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The Cannabis-Psychosis Link

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Acknowledgments- This article was supported in part by the Canada Foundation for Innovation (#16014), the Chair in Addiction Psychiatry from the University of Toronto, and by grants from the Canadian Institute for Health Research (MOP#245931, to T.P.G.) and the Ontario Mental Health Foundation to Dr George. Ms Rabin is supported by Studentships from the Canadian Institutes of Health Research and an Ontario Graduate Scholarship.



Marijuana doesn't count, does it? Clinicians are familiar with this common reply when screening for drug use.

Cannabis- the most common illicit substance- has managed to exempt itself from the hazardous reputation held by other illicit drugs.¹ As mental health practitioners, it is our duty to educate our patients about the potential harms and consequences of cannabis use. This important task is complicated by the disagreement and uncertainty surrounding the nature of the interaction between cannabis and psychotic disorders.

While research suggests that cannabis use can induce an acute psychotic state, there is controversy about whether it may precipitate psychotic disorders, such as schizophrenia. In this article, we provide an update on the literature on this important issue, emphasize areas in need of research, and provide clinically useful recommendations.

More than 16 million Americans use cannabis on a regular basis, typically beginning in adolescence. Notably, it is estimated that approximately 4% of the population have a diagnosis of either cannabis abuse or dependence.¹ A history of cannabis misuse is even more common in patients who are schizophrenic than in the general population;

25% of patients with schizophrenia have a comorbid cannabis use disorder. Cannabis use disorders are especially common in younger and first-episode patient samples and in samples with high proportions of males.²

Neurobiology

Marijuana contains more than 400 chemical compounds, including over 60 cannabinoids that contribute to its psychopharmacological effects. The primary psychoactive constituent of cannabis is delta-9-tetrahydrocannabinol (THC). Other plant cannabinoids include delta-8-tetrahydrocannabinol; cannabinol; and cannabidiol (CBD); CBD is the second major psychoactive constituent of cannabis.³ The ratios of these and other cannabinoids vary enormously in preparations of cannabis, and little information exists about the concentration of each of the particular cannabinoids in commonly used cannabis products. Concerns have been expressed regarding the large increase in the potency of cannabis and the surrounding health implications. In the 1960s, the THC content was thought to be in the range of 1% to 3%; today it can reach up to 20%.⁴

The endogenous cannabinoid system consists of 2 types of G-protein-coupled receptors: cannabinoid 1 (CB1) and cannabinoid 2 (CB2) receptors. CB1 receptors are the most abundant in the brain, while CB2 receptors predominate on immune cells. CB1 receptors are highly concentrated in brain regions implicated in the putative neural circuitry of psychosis and cognitive function. These include the hippocampus, prefrontal cortex, anterior cingulate, basal ganglia, cerebellum, and cortex, with lower levels present in the thalamus, hypothalamus, and amygdala. Activation of CB1 receptors mediates the behavioral and physiological effects of both endogenous and exogenous cannabinoids in the brain.⁴

An important role of the CB1 receptor is to modulate neurotransmitter release in a manner that maintains homeostasis by preventing excessive neuronal activity in the CNS.⁵ CB1 receptors are localized on presynaptic neuron terminals on both inhibitory and excitatory neurons, yet they predominate on G-aminobutyric acid interneurons.⁶ It is the inhibitory neurons that are thought to mediate most of the effects of cannabinoids. In addition, the action of cannabinoids includes interactions, albeit indirectly, with the dopaminergic system.

THC is a partial agonist at the CB1 receptors, where it has modest affinity and low intrinsic activity. In contrast, CBD shows very little affinity for CB1 receptors. Moreover, the precise molecular mechanism of action of CBD remains unclear. The main endocannabinoids are anandamide and 2-arachidonylglycerol. In contrast to classic neurotransmitters, endocannabinoids can function as retrograde synaptic messengers- they are released from postsynaptic neurons and travel backward across synapses, activating CB1 on presynaptic axons and suppressing neurotransmitter release.

Cannabinoids produce an increase in the dopaminergic activity in the mesolimbic reward pathway, which plays a pivotal role in mediating the reinforcing effects of most drugs of abuse. The increased dopaminergic drive elicited by the cannabinoids could underlie the abusive property of the drug and

increases in positive psychotic symptoms induced by THC.⁷ Recurrent cannabis use produces prolonged and excessive stimulation of the CB1 receptor, and this is thought to disrupt endocannabinoid system function.⁸ Several lines of evidence exist to suggest a role for cannabinoids and their receptors in the pathophysiology of schizophrenia. It has also been proposed that this CB1 receptor overstimulation may be a contributing factor in triggering THC-induced psychosis.⁹

The cannabis-psychosis link

Many studies have explored the link between cannabis and psychosis (Table). In a systematic review, Moore and colleagues¹⁰ surveyed the literature on this topic. They looked at population-based longitudinal studies as well as nested case-control studies that assessed the impact of cannabis use on the later development of psychosis. The %psychosis+outcomes required the diagnosis of a primary psychotic disorder or affective psychosis, or the occurrence of delusions, hallucinations, or thought disorder during the study period. Results from 7 cohort studies showed a 40% increased risk of psychosis in cannabis users compared with nonusers. The data also revealed a dose-response effect- the risk of psychotic symptoms was increased approximately 50% to 200% in those who used cannabis frequently compared with nonusers.

What is already known about the link between cannabis use and psychosis?

- There is strong evidence to support the hypothesis that cannabis consumption is a risk factor for the development of psychotic symptoms and schizophrenia.

What new information does this article provide?

- This article emphasizes the negative effects of cannabis use in young populations and in those who may confer a genetic risk. We further believe that even in the face of enhanced cognitive function among cannabis-using patients with established schizophrenia, this cannabis use worsens the clinical course and overall prognosis of the disorder.

What are the implications for psychiatric practice?

- While scientists attempt to clarify the relationship between cannabis and psychosis, it is important that we take the link between cannabis and psychosis seriously by definitively assessing patients for cannabis use. Clinicians should be educating their clients about the potential dangers of using cannabis and the potential benefits of quitting.

Critics of this hypothesis believe that cohort studies have inherent limitations that prevent any clear conclusions from being drawn. McLaren and colleagues¹¹ evaluated the methodological strength of the existing cohort studies. The definition of psychosis was a recurrent limitation in the studies. Many studies used psychotic symptoms, not diagnoses, as their outcome, which may not be of clinical significance. Moore and colleagues¹⁰ also noted this limitation and attempted to correct for it by separately analyzing the 2 studies that required the diagnosis of a primary psychotic disorder. Interestingly, they found an odds ratio of 2.6 for the development of psychotic disorders in those who had ever used cannabis compared with nonusers. Important confounding factors, such as noncannabis drug use, a family history of psychosis, and unmeasured vulnerability to psychosis, were not adequately controlled in these studies.¹¹

Age at onset of psychosis and cannabis use

Certain risk factors have been reported to interact with cannabis use to increase vulnerability to developing psychosis. One suspected important variable is the age at which cannabis use is started. The age effect was first noted in a Swedish conscript cohort study that demonstrated that cannabis use by age 18 led to a 6-fold increase in the risk of schizophrenia later in life.¹² It is unclear, however, whether the psychotic symptoms predated the cannabis use.

To clarify this issue, the Dunedin Multidisciplinary Health and Development Study conducted a prospective longitudinal study of adolescent cannabis use, taking into account psychotic symptoms that occurred before cannabis use.¹³ The data were compiled from a birth cohort that consisted of 1037 individuals born in Dunedin, New Zealand. Information about psychotic symptoms was obtained at age 11, and drug use was assessed by self-reports at ages 15 and 18 and by a standardized interview schedule at age 26. Two psychosis-related outcomes were measured- the presence of symptoms of schizophrenia and the diagnosis of schizophreniform disorder.

The results showed that those who had used cannabis by ages 15 and 18 had more schizophrenia symptoms than controls, a finding that remained significant after controlling for the presence of psychotic symptoms at age 11. However, the increased likelihood of schizophreniform disorder at age 26 was no longer significant after controlling for psychotic symptoms at age 11. Taken together, this suggests that early cannabis use confers higher risk of psychosis.

These findings may be explained as follows: Adolescence represents a sensitive period of neurodevelopment, with the brain more vulnerable to the effects of cannabis. Alternatively, the heightened risk may simply be a consequence of greater cumulative cannabis use, since these subjects began using it at a younger age. These theories are not mutually exclusive, and the latter explanation is consistent with the previously mentioned dose-response relationship observed in many studies.

Genetic vulnerability

A subsequent study conducted with the Dunedin cohort investigated whether specific genes increase the risks associated with early cannabis use.¹⁴ The researchers examined the role of the catechol-O-methyltransferase (*COMT*) gene, whose link with psychosis has been the focus of many studies. The *COMT* gene encodes the enzyme responsible for the synaptic metabolism of dopamine. A functional polymorphism of this gene, Val158Met, has been shown to slow the breakdown of dopamine, which potentially increases the risk of psychosis.^{15,16} The results of the study showed that the presence of the valine polymorphism was not significant unless coupled with adolescent cannabis use.¹³

Persons with Val/Val or Val/Met genotypes and adolescent cannabis use were at increased risk for schizophreniform disorder (with respective odds ratios of 10.9 and 2.5), while individuals with Met/Met genotypes were not. These findings implicate genetic factors as important contributors to the cannabis-psychosis link, but they are in need of replication.

Impact of cannabis use on the course of schizophrenia

The extent to which cannabis use might alter the clinical course of schizophrenia remains a point of contention within the literature. Intuitively, one may expect cannabis to have a negative impact on the expression and course of schizophrenia. Findings suggest that patients with schizophrenia who use cannabis experience increased psychotic symptoms, are more likely to have relapses, have a greater likelihood of rehospitalization, and experience poorer therapeutic response to antipsychotic medication than patients who are cannabis-naïve.^{17,18} Furthermore, pre-onset cannabis use may trigger an earlier age of onset of psychosis, which is of critical importance given the negative prognostic features associated with earlier onset.¹⁹ These effects have been reported to be dose-dependent.

It is interesting to note that other studies have been unable to confirm these adverse findings after controlling for potential confounding factors, which include but are not limited to alcohol and drug use, premorbid functioning, and family history. Moreover, it has been suggested that patients with comorbid cannabis use constitute a clinically distinct subgroup of schizophrenia patients.

In this respect, cannabis use may trigger the onset of psychosis in vulnerable individuals in whom a psychotic disorder otherwise may not have developed. As a result, these patients have a better prognosis, exhibit fewer negative symptoms, have better social skills, and have an enhanced treatment response compared with nonusers. In addition, a recent meta-analysis demonstrated that patients with lifetime cannabis use disorders have superior cognitive function compared with nonuser counterparts.²⁰

These conflicting findings may be due to the varying levels of THC/CBD found in street cannabis. The fact that these constituents have divergent properties may explain the manifestation of different psychological symptoms among users. In fact, CBD may actually attenuate some of the unwanted psychopharmacological effects of THC, because it may have anxiolytic and antipsychotic properties.²¹ Furthermore, CBD has been shown to have neutral or even procognitive effects.²²

Conclusions

Despite all of the uncertainties surrounding the cannabis-psychosis link, we are left with the task of translating these results into clear recommendations for our patients. The evidence suggests that cannabis is associated with an increased risk of psychosis when it is used frequently. Whether cannabis can trigger a primary psychotic disorder that would not have otherwise occurred is unclear. However, in most individuals who use cannabis, psychosis does not develop, which suggests that the increased risk must be related to other vulnerability factors (genetics, frequency, or age of onset of cannabis misuse).

Cannabis also seems to negatively alter the clinical course of schizophrenia. While meta-analyses suggest better cognitive function among cannabis-using patients, this may be a reflection of a higher-functioning subgroup of schizophrenia patients. Accordingly, cannabis-using patients who achieve abstinence may demonstrate improved symptoms and cognitive performance.

The first step in communicating this information to our patients consists of screening for cannabis use and obtaining a thorough substance use history. Psychoeducation and early interventions for young patients who may be vulnerable to psychosis should be used, and motivational interviewing and cognitive-behavioral therapy should be considered to encourage reduction and cessation of use.

There are no accepted pharmacological treatments for cannabis use disorders, yet several potential agents are under investigation. Future studies that control for both environmental and biological risk factors are needed to more clearly elucidate the mechanisms linking cannabis misuse to psychosis.

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