The Intersection Between First Episode Psychosis and Marijuana

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Highlights

- The relationship between marijuana use and first episode psychosis is complex and may be bidirectional.
- Available evidence indicates that marijuana use is neither necessary nor sufficient to cause SSDs on its own.
- A vulnerable minority may be more likely to develop SSDs after adolescent marijuana use.
- Adolescent marijuana use may both hasten the onset of FEP and to exacerbate the severity of SSDs.
- Individuals with SSDs are more likely to develop cannabis use disorders compared to the general population.
- Individuals at increased genetic risk of SSDs and those who have experienced FEP should be cautioned regarding the use of marijuana, especially high-THC forms.

Introduction

Psychosis is a major mental health concern that substantially affects individuals and their families. The term psychosis refers to a state of impaired reality testing reflected in thought or perception, as with delusions, hallucinations, or disorganized behavior. Episodic psychosis is a hallmark of several forms of serious mental illness, called schizophrenia spectrum disorders (SSDs), which include schizophrenia and severe bipolar disorder and may have both positive and negative symptoms. Positive symptoms include delusions, hallucinations, and other forms of disorganized thinking and behavior. Negative symptoms include lack of motivation, lack of pleasure, lack of interest in social contact, reduced speech, and flattened emotional response. In a psychotic episode, positive symptoms manifest for a week or more. First-episode psychosis (FEP) is a first-ever presentation with a psychotic episode. It is estimated that three in 100 people will experience psychosis at some point in their lifetimes. In fiscal year 2013, 18,695 Washington State residents were newly diagnosed with psychotic disorders. In 2017, it was estimated that Washington State had over 190,000 residents living with schizophrenia or severe bipolar disorder.

Cannabis (marijuana) is a plant widely used as a drug for medicinal and non-medical purposes. Since at least the 1930s, an association between marijuana use and psychosis has been documented in the medical literature. In 2012, Washington State voted to pass Initiative 502, which legalized marijuana and authorized the Washington State Liquor and Cannabis Board to regulate and tax marijuana sales to any persons in the state who were aged 21 years and older. The first retail stores opened in July 2014. As shown in Figure 1, the proportion of Washington residents who use marijuana has increased.
risen steadily since 2012. This brief reviews the possible implications of increased marijuana use with respect to the incidence or course of psychosis.

**Relationship Between Marijuana and Schizophrenia Spectrum Disorders**

A 1969 article in the *Journal of the American Medical Association* described 12 cases of apparent marijuana-related psychosis observed in soldiers in Vietnam. The first solid evidence of a relationship between marijuana use and SSDs emerged from a 1987 study of Swedish men who were surveyed in 1969/70 as part of their conscription into compulsory military service (over 45,000 men) that examined the relationship between level of cannabis exposure at conscription (baseline, age 18) and later development of schizophrenia. The men were followed in a national register of psychiatric care through 1983. Findings revealed a strong association. Compared to non-users, those who had used cannabis at least once were 2.4 times more likely to develop schizophrenia. Those who used cannabis more than 50 times were 6.0 times more likely to develop schizophrenia. While such evidence of an association is very strong, the researchers could not rule out the possibility that pre-existing psychotic symptoms drove pre-baseline cannabis use.

Although much research since then has looked at the association between marijuana and psychosis over many decades, the exact nature of the relationship between marijuana use and psychosis remains the source of debate. While some attribute the development of psychosis to marijuana use, others attribute the development of marijuana use to psychosis. The available evidence suggests both perspectives may be at least partially correct, with the relationship between marijuana use and psychosis being bidirectional. Marijuana-related factors that appear to strengthen the relationship between marijuana and psychosis include younger age of onset of marijuana use, higher level of marijuana use during adolescence, and higher potency of marijuana that has been used. Individual differences that appear to strengthen the relationship between marijuana and psychosis include having a familial history of psychotic disorder, early trauma, growing up in an urban environment, and carrying certain genetic variants.

**Biological Bases for a Relationship Between SSDs and Marijuana Use**

The main psychoactive component of marijuana, a cannabinoid known as delta-9-tetrahydrocannabinol (THC), effects the dopamine system in the brain, which has long been implicated in the development of SSD, particularly schizophrenia. Positive symptoms (e.g., hallucinations) are believed to result from increased release of dopamine in certain brain areas while...
negative symptoms are understood to emerge from reduced dopamine receptor activation in other brain areas. THC appears to cause region-specific increases in dopamine release and potentially long-term alterations in nerve activity, but the functional significance of this is unknown. Dopamine release is blunted in cannabis users with schizophrenia but is also directly related to the induction of psychotic symptoms.

Marijuana use also affects the endocannabinoid system, which may play a role in SSDs. Levels of the endocannabinoid anandamide have been found to be significantly elevated in the initial prodromal states of psychosis. In patients with FEP, levels of anandamide are negatively related to psychotic symptoms but are also markedly higher than the levels found in those without SSDs, suggesting that anandamide may be released in the brain in response to acute psychosis. Low-frequency cannabis users with FEP have been found to have markedly higher levels of anandamide compared to high-frequency users with FEP, high-frequency users without SSDs, and low-frequency users without SSDs. This suggests that frequent cannabis exposure may downregulate the anandamide response to psychosis. Thus, endocannabinoid signaling may initially be enhanced with low-level cannabis use but becomes downregulated with heavier or chronic use.

How Might Marijuana Use Cause SSDs?

Marijuana, particularly THC, is known to produce psychotomimetic effects in healthy people who are not otherwise psychotic. Examples of psychotomimetic effects include depersonalization, derealization, paranoia, ideas of reference, flight of ideas, pressured speech, disorganized thinking, delusions of persecution or grandiosity, auditory or visual hallucinations, and impairments in attention and memory. On the other hand, cannabidiol (CBD), a non-intoxicating cannabinoid found in hemp and in some strains of marijuana, has been shown to inhibit the psychotomimetic effects of THC. In fact, CBD has been found to enhance anandamide signaling and to reduce positive and negative psychotic symptoms in SSD.

Marijuana use can also produce effects that are similar to negative symptoms of SSDs, including blunted affect, emotional withdrawal, psychomotor retardation, lack of spontaneity, and reduced social interest. Chronic and heavy marijuana use has been associated with a condition known as amotivational syndrome, characterized by apathy, lack of motivation, social withdrawal, restricted range of interests, lethargy, impairment in memory and concentration, impaired judgment and decision-making, and poor socio-occupational functioning. Notably, amotivational syndrome shares similarities with the negative symptoms of schizophrenia. Conversely, a few studies have shown that patients with schizophrenia who use marijuana have fewer negative symptoms compared to non-users.

Research suggests that there may be a positive relationship between susceptibility to psychosis and sensitivity to psychotomimetic effects of marijuana. Two groups of patients, those with recent-onset FEP and those at ultra-high risk of psychosis, retrospectively assessed subjective effects of marijuana (FEP patients were asked to rate effects before their recent episode). Compared to marijuana-using controls from the general population, both patient groups were more likely to endorse psychotomimetic effects. Of the FEP patients, 37% reported that their first psychotic symptoms occurred during cannabis intoxication. Another study of those with FEP compared to controls suggested that those with FEP may be more sensitive to all of effects of marijuana, not only the positive or psychomimetic ones. It is unclear whether individuals with FEP have intrinsic sensitivity to marijuana effects or whether they became more sensitive after experiencing FEP.

Does Marijuana Use Cause SSDs?

In support of marijuana having a causal role in SSDs, a significant body of research indicates that marijuana use often precedes FEP, even when controlling for other drug or alcohol use, with the level of cannabis use...
being robustly related to the level of risk of psychosis. Risk has been found to be heightened with use of high potency marijuana and synthetic cannabinoids. Evidence against this hypothesis derives from the fact that general population-based increases in cannabis use have not been associated with corresponding increases in SSDs. Prevalence rates suggest that cannabis use has not caused SSDs that would not otherwise have occurred. A meta-analysis of studies of cannabis use among those with FEP found that about a third of those presenting with FEP reported a clinically significant history of cannabis use that was generally initiated around 6 years before the onset of FEP.

**Does Marijuana Use Precipitate First Episode Psychosis?**

A variation on the hypothesis that marijuana use causes SSDs is that marijuana precipitates FEP in susceptible individuals. If this is the case, it would be expected that those who might experience FEP eventually would experience FEP at a younger age if they use marijuana. In support of this hypothesis, a study in Europe found that patients with SSDs and substance use had an almost 3 years earlier onset of FEP compared to patients without substance use, with cannabis use reported by 9 out of 10 substance use, and of all substances, only cannabis use was associated with age of onset of FEP. A study of patients with FEP in the US found specifically that escalation of marijuana use in the preceding 5 years was most predictive of psychosis onset, with any escalation of marijuana use during that time increasing rate of onset, and greater increases predicting greater rates of onset in a dose-dependent fashion. It must be emphasized that not all patients with FEP have a history of marijuana use. Research has found that, among patients with FEP, poorer academic functioning predicted earlier age of initiation of marijuana use and traumatic experiences in childhood and adolescence predicted more rapid escalation and a greater cumulative amount of marijuana used.

On the basis of large genome-wide association studies, research has identified a number of genetic variants that are associated with increased risk of SSDs, including schizophrenia and bipolar disorder. Tallying the number of SSD-related variants found in an individual’s DNA produces a polygenic SSD risk propensity score that is believed to reflect how prone that individual is to develop SSD. Research has found that, in patients with SSD, daily or weekly marijuana use before age of onset was associated with higher risk propensity. That is, those with higher genetic risk propensity for SSD were more likely to use marijuana daily or weekly, particularly at a younger age, compared to those with lower genetic risk propensity for SSD before going on to develop SSD. This suggests that a genetic propensity to develop SSD could also be a genetic propensity to use marijuana. Another possibility is that frequent marijuana use before FEP could represent an attempt to self-medicate premorbid symptoms. With marijuana use being associated with poorer outcomes in SSD, this could create a vicious cycle with attempts to self-medicate actually exacerbating the illness.

**How Might Psychosis Drive Marijuana Use?**

A number of studies have explored self-reported reasons for substance use in patients with psychotic disorders. Regardless of the substance used, motives for use include to relieve dysphoria, to enhance positive mood, to be social, to relieve psychotic symptoms, and to decrease side-effects of medication. Symptoms that motivate cannabis use include social isolation, lack of emotion or feeling for others, lack of energy, difficulty sleeping, depression, anxiety, agitation and tremor or shaking. These symptoms may occur as part of the psychotic illness, be due to anxiety/depressive illnesses, and occasionally may be side-effects of medication. Given that CBD has been found to reduce psychotic symptoms in SSDs, noticing a beneficial effect from marijuana that contains CBD may lead some persons with SSDs to seek out such marijuana.
In support of psychosis having a causal role in marijuana use, research has found that cannabis use and use disorders (CUD) are more prevalent among people with psychotic disorders than among those in the general population. Estimates of prevalence rates among those with SSDs range from 27 to 42%. A meta-analysis of 35 studies found the median rate of current (past 12-months) CUD among those with schizophrenia was 16.0%, and the median rate of lifetime CUD was 27.1%. By comparison, the 12-month and lifetime prevalence of CUD in the general population were recently estimated to be 2.5% and 6.3%, respectively. Persons with SSDs appear to be at elevated risk of developing CUD. However, a meta-analysis of cannabis use in FEP found that cannabis use declined by approximately 50% over time after FEP. The researchers interpreted this finding as contrary to the popular belief that cannabis use is initiated to self-medicate positive symptoms of psychosis. They noted that an average 6 year interval between cannabis use initiation and FEP is several times longer than the average duration of untreated psychosis. On the other hand, those with FEP could have used cannabis to self-medicate other less specific anxiety or depressive symptoms that might predate psychosis.

A retrospective study of individuals with SSD conducted in New York City and Boston found that differences in motives for initial cannabis use distinguished trends in both cannabis consumption and SSD symptomatology. Those who began using cannabis to cope with positive or negative symptoms tended to initiate cannabis use earlier and with a greater associated risk relative to those who began using for social or recreational purposes. More specifically, those who started using cannabis to address positive symptoms before FEP exhibited more severe positive symptoms at FEP onset while those who initiated use to address negative symptoms exhibited more severe negative symptoms at FEP onset. The researchers interpreted their findings as evidence of targeted use of cannabis as an intuitive self-treatment method for emerging prodromal symptoms in adolescence.

**Marijuana Use and the Course of Psychosis**

Acute cannabis use has been related to worse initial clinical presentation in those with FEP. Research shows that persistent marijuana use after FEP is associated with poorer prognosis even after controlling for other substance use. For example, compared to patients who presented to an early intervention service for FEP without a history of cannabis use, those with a history were more likely to be admitted or require compulsory admission to the hospital, to spend more time hospitalized in the 5 years following presentation, and to use a broader number of antipsychotics.

A systematic review of the evidence examining whether marijuana use predicts worse outcomes in psychotic disorders found that cannabis use was consistently associated with increased relapse and non-adherence, controlling for confounding variables such as baseline illness severity and other substance use. The relationships between marijuana use and other outcomes, such as positive and negative symptom severity, were less clear when confounding variables were taken into consideration.

A study of patients with FEP conducted in Washington State found that a quarter of the sample reported recent marijuana use. Compared to non-users, marijuana users had significantly higher ratings of severity of illness and levels of positive symptoms during treatment but showed no difference in quality of life. A large study of patients with FEP in the UK found that cannabis use at baseline was associated not only with younger age of onset of FEP but also with longer duration of untreated psychosis, higher positive and total symptom scores, higher mania symptoms, and poorer functioning, with continued cannabis use being associated with poorer symptomatic and functional outcomes after FEP.

Continued cannabis use after FEP has been associated with increased risk of relapse of psychosis independent of the effects of other possible confounders, including medication adherence and other illicit drug use. Furthermore, continued cannabis use after FEP has been associated with non-adherence to prescribed antipsychotic medication regimens, time until relapse of psychosis, length of relapse, number of relapses, and...
A longitudinal study of patients with FEP conducted in Europe found that half of the sample had a diagnosable CUD at baseline. Over a 30-month follow-up period, those without CUD showed significant improvements in social functioning while those with CUD showed no such improvements, even after controlling for potentially confounding variables such as pharmacological and psychological treatments. A study examining the effects of substance use disorders on outcomes after FEP found that those with CUD were the least medication-compliant of all groups at 2-year follow-up, with cannabis misusers' condition worsening over time on all examined outcome dimensions, including functioning and service utilization.

Conclusions

In summary, the role of marijuana in the development of SSDs more generally and FEP specifically is complex. Marijuana can induce psychotomimetic effects in some individuals and is also associated with effects that resemble negative symptoms observed in psychotic disorders. Based on the available evidence, it appears that marijuana use is neither necessary nor sufficient to cause SSDs on its own. Most who use marijuana in adolescence do not experience harm; however, a vulnerable minority may be more likely to develop SSDs after adolescent marijuana use. Indeed, adolescent cannabis use appears to both hasten the onset of FEP and to exacerbate the severity of SSDs. Furthermore, those with SSDs are more likely to develop cannabis use disorders compared to the general population. Therefore, those at increased genetic risk of SSDs and those who have experienced FEP should be cautioned regarding the use of marijuana.

At-risk users of marijuana who are reluctant to discontinue their use should be counseled regarding the potential risk associated with high THC strains of cannabis and monitored closely for the development or exacerbation of psychotic symptoms.

References


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