Cannabis and Psychosis

A Review of the Links

Abstract

This summary of a larger review attempts to concisely state the findings linking psychosis and cannabis. It is designed to address a number of common questions that arise when considering the effects of cannabis use on onset and course. The complete review with in-depth analysis and references is available from the BC EPI Advanced Practice.

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This summary document is primary derived from a longer review written by TE with assistance from Fred Ott for the cognition section. AB condensed material from the original review and added information on the cannabis system and use in BC. AB is a faculty member of the Department of Pharmacology at UBC, and his research focuses on the relationship between drugs and psychosis. He is also involved with a number of local companies that are studying the side-effects and potential therapeutic benefits of cannabinoids. TE has no interests to declare. Conclusions are those of the author(s) but the document is approved by the EPI Advanced Practice Advisory Committee.

Introduction

The consumption of cannabis and its links to the development of psychosis has become increasingly important given recent trends towards legalization for medicinal and recreational use. A steady output of scientific research over the past three decades has markedly increased our understanding of cannabis and psychosis. However, media reports usually fail to address the importance of both replication of results and the degree of convergence of results arising from different approaches to the issue. The development of psychotic disorders tends to first occur in adolescence or early adulthood, a developmental period when cannabis use also tends to begin. Early psychosis intervention programs need to be well informed of the key understandings and controversies concerning cannabis, since they are at the leading edge of interventions provided by the mental health system.

The following brief review summarizes the literature with respect to key questions of particular relevance cannabis's effects on the onset and course of schizophrenia and related disorders. A substantially more detailed review, complete with full references, is available from the BC EPI Advanced Practice website. The intent is to educate clinicians and administrators so that a consistent evidence-based message can be communicated to the public, clients and families, and other professionals. It is also hoped that the review will spark a self-examination of clinical practices including diagnosis and treatment. The conclusions are followed by several recommendations for users of this report.

The review is divided into sections that are each composed of typical questions of interest noted in the table of contents above.

What is cannabis and the endocannabinoid system in humans?

Cannabis (or "marijuana", slang) refers to the genus of flowering plants that most commonly include the species *Cannabis sativa* and *Cannabis indica.* Cannabis plants have been used for their medicinal properties for thousands of years, by many different cultures. In Canada, medical cannabis can presently be purchased legally, provided that the patient has a valid prescription, and cannabis will soon be available for adult recreational use. Cannabis contains at least 460 different compounds, and more than 100 of these are cannabinoids, which means that they bind to either the CB1 receptor (primarily located in the brain) and/or to the CB2 receptor (located in peripheral organs, such as the immune system). The two CB receptors and the naturally occurring chemicals in the body that bind to them constitute the endocannabinoid system, which regulates many developmental and physiological processes. In the brain the system functions to adjust information processing and help preserve the structure and function of

major brain circuits. The two most important cannabinoids found in cannabis are delta-9-tetrahydrocannabinol (THC), which produces most of the psychoactive effects of cannabis, and cannabidiol (CBD), which partially acts to counter the effects of THC.

Is cannabis use frequent among those with a psychotic disorder?

A recent meta-analysis of 37 studies indicated that the estimated prevalence of cannabis use was 33.7% in first episode psychosis samples. With regards to heavier cannabis use, another meta-analysis reported that 16% of schizophrenia patients had a *current* diagnosis of cannabis use disorder (CUD), and 27.1% had a *lifetime* diagnosis of CUD. The median rate of CUD across the 35 studies in the meta-analysis was markedly higher in first-episode than long-term samples, as well as in samples with a higher proportion of males and youth. However, there are notable regional differences in cannabis use, and there is little information on cannabis use in first episode psychosis patients in British Columbia, which has the second highest rates of cannabis use in Canada. It is important to remember that although persons with schizophrenia commonly use cannabis, they are also more likely to use other substances as well, meaning that cannabis use is not specific to schizophrenia or other psychotic disorders.

Can cannabis acutely induce psychosis?

Anecdotal studies describe an acute psychosis caused by cannabis that includes depersonalization, de-realization, paranoia, disorganized thinking, delusions, auditory and visual hallucinations, and impairments in attention and memory. Experimental studies have shown that intravenous administration of THC can cause transient psychotic symptoms in healthy subjects, and that the degree of psychosis is positively correlated with dose. These studies do not demonstrate that cannabis causes a long lasting, distinct psychotic disorder such as schizophrenia. In large community samples, between 20 and 50% of individuals report acute, transient psychotic symptoms while under the influence of cannabis. Severe persistent psychotic reactions following cannabis use are rare, and are more likely to occur in individuals with a pre-existing psychiatric condition such as schizophrenia or personality disorder.

Is there a link between cannabis use and future development of psychosis?

At this point, there is not a definitive answer to this question, and research in this area continues to be a priority for many groups around the world. The question is complicated by the wide variations in the cannabinoids contained in cannabis and its products (discussed in further detail below), as well as how one defines the term “psychosis”. However, a number of case-control and cohort studies have sought to determine if cannabis use prior to illness onset can predict subsequent development of psychosis. While results vary, the majority of these studies indicate that prior cannabis use is significantly associated with an increased risk of later psychosis by approximately 2-3 times. Effects were usually found to be dose-dependent with longer and heavier use increasing risk. However, most studies could not determine if a subtle form of psychosis existed prior to the onset of cannabis use. The finding that drug use precedes onset is not specific to schizophrenia, as other psychiatric illnesses are also increased by prior exposure to both cannabis and other substances. Overall, there is a trend for an increase in psychotic symptoms and the onset of schizophrenia spectrum disorders with prior cannabis use.

Is cannabis use associated with earlier onset of psychotic disorders?

A number of studies have sought to determine if exposure to cannabis during adolescence can cause an *earlier* onset of psychosis, independent of a general increase in the rates of psychosis. Many of these studies were analyzed in a recent meta-analysis. The result from comparing 83 relevant studies found that the age at onset of psychosis was 2.70 years earlier among cannabis users, and was 2.00 years earlier in people with unspecified substance use, compared with non–substance-using controls. The study concluded that cannabis and other drugs of abuse, except alcohol, were associated with an earlier age of psychosis onset, and that cannabis (and other drug abuse) may be one of the only modifiable factors associated with age of onset, which itself is a predictor of poorer outcomes. Contrary to popular clinical belief, one study found that cannabis users may actually have shorter DUP (duration of untreated psychosis) and this may account for some of the time associated with earlier onset. The related issue of whether those who begin cannabis at an earlier age are especially at risk because of incomplete brain maturation has not been clarified.

If only some cannabis users develop psychosis, are there subgroups who are more prone to developing psychosis if they consume cannabis?

While the absolute risk of developing a lasting psychosis from cannabis use remains small, there is evidence that some factors can increase the risk in certain subgroups. One of the most studied of these factors has been the role of genetics. In a large study of persons with schizophrenia, their unaffected siblings and unrelated controls, it was observed that the unaffected siblings were more sensitive to the psychotomimetic effects of cannabis than controls, suggesting that familial liability to psychosis is expressed in part as the tendency to develop psychotic experiences in response to cannabis. Other studies have examined specific genetic markers. One study found that genetic variations in the catechol-O-methyltransferase (COMT) gene, which is an enzyme involved in regulating neurotransmitters in the brain (such as dopamine), could increase the relative risk of developing psychosis after adolescent cannabis exposure by 10.9 times. However, this effect was not replicated by another group. Others have studied the AKT1 gene, which is involved in dopamine signalling. After performing genetic tests and assessing cannabis use in patients with first episode psychosis and healthy controls, they noted that cannabis users who carry a particular variant in the AKT1 gene had a two-fold increased probability of a psychotic disorder, and this increased up to seven-fold if they used cannabis daily; these results also require replication. In addition to genetic factors, living in cities and childhood trauma have also both been linked to greater sensitivity to THC's psychotogenic (i.e. psychosis generating) effects.

Does cannabis trigger psychosis onset in persons deemed Ultra High Risk (UHR)?

Two meta-analyses of seven prospective studies looked at the lifetime use of cannabis or heavy use during UHR and the risk of progression. In the first review, lifetime cannabis use was not significantly associated with transition to psychosis. The second meta-analysis yielded an increased risk of 1.75 times, indicating a significant association between current cannabis abuse or dependence and transition to psychosis. Cannabis use was only predictive of transition to psychosis in those who met criteria for cannabis abuse or dependence, tentatively suggesting a dose–response relationship between current cannabis use and transition to psychosis. A recent Australian study of 190 UHR cases with mean follow-

up of 5.0 years found a history of cannabis abuse in 58% of the sample. Of these, 26% reported a history of cannabis-induced Attenuated Psychotic Symptoms (less severe psychotic symptoms). These individuals were 4.90 times more likely to transition to a psychotic disorder, and greater severity of cannabis abuse also predicted transition to psychosis. These findings suggest that cannabis use poses risk in a subpopulation of UHR individuals who manifest cannabis-induced attenuated psychotic symptoms, potentially revealing an important early marker of risk with significant prognostic utility for UHR individuals.

Is Cannabis Induced Psychosis a distinct disorder?

Various forms of "cannabis-induced psychosis" have long been described in the literature through case reports, which are typically characterized by rapid remission after cannabis discontinuation, the absence of other features associated with schizophrenia (such as negative symptoms), few or no residual symptoms after remission, the frequent presence of confusion or amnestic symptoms, and often no family history of a psychotic disorder. European studies have found that, within three years, approximately 85% of those with a diagnosed of Cannabis-Induced Psychosis will be re-diagnosed with schizophrenia. Most experts believe a longstanding cannabis-induced psychosis is rare. Although ICD-10 allows for the diagnosis of Cannabis-induced Psychotic Disorder (with or without cannabis use disorder), DSM-5 does not have such a diagnosis. It does note that "…concern has been raised about cannabis use as a causal factor in schizophrenia and other psychotic disorders. Cannabis use can contribute to onset of an acute psychotic episode, can exacerbate some symptoms and can adversely affect treatment of a major psychotic illness".

What effects does cannabis have on those who already have a psychotic disorder?

Use of cannabis by patients with an existing psychotic disorder has been associated with a number of negative consequences. A systematic review of 13 longitudinal studies in psychosis patients concluded that cannabis use was consistently associated with increased relapse and non-adherence. Others have found that adherence underlies much of the relationship between cannabis use and relapse thus suggesting that great effort should be put towards addressing adherence. In first episode cohorts, a three-year follow-up study of 203 early psychosis patients found that 33% were diagnosed with cannabis abuse or dependence at baseline, with the rate declining to 7% after 2 years. Controlling for differences between cannabis users and nonusers, continuing users showed significantly more severe positive symptoms but no difference in depression, negative symptoms or quality of life. A London, UK study of 502 patients with first-episode psychosis found that amount of cannabis use was associated with a younger age at presentation, manic symptoms and conceptual disorganization, but not with delusions, hallucinations, negative symptoms or daily functioning. Cannabis users who reduced or stopped their use following contact with services had greater improvement in symptoms at 1 year compared with continued users and non-users. Also, relapse rates were equal for those who discontinued and for those who never used cannabis.

If cannabis can cause psychosis and rates of its use have increased, then are there more people diagnosed with psychotic disorders?

There is little evidence that rates of schizophrenia are increasing, while rates of cannabis use have climbed. One study noted that despite the increased use of cannabis over the past 30 years, accompanied by a decrease in age of first use, there was no evidence of a significant increase in the incidence of schizophrenia over that period. A recent analysis showed no change over time (1950-2009) in the incidence of psychotic disorders in the UK. Others have examined earlier epidemiological surveys and noted that the rapid expansion of use of cannabis in the 1960s to the mid-1980s was accompanied by a reduction in the incidence of schizophrenia during that period. These findings are consistent with the relative uniformity of incidence rates of schizophrenia across cultures that vary immensely in their consumption rates of cannabis.

What effects does cannabis use have on the cognitive functioning of persons with psychosis?

A review of 23 relevant studies found that 14 reported cannabis users with schizophrenia had better cognitive performance than schizophrenia non-users, while eight studies reported no or minimal differences in cognitive performance in the two groups, and only one study reported better cognitive performance in the schizophrenia non-user group. The authors ascribed this "paradoxical" effect (i.e. contrary to an intuitive worsening of cognition with cannabis use) as likely due to important differences between the two groups, including better social skills in the cannabis-using group. The results from studies that assessed premorbid cognitive functioning are mixed so it is not at all clear that the cannabis users simply started out with better cognition. Even more perplexing is a finding that better cognition was found in those who started cannabis use at an earlier age. Although longitudinal studies are needed, we know that cognitive changes tend to remain stable in schizophrenia and that healthy identical twins discordant for cannabis use show similar cognitive changes over time.

What influence does cannabis dose and potency have on psychosis?

The majority of studies have found that heavier and/or more prolonged cannabis use are associated with greater risk of onset of a psychotic disorder and/or more severe symptoms. For example, a recent meta-analysis of 10 studies concluded that risk for schizophrenia and other psychoses is related to cannabis use in a dose-related fashion: overall risk for psychosis was increased 2 times with any cannabis use, while the heaviest users were 3.9 times more at risk. However, it is possible that these effects simply reflect a greater tendency of psychotic or psychosis prone people to use larger doses of cannabis. Also, genetic studies suggest that an underling vulnerability may lead to both cannabis use and development of psychosis. Potency has become of increasing concern given the rise in THC content over the past several decades. In particular, the amount of THC consumed and the ratio of THC to cannabidiol may play an important role. Recent years have also seen the development of super-strength forms of THC, such as Butane Hash Oil (with nicknames such as "budder" and "shatter"). The THC potency of these compounds can be as high as 80%, which results in highly psychoactive effects: there is virtually no literature on psychosis risk with these high potency cannabis products. The ratio of cannabidiol to THC may be important since cannabidiol has been shown to act in opposite ways to THC and may have antipsychotic properties in high doses.

Does psychosis lead to cannabis use? Self-medication and reverse causation hypotheses.

The theory of reverse causation holds that those who are predisposed to developing psychosis tend to become cannabis users. This has been found in several studies where the presence of mild psychotic symptoms at baseline predicted the future use of cannabis. This could mean that people who are prone to psychosis are both more sensitive to the psychotomimetic effects of the drug, as well as more likely to come into contact with cannabis itself for other reasons. Some think that cannabis may be used for self-medication in people with subthreshold symptoms prior to full onset of psychosis.

In summary, what are the possible links between cannabis use and psychosis?

Multiple possible associations between cannabis and psychosis have been proposed, based on scientific evidence, and not all are mutually exclusive for any particular individual:

1. There is no relationship at all between cannabis exposure and psychosis.
2. Any link between cannabis use and psychosis may be due to variables common to both, such as socio- and demographic factors, or etiological variables such as genetics and/or altered dopamine neural pathways
3. Cannabis use may uncover a previously latent psychosis in psychosis-prone individuals
4. Cannabis use may precipitate relapse of a pre-existing psychosis
5. Cannabis intake may cause psychosis where none would have otherwise existed
6. Reverse causation, where psychosis or psychosis proneness leads to cannabis use, to self-medicate dysphoria, anxiety, negative symptoms and adverse side-effects of medications
7. Misreporting of cannabis use and/or psychosis could lead to an erroneous association between the two

Methodological Issues

While there have now been many studies of the links between cannabis and psychosis, most have inherent limitations. As we cannot ethically expose people to cannabis to determine their risk of psychosis, most such studies are naturalistic and observational – meaning that we observe people's natural behavior, of which we record only a part. Cannabis use therefore may relate to psychosis in multiple different ways, as listed above, and causality can be difficult to determine. It has therefore been recommended that there is a strong need for more studies with a "longitudinal design, with repeated measures of psychopathology, use of cannabis, alcohol and other substances, as well as baseline measures of function, illness severity and other characteristics that are known to be associated with poorer outcome in schizophrenia".

Conclusions

1. Those diagnosed with first episode psychosis or with schizophrenia are more likely to report current or prior use of cannabis, compared to the general population
2. Cannabis can lead to short-lived psychotic states but a chronic cannabis-induced psychosis is rare
3. Onset of schizophrenia is likely due to a combination of risks. Cannabis appears to be one of the risks but it is neither necessary nor sufficient to cause schizophrenia. There appear to be a number of findings that limit the simple assertion that cannabis causes psychosis including the

fact that rising cannabis use has not been accompanied by a rise in psychotic disorders. Cannabis cannot be regarded as a solitary cause nor can the possibility that the propensity to both cannabis use and develop a psychotic disorder are both due to an underlying third variable such as a genetic vulnerability.

4. Most studies agree with the theory that cannabis use could be a risk factor but only among those who have a predisposition.
5. Prolonged and heavy use appears to increase risk of onset and onset appears several years earlier among users.
6. Cannabis is one of numerous drugs thought to increase the risk for onset of schizophrenia. When other substances and other risk factors are controlled for in studies, the resulting associations between cannabis and onset are reduced by 50-80%.
7. Ongoing use after onset increases risk for relapse and nonadherence. Increases in positive symptoms are likely modest as increases were not found in most studies. Negative symptoms appear unaffected. Although most studies find cognition to be better in cannabis users, longitudinal studies are needed to assess long term cognitive outcomes associated with ongoing cannabis use.
8. Psychotic experiences, common in the general population, may serve as a marker of vulnerability and cannabis consumers who experience transient or attenuated psychotic experiences are at greater risk to develop a psychotic disorder.

Recommendations

1. The public should be made aware that media reports of cannabis use causing schizophrenia are oversimplified and that other factors must be present for cannabis users to develop schizophrenia-spectrum disorders. Note that perhaps 2-3% of heavy users *might* develop schizophrenia (or a similar disorder), and that the huge rise in cannabis consumption has not been echoed by a rise in the numbers of new cases of schizophrenia. Even though odds may double or triple, the absolute risk remains very low.
2. Educate others to the fact that family history is one of the most important factors contributing to being vulnerable to psychotic disorders and that an interaction with other variables, possibly including cannabis, can lead to onset.
3. Current theories emphasize two main ways of thinking about cannabis and psychosis. In the first, cannabis use is interpreted as a risk factor (probably along with other risk factors) that interacts with a genetic/developmental vulnerability to cause schizophrenia. The second model interprets both cannabis use and psychosis as manifestations of a shared prior vulnerability. Both models have considerable empirical support.
4. If the use of cannabis leads to experiencing psychotic symptoms then continuing use places a person at very high risk. Counsel reduction or discontinuation. As psychotic effects of cannabis appear to be THC dose dependent, avoid in particular super-strength THC products.
5. Those currently in an UHR state who find that cannabis use exacerbates attenuated psychotic symptoms are at very high risk. Counsel discontinuation.

6. Ensure medication adherence via use of injectable medications, psychological therapies, cognitive remediation etc. since adherence partially mediates the relationship between ongoing cannabis use and relapse.