Cannabis and Schizophrenia: Is there a link?

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Abstract

Background
Schizophrenia is serious mental disorder that affects an estimated 1 in 100 Canadians and their families. Typically, those suffering from schizophrenia start to present a wide variety of symptoms, including delusions, hallucinations, disturbances of thought, and social withdrawal, between the ages of 15 to 25. The role of cannabis as a causal risk factor for the development of schizophrenia remains largely debatable. In the last decade, countless studies have been performed to determine whether cannabis use in adolescence is associated with the development of schizophrenia in adulthood.
Objective
The objective is to determine whether there is an association between cannabis use in adolescence and later development of schizophrenia by reviewing several pieces of epidemiological literature.
Methods
By conducting a literature review, we were able to identify a number of epidemiological studies that assessed the relationship between cannabis use and the development of schizophrenia. Through the use of keywords, such as "schizophrenia", "adulthood", "adolescence", and "cannabis", we were able to obtain and analyze 12 studies published in scholarly peer-reviewed journals located on PubMed, Medline, and The University of Ottawa Library. In our review, we included only the most recent studies conducted after 2009 and included studies only written in English.
Results
12 studies were analyzed to provide evidence that there is an association between the use of cannabis in adolescence and development of schizophrenia in those that are vulnerable to its effects. Individuals were more likely to develop schizophrenia if they smoked at an earlier age (<18 years), had a genetic predisposition, and/or had high cumulative exposure.
Conclusions
The current literature indicates that cannabis is not a necessary nor sufficient cause of schizophrenia but evidence demonstrates that a history of cannabis use in adolescence can increase the risk of developing schizophrenia in vulnerable individuals.

Introduction

Schizophrenia is a serious psychiatric disorder that affects an estimated 1 in 100 Canadians and their families [14]. The annual incidence rate of schizophrenia is 10 per 100 000. According to the *Diagnostic and Statistical Manual of Mental Disorders* (5th edition), schizophrenia is characterized by psychotic symptoms, social or occupational dysfunction, and continuous signs of disturbance persisting for at least six months. Psychotic symptoms are further divided into positive and negative symptoms. Positive symptoms include delusions and hallucinations, whereas negative symptoms consist of apathetic withdrawal, lack of speech, diminished thought content, and a reduced range of emotions [4]. In most cases, those suffering from schizophrenia begin to present a variety of symptoms between the ages of 15 and 25 [14]. The precise cause is yet to be determined but researchers have identified a number of possible genetic and environmental risk factors that may contribute to the development of schizophrenia. Some of these risk factors include genetic vulnerability, exposure to viral infections, childhood trauma, and illicit drug use [14]. In the last decade, countless studies have been performed to determine whether cannabis use in adolescence is associated with the development of schizophrenia later in life.

Cannabis is one of the most widely used recreational drugs across the globe [3, 11]. Cannabis has become increasingly popular in several English-speaking countries including Canada, the United States, New Zealand, and Australia [15]. It has been well established that the active ingredient in cannabis, delta-9-tetrahydrocannabinol (THC), is psychomimetic. Psychomimetic refers to the ability of THC to induce psychotic-like symptoms, similar to those evident in schizophrenia patients, depending on the dose and vulnerability of an individual [4]. THC exerts its effect on the brain by acting as an agonist at the CB_1 cannabinoid receptor [9]. In addition, a second CB_2 cannabinoid receptor, located in the peripheral tissues of the body, is also activated in response to the binding of THC [9]. Both types of cannabinoid receptors are G-protein receptors that when activated inhibit the activity of adenylate cyclase [9]. Despite existing knowledge of the THC on the nervous system, the role of cannabis as a causal risk factor for the development of schizophrenia remains largely debatable.

Research Question

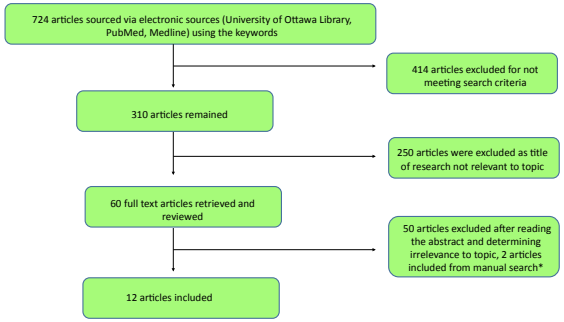
The purpose of this literature review is to answer one question: does cannabis use in adolescence increase the likelihood of developing schizophrenia in adulthood?

Methods

Information was extracted from the University of Ottawa Library, PubMed, and Medline databases. Keywords used in the literature search included: "schizophrenia", "cannabis", "adolescence", "adulthood". Articles meeting the inclusion criteria were published since 2009*, in English, and from peer-reviewed journal articles related to the relationship between cannabis use and the development of schizophrenia.

*Despite having been published before 2009, two longitudinal studies were specially included from 1987 and 2002. Studies conducted by Andreasson [1] and Arseneault [2] were frequently mentioned in almost all studies reviewed.

Search Strategy



Results

After collecting and analyzing 12 relevant studies, the results of the literature review indicate that there is an association between cannabis use in adolescence and the development of schizophrenia in adulthood. The studies below are presented in order of strength of the evidence, from the strongest evidence (systematic review) to the weakest evidence (grey literature).

Table 1. Summary of studies linking cannabis and schizophrenia

Authors	Country (year)	Study Design	Results
D'Souza et al.	U.S.A (2009)	Systematic Review	Studies were reviewed to conclude that a variety of risk factors contribute to the development of schizophrenia. Risk factors include: heavy and early users of cannabis as well as genetic vulnerability.
Loberg et al.	Norway (2009)	Systematic Review	23 studies were reviewed to conclude that cannabis use contributes to the development of schizophrenia. Risk factors include: genetic vulnerability and early onset of cannabis use. Early use of cannabis has a more pronounced negative effect on the development of the brain.
Shapiro et al.	Canada (2010)	Systematic Review	Studies were reviewed to conclude that cannabis is a significant risk factor in the etiology of schizophrenia. Adolescents are more vulnerable because of their stage of mental development.
Casadio et al.	Italy, UK (2011)	Systematic Review	10 longitudinal studies were reviewed to conclude that cannabis use does play a causal role in the etiology of schizophrenia but it is not essential nor sufficient for its development. Some individuals are more vulnerable to its effects depending on their exposure, ages of first use, developing brain, and predisposing genetic factors.
Hill	Canada (2014)	Systematic Review	Studies were reviewed to conclude that there is little evidence that cannabis is a primary contributing factor to developing schizophrenia. However, results reveal that high risk populations have a higher vulnerability to developing schizophrenia.
Malone et al.	Australia, U.S.A, Italy (2010)	Systematic Review	Studies were reviewed to conclude that cannabis use is a risk factor for schizophrenia. Individuals with a genetic predisposition are more vulnerable to developing schizophrenia and more likely to experience an unfavourable prognosis.
Gage et al.	UK (2013)	Systematic Review	Studies were reviewed to conclude that cannabis is a risk factor increasing the risk of developing schizophrenia.
Arseneault et al.	Canada, New Zealand (2002)	Cohort Study	A follow-up at ages 11, 15, 18 and 26 conducted on 1037 individuals revealed that earlier use of cannabis in adolescence increases the likelihood of experiencing psychotic symptoms in adulthood. When psychotic symptoms were controlled for at age 11, the study found that cannabis users at age 15 and 18 had more schizophrenia symptoms than controls at age 26.
Andreasson et al.	Sweden (1987)	Cohort Study	During a 15-year follow-up of 45 570 Swedish conscripts, researchers found that there was a strong association between level of cannabis exposure at baseline and the development of schizophrenia in the follow-up period. Use of cannabis at least once resulted in a relative risk of 2-4, while the relative risk of developing schizophrenia in heavy users (50 or more occasions) was 6.
Manrique-Garcia et al.	Sweden (2011)	Cohort Study	During a 35-year follow-up of 50 087 military conscripts, researchers found that cannabis use increases the risk of schizophrenia in a long-term study. The odds ratio for psychotic outcomes in frequent cannabis users compared to non-users was 3.7.
McGrath et al.	Australia (2010)	Cohort Study	During a 21-year follow-up of 3801 young adults, researchers found that early cannabis use is associated with schizophrenia. Longer duration since first cannabis use predicted a higher risk of developing schizophrenia. This association persisted in sibling pairs reducing the likelihood of confounding variables impacting the results of the study.
Health Canada	Canada (2013)	Grey Literature	Data obtained from the government of Canada suggests that there is a positive association between cannabis use and development of schizophrenia, especially in people that are genetically vulnerable.

Discussion

All twelve studies demonstrated similar results concluding that there is a positive association between cannabis use in adolescence and schizophrenia development in adulthood. Three common risk factors found in the literature review were genetic susceptibility, early-life use, and heavy cannabis use.

Genetic Susceptibility

It is known that individuals with a family history of schizophrenia have an increased risk of developing schizophrenia. Researchers have determined that a single-nucleotide polymorphism in the gene, catechol-o-methyltransferase (COMT), is found in families with a history of schizophrenia [7]. The COMT gene codes for an enzyme that degrades dopamine, epinephrine, and norepinephrine in the prefrontal cortex. Research shows that cannabis interacts with the mutated COMT gene leading to increased gene expression. This results in reduced dopamine neurotransmission (cognitive deficits) and increased levels of dopamine signaling (psychosis) [5]. Multiple studies demonstrate through scientific evidence that the mutated COMT gene acts as a specific risk factor for the development of schizophrenia [3, 5, 7, 8, 10].

Degree of Exposure

Studies have shown that the degree of exposure is a significant risk factor to the development of schizophrenia. Individuals considered to be heavy users of cannabis (>50 occasions) were found to be 6 times more likely than non-users to be diagnosed with schizophrenia [1, 3, 5]. Cannabis users in their first episode of psychosis were more likely to report using cannabis on a daily basis [3]. Cumulative exposure and duration of cannabis present a dose-response relationship with schizophrenia.

Time of Initiation

Researchers found that early use of cannabis under 18 years of age is associated with a two-fold increase in the risk [3]. Earlier use (<12 years of age) was strongly and independently associated with an increased likelihood of psychiatric hospitalizations [3, 15]. Those who used cannabis at age 15 were 4 times as likely to develop a diagnosis for schizophreniform disorder at age 26 than controls [2, 11].

During adolescence, several regions of the brain undergo dramatic levels of growth and synaptic remodelling. THC exerts its effects by acting as an agonist at the cannabinoid receptors in the prefrontal cortex. The prefrontal cortex is most heavily implicated in schizophrenia [8]. Therefore, adolescents are more vulnerable to the effects of THC because their brains are still maturing.

Bradford Hill Criteria [5, 11, 15]
Consistency and Coherence: There is a consistent and coherent number of studies in the literature that conclude an association between cannabis use and the development of schizophrenia.
Dose-Respondent Relationship: The risk of developing schizophrenia increases in a dose-dependent manner following repeated exposure to cannabis.
Temporality: Multiple studies have shown that the onset of cannabis use precedes schizophrenia development.
Direction: Evidence shows that the risk of schizophrenia does not predispose to cannabis use.
Biological Plausibility: Higher levels of THC exposure leads to an increased risk of developing schizophrenia.

Strengths and Limitations

In evidence-based medicine, systematic reviews are considered the best evidence for making informed clinical decisions and implementing policies. Longitudinal cohort studies have been some of the most effective studies because researchers are able to follow individuals over time to determine the "temporal sequence of putative cause and putative effect" [4]. Furthermore, cohort studies allow researchers to calculate the relative risk of developing an outcome and yield information on the incidence of an outcome (schizophrenia) in a desired population following exposure to a particular risk factor (cannabis).

Cohort studies are vulnerable to potential biases including non-response bias and loss to follow-up bias. For example, underestimations of the relationship between cannabis use and psychotic symptoms may be present in cohort studies due to follow-up bias, in which cannabis users and people with psychotic symptoms are more likely to drop out of the study [6]. Researchers need to be familiar with the laws and regulations pertaining to cannabis use in the country of study. If the use of cannabis is illegal, individuals are more likely to underreport their use of cannabis throughout the study resulting in response bias. Furthermore, some of the studies analyzed did not control for confounding factors, such as tobacco and other illicit drug use.

Conclusions

Currently, there is sufficient evidence to conclude that there is an association between cannabis use in adolescence and the development of schizophrenia in adulthood. In the literature, three main risk factors, genetic predisposition, early-life use (<18 years of age), and/or heavy cannabis users, have been found to increase the likelihood of developing schizophrenia. Cannabis is clearly not necessary for the development of schizophrenia because not all adults with schizophrenia used cannabis in adolescence. Nor is cannabis a sufficient cause for schizophrenia because the majority of adolescent cannabis users did not develop schizophrenia in adulthood [3, 5]. According to the Bradford Hill Criteria, existing evidence fulfills most but not all the useful criteria for determining causality. The role of cannabis in schizophrenia development is still not fully understood.

Recommendations for Further Study

Schizophrenia is a complex mental illness that is still not fully understood by medical professionals. Further research needs to be conducted to determine the precise biomechanical mechanism in which cannabis exerts its effects on the adolescent brain. Current literature focuses on the ability of cannabis to induce positive symptoms without acknowledging the possibility of cannabis use in contributing to the development of negative symptoms [6]. Future research should to focus on the relationship between cannabis use and the negative symptoms of those suffering from schizophrenia.

Contributions
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