and cannabis-induced psychosis. A clearly increased risk of having a family member with SSD to the index case developing SSD was demonstrated. Interestingly a similar increase of risk for 'cannabis-induced psychosis' was also demonstrated. However, further follow-up showed that of those treated for cannabis-induced psychosis, more than half developed schizophrenia spectrum disorders in the next 9 years, and this risk was independent of familial predisposition.^[25] In a case-control study involving schizophrenic patients and 2 groups of controls (siblings of patients, normal population), Veling *et al.*^[26] have also demonstrated that while cannabis use was associated with schizophrenia, it was independent of familial predisposition for schizophrenia.

Further evidence on 'inducement' of onset of psychosis by cannabis was explored by Kristensen *et al.*^[27] who prospectively followed up 48 individuals considered at risk for schizophrenia (based on family history and the structured interview for prodromal symptoms).^[28] Five patients were diagnosed with schizophrenia spectrum disorders in the next year, and cannabis use was significantly associated with psychosis ($P < .012$).

Corcoran *et al.*^[29] have also demonstrated that in at-risk individuals (with prodromal symptoms), cannabis use was temporally and significantly associated with anxiety symptoms and perceptual disturbances compared to non-users. Alcohol and cocaine failed to show such an association in both these studies.

Arendt *et al.*^[30] in a retrospective comparison of cannabis abusers with other drug users have shown that the former group had significantly higher levels of depression and personality disorders ($P < .001$, 0001 , respectively) after adjusting for age, gender and secondary abuse. The association with schizophrenia was less but significant ($P < .05$). A follow-up study of 535 patients treated for cannabis-induced symptoms in Denmark observed that 238 (44.5%) of them were subsequently treated for schizophrenia spectrum disorders within the follow-up period. Male gender and younger age were associated with increased risk. A comparison with non-cannabis-using patients showed that cannabis users were diagnosed with SSD at a younger age.^[31] The higher risk of schizophrenia in young cannabis abusers has also been observed by Arseneault *et al.*^[32] who analyzed data from a birth cohort in Dunedin, New Zealand. Younger age at first use of cannabis (15 vs. 18 years) was associated with a greater risk of schizophrenia, and the cannabis users as a group were more likely to be symptomatic by the age of 26 years than controls. Still, it was noted that majority of abusers did not develop psychotic symptoms. Barnes *et al.*^[33] have also shown that male gender and cannabis abuse are significantly associated with younger age of onset of schizophrenic symptoms. They further showed that such an association did not exist for alcohol or any other substance examined. However, Veen *et al.*^[34] in a population-based incidence study have reported that cannabis use but not gender predicts an earlier onset of psychosis. Several other studies have also demonstrated a link between cannabis abuse and a younger age for onset of symptoms.^[35-39]

A more recent study by Compton *et al.*^[40] while confirming the association between cannabis and SSD showed that alcohol too may have a role to play. However, this study concentrated on the first-degree relatives of schizophrenia patients with schizotypal traits, rather than the patients themselves. Such traits are seen in a continuum pattern in the general population and are thought to be linked to schizophrenia. The results showed that people who had ever used cannabis had more schizotypy scores and younger age at first use was associated with more interpersonal schizotypy (a subscale of assessment). Interestingly, individuals with younger age at first use of alcohol also had more schizotypy scores compared to controls. Stirling *et al.*^[41] have also confirmed that high-scoring schizotypal personalities are more likely to

experience psychotic-dysphoric events (when compared to normal population) and more intoxication following cannabis abuse.

Cannabis use was associated with induction of both positive and negative symptoms with cognitive deficits in both healthy individuals and schizophrenic patients.^[11] However, several studies have shown that the patients with 'cannabis-associated psychosis' and those subsequently diagnosed with schizophrenia demonstrate more positive symptoms and less negative symptoms.^[35,42-45] Interestingly Dubertret *et al.*^[39] have shown that while there is a clear reduction in negative symptoms in cannabis-using schizophrenic patients compared to non-using patients, the significance of positive symptoms disappears when comorbid substance use is taken into account. Authors suggest that the predominance in positive symptoms may not be due to cannabis alone but due to other substance abuse also.

Impaired cognition has been demonstrated in cannabis users in several studies, and this impairment was observed in both healthy and schizophrenic individuals, with the patients showing more deterioration.^[10,46] Still, some experimental studies have shown results to the contrary. Sevy *et al.*^[47] assessed cognitive functions of healthy individuals versus 2 groups of schizophrenic patients (with and without cannabis abuse). The emotion-based decision-making capacity was assessed by a laboratory task called Iowa gambling task, which has been used previously to compare schizophrenic patients with healthy individuals. While the patients in general fared badly compared to healthy people, there was no significant difference between cannabis-using and the non-using patients. Pencer *et al.*^[48] have assessed various domains of cognitive functioning in patients with first-episode psychosis and found no difference in those with substance abuse and those without. A majority in the substance abuse group had a history of cannabis use. The findings were the same at 1-year follow-up. The contrasting findings by Coulston *et al.*^[49] are also worth mentioning. They compared the cognitive functions in several domains between healthy individuals and schizophrenic patients. The patients were divided into 3 mutually exclusive groups depending on lifetime cannabis dependence, recency of use and frequency of use. While healthy individuals performed better than patients, among patients, those with lifetime dependence, high-frequency use and with more recent use performed better in some or several components of cognitive testing. They concluded that cannabis use is associated with enhanced cognitive function in schizophrenia.

The impact of cannabis use on follow-up and management of patients with schizophrenia is another

area of interest. Archie *et al.*^[50] studied the impact of an early intervention program (low-dose antipsychotic medication, avoiding delays in prescription, education of family members, etc.) on patients with first-episode psychosis with and without substance abuse. At one-year follow-up, the rate of drug abuse (including cannabis) had dropped significantly ($P = .002$) and the involuntary hospital admissions during the follow-up period did not differ between the drug abusers and non-abusers. However, a similar follow-up of 112 patients with first-episode psychosis (43.7% admitting to cannabis abuse) with SSD has shown that cannabis abuse was the most significant predictor for non-adherence to treatment and dropping out ($P < .001$, $P = .34$, respectively).^[51] In a case-control study making a comparison between schizophrenic patients with cannabis abuse and those without cannabis abuse, Rehman *et al.*^[38] demonstrates that cannabis-abusing patients are more likely to have relapses ($P < .05$ for admissions), encounters with police ($P = .001$) and less compliance with treatment ($P = .085$).

DISCUSSION

Association between cannabis use and schizophrenia spectrum disorders

It is clear from the studies quoted above that there is an association between cannabis use and psychosis. Three models have been developed to explain the possibilities in such an association.^[11,52]

1. Individuals prone to psychosis are also attracted to cannabis use (self-medication hypothesis)
2. Causal model — cannabis abuse increases proneness to psychosis
3. An underlying factor is responsible for both psychosis and cannabis abuse (psychosis proneness and cannabis use may have synergistic effects on development of SSDs)

In the first model, if individuals prone to psychosis are attracted to cannabis use, then it is expected to have more cannabis users among psychosis-prone individuals than among the general population. Still, the evidence in this regard is conflicting. Some studies show an increased rate of cannabis abuse in psychosis-prone individuals.^[40,53,54] while others do not show such a relationship.^[55,56] While there are many studies to show a temporal association of cannabis use with onset of psychosis following it, the evidence for a reverse relationship is less convincing. In fact, Archie *et al.*^[50] have shown that with early intervention there is a significant reduction in drug abuse. Veling *et al.*^[57] have also demonstrated that though cannabis abuse was more among schizophrenic patients, a genetic risk for

schizophrenia did not predict an increased cannabis use.

The causal model has been debated with much enthusiasm over the last decade. Still, any concrete evidence for cannabis abuse resulting in schizophrenia is lacking. Clearly, it is not an essential factor to develop SSDs as people without any exposure to cannabis develop the illness. While a temporal association between cannabis abuse and subsequent development of SSD has been demonstrated,^[21,23,29] it is not clear whether cannabis causes schizophrenia. The main argument against this model is that while cannabis use is on the rise worldwide, the incidence of schizophrenia has not increased.^[1] An analysis by Frisher *et al.*^[58] suggests that the annual incidence of schizophrenia and psychosis is either stable or declining in UK. However, in this retrospective analysis, trend of cannabis abuse was not traceable, though it was assumed to be on the rise. Still, it is important to note that this was a nationwide study representing 2.3% of the population in UK. While the numbers are large, the rising incidence of psychosis in high cannabis-use pockets (urban, disadvantaged communities) may be 'diluted' in the broader picture. Interestingly, Boydell *et al.*^[59] have shown that schizophrenia incidence in the urban southeast London has doubled over the three decades from 1965 to 1995 (diagnosis based on DSM-III-R). Many factors, including increasing population, may account for this. However, the increase in substance abuse also has to be considered. Still, there is the unchallengeable evidence that the majority of cannabis-abusing youth does so without developing psychosis, and it indicates that cannabis is not etiologically linked with psychosis in a majority. However, in a vulnerable group, cannabis use may contribute to onset of SSDs at a younger age with more positive symptoms. Whether it causes schizophrenia or simply acts as a stimulant in a vulnerable person is yet to be determined.

Regarding the third model, the higher risk of cannabis-induced symptoms in SSD-prone individuals may support the theory that a third factor is independently increasing risks for both.^[25,26] This third component may be genetics or concurrent drug abuse or other societal factors. In this 'vulnerable' group, psychosis proneness and cannabis use may have synergistic effects on development of full-blown SSDs.^[55]

The role of genetics in psychosis proneness has been explored in recent research. The polymorphism of the gene encoding the catechol-O-methyl transferase (COMT) enzyme (which degrades catecholamines such as dopamine, noradrenaline, etc.) is one such area of interest. A functional polymorphism of the gene results in 2 alleles — those of high (Val) and

low (Met) enzymatic activity. The highly active variant is hypothesized to cause imbalance in dopamine concentrations in prefrontal and mesolimbic areas, resulting in cognitive defects and psychotic phenomena, respectively. One study has shown that those homozygous for Val gene or even carriers of it are more likely to have psychotic symptoms and a subsequent diagnosis of a SSD following cannabis use.^[60] These findings were supported by Henquet *et al.* in a study of individuals with exposure to THC in a double-blind placebo-controlled randomized trial.^[61] Cannabinoid receptor 1 (CB1R) polymorphism is another factor assumed to influence cannabis abuse and development of SSDs. Still, the studies to date have yielded conflicting results.^[12,62,63]

Schizophrenia is not a pure consequence of genetic preponderance. Many environmental factors also predispose to its onset. On this premise, it can be assumed that environmental factors such as socioeconomic disadvantage may also contribute to cannabis abuse, as well as subsequent development of psychosis. Studies in this regard are limited. Compton *et al.*^[64,65] have demonstrated that among patients with a dual diagnosis of first-episode SSD and cannabis use, physical abuse and sexual abuse were significantly more in childhood. However, the numbers were too small to come to a valid conclusion. Concurrent drug abuse is another area of interest. Some authors suggest the possibility that cannabis is a 'gateway' drug to experimenting with other more potent drugs. And several other drugs of abuse, such as amphetamine and lysergic acid diethylamide (LSD), are known to have psychomimetic properties.^[4] Concurrent use of these drugs may contribute to the psychotic phenomena. However, again the evidences are conflicting, with some studies showing evidence for this hypothesis^[39] and some against.^[66]

So far, the evidence suggests a relationship between cannabis abuse and development of a SSD in a vulnerable minority. While some authors support the diagnosis of a separate cannabis-induced psychosis different from acute schizophrenia,^[67] others doubt such a diagnosis and suggest that this may in fact be schizophrenia itself.^[25,68] However, the characteristics of this 'psychosis' include younger age of onset and the presence of both positive and negative symptoms with predominance of positive symptoms.^[11]

Impact of cannabis use on the course of schizophrenia spectrum disorders

The impact of persistent substance use following a diagnosis of SSD varies according to different studies. Some suggest no impact of continued substance use on SSD,^[69] while others suggest that it is associated

with further deterioration of cognition, relapses, poor compliance and social functioning.^[38,45,51] The evidence favors the latter suggestion, as this fact has been observed by many authors in prospective studies with a larger sample size ($n > 50$).

Though there is evidence for an immediate impairment of cognition with cannabis use in both healthy and schizophrenic patients, whether it has lasting effects on cognition is unclear.^[9,10] Some authors suggest only a transient period of cognitive impairment,^[70] while others suggest a more persistent disability related to the dose, frequency and earlier cannabis use.^[71-73] However, it is interesting to note that while people with a diagnosis of SSD fare badly in comparison to normal individuals, those with a dual diagnosis of SSD + cannabis abuse have performed better in several aspects of cognitive testing.^[49] More recent and more frequent users of cannabis fared better in attention/processing speed and components of executive functions (which are predominantly frontal lobe functions), giving credit to the hypothesis that cannabis may tend to restore the imbalance of neurotransmitters in schizophrenics towards normalcy. Though this adds weight to the self-medication theory, this study only had 44 cannabis users and 34 of them were 'low-frequency' users (infrequent use during last year). Therefore, the validity of the conclusions is doubtful.

More evidence is needed with regard to the course of illness and treatment-related issues to see if patients with a dual diagnosis of SSD and cannabis use fare better with certain medications. There is already evidence that aripiprazole (case report) and quetiapine (open-label trial) reduce craving for cannabis and result in a better outcome for patients.^[74,75] Though not solid evidence, these observations identify the potential areas for further research.

Limitations

For this review, the search was limited to articles published in English within the last 10 years. While attempts were made to search and include related literature from bibliographies of cited articles, some relevant studies, especially the ones falling outside the search limits, may have been missed.

One important factor to consider is the variability of diagnostic criteria used by different authors. The older literature^[21,22] had used DSM-III-R (Diagnostic and Statistics Manual), and many of the more recent articles have used DSM-IV. A few authors^[38] have used ICD-10 (International Classification of Diseases). The differences in criteria used for diagnosis make it difficult to compare results. (A diagnosis of schizophrenia requires a minimum period of 6 months with symptoms

in DSM-IV, while it is just 1 month in ICD-10. This may result in a large number of formal diagnoses with ICD-10.)

Furthermore, many studies reported aspects of cannabis use based on self-reporting. While the indices such as 'ever having used cannabis' may be valid with such an approach, more detailed data such as usage frequency and recent use may not be accurate due to voluntary withholding of information or inability to recall accurately due to cognitive impairment.

Many studies showing an association between schizophrenia and cannabis use do so retrospectively. Though the individuals may have appeared healthy at the time of use of cannabis, it is not clear whether they demonstrated prodromal symptoms of schizophrenia at that time. This fact limits validity of establishing a temporal association between substance use and subsequent SSD. Few authors^[27,29] have designed their studies to follow up the 'at risk' individuals. However, the numbers used in these studies were small, but it is understood that a large-scale study of following up 'at risk' individuals would require significant amount of resources.

Much of the published data are from cohorts of developed countries and the impact of cannabis use in less privileged economies, where the burden may be more, has been overlooked. This is another area needing immediate attention.

CONCLUSION

The recent surge in research activity into cannabis use and its link to psychosis is timely, given the trend of increasing cannabis use worldwide. Despite the new clinical, biochemical and genetic evidence, the exact relationship between cannabis use and SSD is unclear. It is observed that not all schizophrenic patients use cannabis and not all cannabis users develop SSD. The evidence for the argument that schizophrenic patients are attracted to cannabis is not strong. There is also no firm evidence that cannabis causes SSDs. The most plausible explanation is that cannabis may precipitate a psychosis in minority of abusers who are vulnerable. Still, 2 issues are unclear in this argument. First, what constitutes this vulnerability: Is it genetic, behavioral, socioeconomic or a combination of these factors? Second, whether this psychosis is a separate diagnosis or is it schizophrenia occurring early?

More research is needed into resolving these issues; and also on areas of drug combinations in treatment, rehabilitation and socioeconomic burden on patients with a dual diagnosis, especially in developing nations.

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