

Cannabis Use and Risk of Schizophrenia: A Literature Review

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Abstract

Background and Objective: Cannabis remains the most widely used illicit drug worldwide. The similarity in the chemical structure of tetrahydrocannabinol to the brain chemical anandamide allows the body to recognize it and alter normal brain functioning. The objective of this review article is to summarize the evidence for the association between cannabis and schizophrenia.

Methods: A literature search was conducted using the PubMed database and other sources. The keywords used were “cannabis” and “psychosis” and “schizophrenia.” Fifty-two articles relevant to our topic have been selected for this review.

Results: Evidence from observational epidemiological studies has shown a positive association between regular cannabis use and schizophrenia risk. Meta-analyses and Mendelian randomization studies support the evidence from observational study designs. **Discussion and Conclusions:** The association between cannabis and schizophrenia is biologically plausible. Moreover, there has been emerging evidence of genes interacting with cannabis use to confer a higher risk for schizophrenia. There are enough reason and sufficient epidemiological evidence to warn people about the risk of developing schizophrenia with cannabis use.

Scientific Significance: The increasing legalization of cannabis for recreational use is of significant concern. Long-term cannabis use might predispose people to increased risk of developing schizophrenia. Health professionals have a major role to play by taking maximum advantage of social and psychological interventions to educate people about the potential danger associated with cannabis and avoid its use.

Keywords: Cannabis, Schizophrenia, Psychotic Disorder, Psychosis, Tetrahydrocannabinol

Background and Objective

Several articles have alarmed the nation about the risks associated with using cannabis [1]. It is worthwhile to mention that cannabis is the most widely consumed illicit drug worldwide. In 2016, 192.2 million people aged 15-64 years used cannabis globally, out of which 13.8 million users were young population aged 15-16 years. Its annual prevalence rate of use in North America during the same year was 12.9 percent [2].

As more states have legalized cannabis for recreational use, there is a responsibility to understand whether there are associated risks with its use [3]. The most recent report from the global drug survey shows that cannabis is the most commonly used drug (excluding alcohol and tobacco/nicotine products) [4]. Further, it remains the most widely used drug among those receiving drug treatment in several regions of the world, including North America (Figure 1) [2].

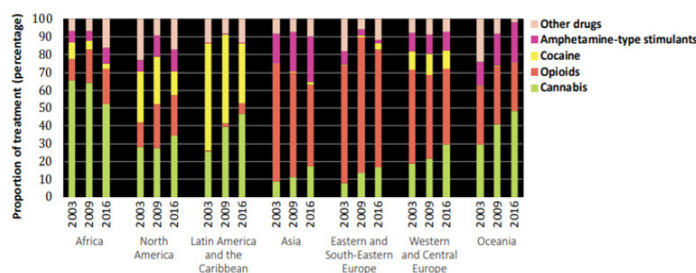


Figure 1: Trends in the proportion of primary drug of use in drug treatment admissions, by region, 2003, 2009, and 2016 [2].

Cannabis has two key ingredients, namely delta-9-tetrahydrocannabinol (Δ -9-THC or simply THC) and cannabidiol. The psychoactive property of THC is responsible for the psychotic outcomes, but cannabidiol, on the contrary, is believed to have opposite effects [5]. The similarity in the chemical structure of THC to the

Table 2: Synopsis from general population studies assessing the effect of cannabis use on the risk of schizophrenia.

Authors	Aim	Criteria	Result	Odds ratio (crude)
Regier et al [14]	Find the prevalence of comorbid substance use disorder and mental disorder	Interview-based psychotic experiences measure	Higher odds of co-morbid occurrence of cannabis use disorder and schizophrenia	4.5
Rolfe et al [15]	Determine the association between cannabis use and psychotic illness	DSM III criteria for schizophrenia	Cannabis use as a significant risk factor for schizophrenia	4.4
Hall et al [16]	Evaluate the relationship between cannabis use and psychotic disorder	Self-reported 'diagnosed with schizophrenia'	Cannabis use may precipitate schizophrenia or exacerbate its symptoms	2.9

Note: DSM, Diagnostic and Statistical Manual of Mental Disorders.

Additionally, a register-based study of patients with cannabis-induced psychosis reported significant risk (eight-year cumulative risk 46%; 95% CI 35%-57%) of converting to schizophrenia diagnosis later in life [17]. Still, the possibility of recall bias cannot be ruled out in a case-control study [8, 18]. Additionally, sampling bias is a potential bias in both of these study designs [8, 19]. Therefore, other study designs were also examined for additional evidence in support of an association between cannabis and schizophrenia.

Evidence from Cohort Studies

Cohort studies provide a better design to look for an association between cannabis use and schizophrenia or related disorders as compared to case-control and cross-sectional studies [8]. Most of the cohort studies have found an association between cannabis use and psychotic disorders such as schizophrenia (Table 3). The

historical Swedish prospective cohort study has been followed up twice for 15 and 27 years, respectively, and on both occasions, it founded an increased risk of developing schizophrenia with cannabis use in a dose-dependent fashion. The result remained statistically significant even after adjusting for potential confounders [20, 21]. A recent study with 35 years of follow up on the same cohort supported the earlier findings [22].

Adolescent use of cannabis showed association to adulthood diagnosis of schizophreniform disorder [23]. Another study which was a 30-year follow-up prospective cohort study found an association between substance use and later onset of subclinical psychosis. Schizotypal signs were found to be strongly associated with regular cannabis use in adolescence, whereas development of schizophrenia nuclear symptoms was significantly related to casual cannabis use in adulthood [24].

Table 3: Synopsis from cohort studies assessing the risk of schizophrenia or related disorders with cannabis use.

Authors	Sample size	Follow-up period	Outcome	Odds ratio (95% confidence interval)
Andreasson et al [20]	45,570	15 years	Schizophrenia	6.0 (4.0-8.9)
Zammit et al [21]	50,087	27 years	Schizophrenia	3.1 (1.7-5.5)
Manrique-Garcia et al [22]	50,087	35 years	Schizophrenia	3.7 (2.3-5.8)
Arseneault et al [23]	1037	15 years	Schizophreniform disorder	4.5 (1.1-18.2)
Arseneault et al [23]	591	30 years	Schizotypal signs; Schizophrenia nuclear symptoms	2.6 (1.6-4.2); 1.6 (1.0-2.5)

Meta-analyses and Mendelian Randomization Studies

The outcome from several meta-analyses is in favor of an association between cannabis and schizophrenia or related disorders (Table 4). A systematic review by Semple and colleagues showed cannabis use as an independent risk factor for development of schizophrenia [25]. In another meta-analysis, Moore and colleagues found a positive association between cannabis use and

risk of developing a persistent psychotic illness later in life [26]. A more recent meta-analysis of ten observational studies showed a similar dose-response relationship between cannabis use and psychotic outcomes like previous meta-analyses. In addition, it supported the evidence that the risk of cannabis use is not only limited to transient psychotic symptoms but rather a continuum between psychotic experiences and schizophrenia [27].

Table 4: Synopsis from meta-analysis studies looking for an association between cannabis and schizophrenia.

<i>Authors</i>	<i>Objective</i>	<i>Method</i>	<i>Outcome</i>	<i>Odds Ratio (95% confidence interval)</i>
Semple et al [25]	Evaluate the association between cannabis use and psychotic outcomes	Systematic review of case-control and cohort studies relevant to cannabis use and schizophrenia, psychosis, or psychotic symptoms	Cannabis as an independent risk factor for schizophrenia, psychosis or psychotic symptoms	2.9 (2.4-3.6)
Moore et al [26]	Assess the persistent psychotic outcomes with cannabis use	Systematic review of longitudinal and population-based studies relevant to cannabis use and psychotic outcomes	Cannabis use increases psychotic outcomes independently of transient intoxication effects; risk of developing a psychotic illness later in life	1.4 (1.2-1.7)
Marconi et al [27]	Investigate the association between the degree of cannabis consumption and psychotic outcomes, and to quantify the magnitude of the effect	Systematic review of case-control, cross-sectional, and cohort studies relevant to cannabis use and psychotic outcomes	Cannabis use as a continuum between transient psychotic symptoms and schizophrenia	2.0 (1.7-2.3)

Also, Mendelian randomization studies results are in favor of an association between cannabis and schizophrenia (Table 5). Two-sample Mendelian randomization (MR) of genetic variants of interest extracted from genome-wide association study (GWAS) allows for causal inference (subject to certain assumptions) from observational data [28]. Single nucleotide polymorphisms (SNPs) associated with schizophrenia extracted from the GWAS schizo-

phrenia and identified in the GWAS cannabis initiation were combined together using an inverse-variance-weighted approach. It showed that cannabis initiation increased schizophrenia risk [29]. Using MR principals, a recent study matched SNPs-risk of schizophrenia to the SNPs-ever use of cannabis and supported the previous evidence of an association between cannabis and increased risk of schizophrenia [30].

Table 5: Synopsis from Mendelian randomization studies assessing the association between cannabis and schizophrenia.

<i>Authors</i>	<i>Procedure</i>	<i>Result</i>	<i>Odds Ratio (95% confidence interval)</i>
Gage et al [29]	Ascertain association between cannabis and schizophrenia using Mendelian randomization	Positive association between cannabis initiation and increased risk of schizophrenia	1.04 (1.01-1.07)
Vaucher et al [30]	Determine the nature of the association between cannabis use and risk of schizophrenia using Mendelian randomization	Positive association between ever use of cannabis and increased risk of schizophrenia	1.37 (1.09-1.67)

Experimental Studies

Outcome from several experimental study designs have shown an association between cannabis and psychosis, indicating the possible role of cannabis in the pathophysiology of psychotic disorders such as schizophrenia (Table 6). Azorlosa and colleagues have shown smoked cannabis dose-effects on acute subjective and performance impairment [31]. A balanced double-blind cross-over study design demonstrated temporary impairment of episod-

ic memory and learning with oral Δ -9-THC in a dose-dependent fashion [32]. Randomized controlled trials using the psychoactive constituent of cannabis has produced acute psychotomimetic effects. Intravenous injection of synthetic Δ -9-THC in psychiatrically healthy individuals under controlled laboratory condition has produced temporary cognitive impairments along with a full range of transient schizophrenia-like positive and negative symptoms [33, 34].

Table 6: Synopsis from experimental study designs assessing the association between THC and psychotic outcomes.

<i>Authors</i>	<i>Aim</i>	<i>Method</i>	<i>Outcome</i>
Azorlosa et al [31]	Determine smoked cannabis effects on subjective and performance measures in moderate users of cannabis	4, 10 or 25 puffs from cigarettes containing either 1.75% or 3.55% THC on six separate days	25-puff, 3.55%-THC condition produced reliably impaired performance on a battery of psychomotor and cognitive tasks
Curran et al [32]	Detail the acute and residual cognitive effects of oral Δ -9-THC in infrequent cannabis users	7.5 mg and 15 mg of oral Δ -9-THC with matched placebo assessed pre and 1, 2, 4, 6, 8, 24, and 48 h post-drug	Oral Δ -9-THC impaired episodic memory and learning in a dose-dependent manner
D'Souza et al [33]	Characterize the psychomimetic effects of intravenous Δ -9-THC in healthy individuals	2.5 mg and 5 mg of intravenous Δ -9-THC with matched placebo assessed pre and 10, 80, and 200 min post-injection	Intravenous Δ -9-THC impaired cognition and produced schizophrenia-like positive and negative symptoms
Morrison et al [34]	Study the psychomimetic effects of intravenous Δ -9-THC in healthy humans	2.5 mg of intravenous Δ -9-THC with matched placebo assessed pre and 30, 80, and 120 min post-injection	Intravenous Δ -9-THC impaired cognition and produced schizophrenia-like positive and negative symptoms

Note: Δ -9-THC (or simply THC), delta-9-tetrahydrocannabinol.

Discussion and Conclusions

Several observational epidemiological studies have shown a positive association between cannabis use and risk of development of schizophrenia, even after adjustment for covariates [8]. A follow-up study from the Dunedin cohort assessing the association between cannabis use and cognitive impairment noted neurocognitive decline (a core feature of schizophrenia) in several domains such as executive functioning, processing speed, memory, and verbal comprehension. The deficits persisted even after the cessation of use, indicating the effects are not only short-term but rather has long-term consequences [35]. Similarly, meta-analyses have shown cannabis use as a continuum between acute psychotic experiences and schizophrenia [27, 36]. Therefore, there is a strong tendency for the conversion of cannabis-induced psychosis to schizophrenia diagnosis justifying the notion that cannabis-induced psychosis is not a distinct diagnostic entity [17]. Results from Mendelian randomization having the least possibility of residual confounding and reverse causation supports the evidence from observational designs [29, 30].

Psychotic symptoms have shown exacerbation in chronic, stable schizophrenia patients maintained on antipsychotics with Δ -9-THC administration [37]. Although experimental manipulation of cannabis use assessing the development of psychotic disorders has not been conducted so far for obvious ethical reasons, the randomized controlled trials under laboratory condition have shown the development of acute schizophrenia-like symptoms with the administration of Δ -9-THC. This indicates the possible involvement of brain cannabinoid receptors in the pathophysiology of the development of psychotic disorders such as schizophrenia [7, 33].

Biological plausibility of the association between cannabis and schizophrenia is demonstrated by the cannabis-induced increase in dopaminergic activity in the mesolimbic tract producing schizophrenia-like positive symptoms and decreased dopaminergic activity in prefrontal cortex resulting in schizophrenia-like negative symptoms and cognitive deficits [38, 39]. Further, researchers have shown up-regulation of cannabinoid-1 (CB1) receptors in specific brain regions in schizophrenia, and their down-regulation with the use of antipsychotics [40, 41]. Additionally, both positive symptoms of schizophrenia and Δ -9-THC has shown a similar reduction in electroencephalographic coherence on electroencephalogram (EEG) [42, 43].

Further, it is the endocannabinoid system of the brain, which plays a central role in many neurodevelopmental processes, including neuronal formation, maturation, migration, and specification [44]. Exposure to cannabis might impair the endocannabinoid system affecting the development of mature brain functioning resulting in increased schizophrenia risk [45]. Further, chronic cannabis use has shown changes in brain structure such as smaller cerebellar white-matter volume similar to as in schizophrenia [46].

There has also been emerging evidence of genes interacting with cannabis use to confer a higher risk for schizophrenia. Functional polymorphism in the Catechol-O-methyl transferase (COMT) gene which metabolizes dopamine in the prefrontal cortex results in two allelic variants, the valine (Val), and the methionine (Met) allele, associated with high versus low enzyme activity, respectively (Figure 4). Individuals with the Val/Val genotype were at a high risk of developing schizophrenia-type disorders after cannabis exposure [47].

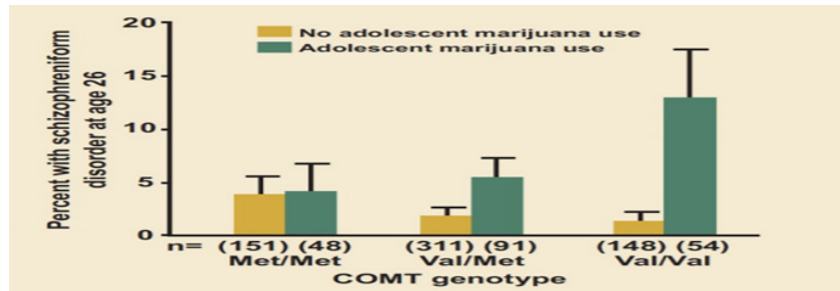


Figure 4: Genetic variations in COMT (Catechol-O-methyl transferase) influences the psychotic outcome with cannabis use [6].

There has been an increase in interest in studying the AK strain transforming (AKT1) gene in recent years which codes for a phosphorylating enzyme that is activated by cannabinoid receptors. The AKT1 gene implicated in schizophrenia risk exists in three

functional variants (Figure 5). Individuals with the C/C variant who were using cannabis daily (green bars) had a higher risk of developing schizophrenia-type disorders than cannabis users with the T/T or C/T variants [48].

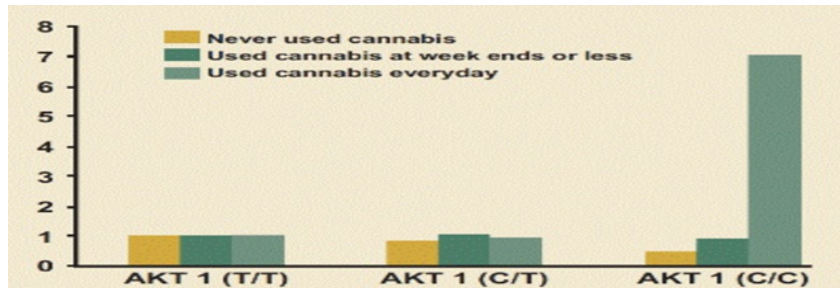


Figure 5: AKT1(AK strain transforming) gene variations and susceptibility to schizophrenia-type disorders [6].

Further, variation in the SNP rs2494732 of the AKT1 gene moderated both short- and long-term psychotic outcomes with cannabis use. Other candidate genes such as brain-derived neurotrophic factor (BDNF), dopamine transporter (DAT1), and variation in another SNP of the AKT1 gene (SNP rs1130233) has shown promising evidence in support of an association between cannabis use and risk of schizophrenia [35].

biological evidence to warn people about the risk of developing schizophrenia with long-term cannabis use [49]. At the same time, we suggest considering reclassification of cannabis as a schedule II drug which will open up more research possibilities in this area [50].

We conclude that there are enough reason and sufficient epide-

Scientific Significance

Despite the decline observed in 2016, cannabis continues to be the drug seized in the largest amount worldwide (Figure 6) [2].

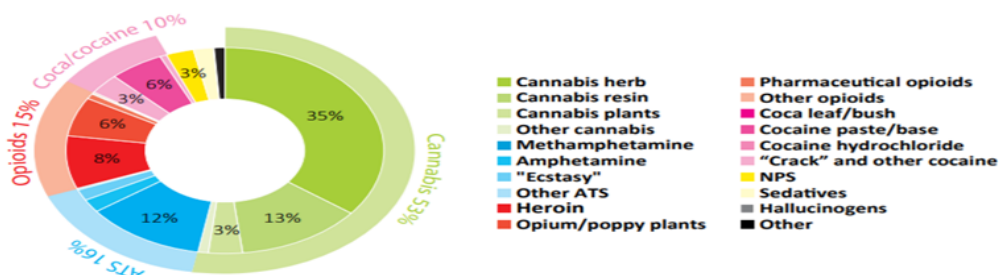


Figure 6: Distribution of the global number of drug seizure cases, 2015-2016 [2].

The increasing legalization of cannabis for recreational use is already reporting a higher rate of people requiring hospitalization for symptoms related to its use [51]. Long-term use might very well predispose those people to increased risk of developing schizophrenia [49]. It is a meaningful approach to maximize the advantage of social and psychological interventions to educate people about the potential danger associated with cannabis and avoid its use [52].

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