

Cannabis and psychosis: what causes what?

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Abstract

It is well established that delta-9-tetrahydrocannabinol (THC) is psychomimetic. The propensity for the induction of psychotic-like symptoms depends upon the potency of the compound administered (i.e. the THC content and the amount of cannabidiol, which appears to have antipsychotic effects) and the underlying vulnerability of the individual. Schizophrenia is a disorder with extreme vulnerability to psychosis, and cannabis use by people with schizophrenia is likely to cause a worsening of outcomes. Whether cannabis can actually cause schizophrenia is rather a more contentious question, but a number of cohort studies converge on their conclusions that cannabis exposure in youth can act as a cumulative causal factor in some cases of schizophrenia.

Introduction

The term *psychosis* is often used rather broadly to encompass a group of symptoms, none of which is specific to any disorder as such, and which can manifest in anyone given certain stimuli, such as exposure to dopaminergic agonists. *Schizophrenia* is a psychiatric disorder characterised by psychotic symptoms: pragmatically, albeit over-simplistically, these symptoms can be divided into "positive" (delusions and hallucinations) and "negative" (apathetic withdrawal, reduced range of emotions, diminished thought content – i.e. having a paucity of thoughts, demonstrated by lack of spontaneous speech and tendency to short unembellished conversation). It is the latter that is arguably the core of the schizophrenia syndrome, with positive symptoms being what may be considered "secondary". Cognitive deficits are also considered part of the core syndrome and, along with negative symptoms, drive most of the disability associated with the condition [1].

There is little doubt that ingestion of the plant *Cannabis sativa* can cause positive psychotic-like symptoms. An early study by Ames [2] using the plant product showed a fairly uniform response in human volunteers, with features including depersonalisation/derealisation, a prolonged sense of the passage of time, transient paranoid ideation and hallucinations. Of course, *Cannabis sativa* has multiple chemical constituents, but delta-9-tetrahydrocannabinol (THC) confers the psychomimetic properties, acting via cannabinoid CB1 receptors, which are ubiquitously distributed in the brain [3]. Intriguingly, another constituent of the plant, cannabidiol seems to have antipsychotic effects [4]. Isbel *et al.* [5] used synthetic THC and found a dose-response relationship with psychotic symptoms in most subjects, although some had an idiosyncratically profound response to even a modest dose. More modern studies using more sophisticated techniques support these conclusions [6], whilst elegant work from Huestis *et al.* [7] has shown that the

psychotomimetic effects of THC are mediated by the cannabinoid CB1 receptor and that antagonism of the receptor blocks these effects.

Cannabis susceptibility to psychosis

These findings suggest that some individuals are simply more prone to the psychotomimetic properties of cannabis. Verdoux and colleagues [8] confirmed this in a non-clinical sample, with the individuals' degree of "psychosis proneness" correlating with intensity of psychosis-like symptoms upon exposure to cannabis in a daily-life situation. Extrapolating from this, it would seem obvious that people with schizophrenia are very "psychosis prone" and they would be expected to manifest positive symptoms of psychosis (delusions, hallucinations) at even low doses, similar to someone with diabetes eating sugar and becoming hyperglycaemic. An association between cannabis consumption and worse psychotic symptoms and an overall more severe illness course has been pretty consistently shown in the schizophrenia literature, be it in chronic [9] or first-episode [10] patients (see review by Linszen *et al.* [11]); however, confounding and other methodological problems do bedevil this literature [12]. Also, a distinction needs to be drawn between acute effects (i.e. precipitation of an acute episode of illness) and longer-term, more insidious detrimental effects: obviously the former are easier to demarcate in terms of temporal sequence of cannabis exposure and symptom exacerbation.

Cannabis and negative symptoms

Another problem is that the literature has largely focussed on positive rather than negative or cognitive symptoms. It is clear that cannabis and related compounds can cause acute transient impairments in memory, attention, and executive function [13]. But whether exposure to cannabinoids is associated with persistent cognitive deficits is not as clear, more controversial and difficult to study [14]. In terms of negative-like symptoms, an "amotivational syndrome" has been described in chronic, heavy cannabis users. The syndrome resembles the negative symptoms of schizophrenia and is characterized by apathy, amotivation, social withdrawal, narrowing of interests, lethargy, impaired memory, impaired concentration, disturbed judgment, and impaired occupational achievement. However, polydrug use, poverty, low socio-economic status, or pre-existing psychiatric disorders confound interpretation of these studies and other investigators have argued that the syndrome does not exist [15].

What has been consistently found is that people with schizophrenia use more cannabis than the general population. For example, in the recent Australian Study of High Impact Psychoses [16], people with schizophrenia

had a lifetime rate of cannabis exposure of 97%, and last-year rates of 49% [17]. This begs the question as to why people with schizophrenia should use an agent that worsens their illness course and makes their positive symptoms worse. One way of looking at this is to consider that people with schizophrenia have an excess of negative emotions and that these symptoms drive cannabis use in much the same way as those that drive its use in people without schizophrenia [18]. So, the self-medication hypothesis may be true, but self-medication is for negative rather than positive symptoms [19]. This conclusion is, in part at least, supported by a study of 42 patients with psychosis and 38 controls, using experience sampling methodology: both groups experienced increases in positive emotions on exposure to cannabis and, in patients, there was also a reduction in negative emotions [20].

Hence, the message must be that anyone highly prone to psychosis should avoid cannabis: the tough part is helping people with negative emotions to find alternative ways of ameliorating those symptoms. Indeed, the effective management of people with schizophrenia and cannabis use remains suboptimal and requires much more research [21,22].

Can cannabis cause schizophrenia?

A rather more contentious issue is whether cannabis can actually *cause* schizophrenia. This, of course, is very difficult to determine definitively, and the best study design is the longitudinal cohort. Cohort studies have the great advantage of determining temporal sequence of putative cause and putative effect: any causal model of cannabis for schizophrenia would necessarily require the cannabis exposure to antedate the illness, as symptoms of the illness can drive cannabis consumption, as detailed above. A problem, though, even for the cohort design, is that non-specific symptoms characterised by negative emotions (see above) and sub-threshold positive symptoms can occur in the prodromal phase heralding the first definitive psychotic episode [23], and might lead to cannabis consumption (discussed by Kuepper *et al.* [24]). But this aside, a number of cohort studies from different parts of the world have converged in finding an association between cannabis consumption in youth and later schizophrenia/schizophreniform disorder. The first of these was a study of 50,087 Swedish conscripts [25], which showed an adjusted hazard ratio for schizophrenia of 3.1 (CI 1.7, 5.5), with a dose-response relationship with increasing exposure to cannabis. The Dunedin birth cohort [26] is particularly instructive in that it assessed individuals from a representative birth cohort at a number of time points and had excellent participant retention. In that study, the risk of schizophreniform psychosis at age 26 was 10.3% in those who had used cannabis in their teens, as

opposed to 3% in the rest of the cohort (adjusted odds ratio 2.9 [CI 1.2, 7.0]). Relevant to the cause-effect issue discussed above, it was those individuals who, at age 11, had experienced psychosis-like phenomena in association with cannabis use at age 18, who were most vulnerable to developing later schizophreniform psychosis (age 26).

Zammit *et al.* [27] recently reviewed the published studies of cannabis and later schizophrenia/schizophreniform psychosis. Those authors concluded the following: “we believe there is a strong body of evidence from epidemiological studies that use of cannabis increases risk of psychotic disorder, supported by findings in other research fields” (pg 181). Thus, in a small group of people, cannabis can be the “straw that breaks the camel’s back” and acts as a cumulative causal factor for schizophrenia. THC would thus act in concert with other risk factors in some “cases” of schizophrenia. Precisely what such other risk factors are is not clear, but more and more interest is being shown in gene-environment interaction effects in mental illnesses generally, and schizophrenia in particular. In the Dunedin cohort [26] there was an intriguing interaction effect, such that individuals homozygous for the valine allele at the position coding for Val158Met within the gene for catechol-o-methyl transferase (one of the determinants of dopamine metabolism) were more likely than those homozygous for the methionine allele to develop a later psychotic illness in association with cannabis exposure [28]. However, this has not been robustly replicated. Other genes of interest in this context include AKT1, but more work needs to be done in elucidating such effects [29].

Conclusions

Applying the cumulative causal factor model, very few “cases” of schizophrenia (estimated population attributable fraction - PAF- around 8%) would actually be “prevented” with the global abolition of cannabis [30]. This low PAF is compatible with epidemiological findings that schizophrenia is a ubiquitous accompaniment of the human condition and rates do not vary very much between cultures and settings despite wide variations in cannabis use [31]. At an individual level, though, it would seem important to educate people at heightened risk of schizophrenia (e.g. through having a family history of the disorder, or having experienced psychosis-like symptoms) of the potential additive causal risk cannabis exposure might bestow. For a full discussion of the public health implications, the reader is referred to a recent chapter by Hall and Degenhardt [32].

Abbreviations

THC, delta-9-tetrahydrocannabinol; PAF, population attributable fraction.

Disclosures

The author declares that he has no disclosures.

References

1. Castle D, Buckley P: *Schizophrenia*. Oxford: Oxford University Press; 2011.
 2. Ames F: **A clinical and metabolic study of acute intoxication with Cannabis sativa and its role in the model psychoses**. *J Ment Science* 1958, **104**:972-999.
- F1000Prime RECOMMENDED**
3. Iversen L: **How cannabis works in the brain**. In *Marijuana and Madness, 2nd edition*. Edited by Castle DJ, Murray RM, D'Souza CD. Cambridge: Cambridge University Press; 2012:1-16.
 4. Leweke FM, Koehthel D, Gerth CW, Nolden BM, Mauss C, Schreiber D, Hänsel A, Neatby MA, Juelicher A, Klosterkötter J: **Cannabidiol as an antipsychotic: a double-blind, controlled clinical trial of cannabidiol versus amisulpride in acute schizophrenia**. *15th Annual Symposium on Cannabinoids*. Clearwater, Florida: Cannaboid Research Society.
 5. Isbell H, Gorodetzky CW, Jasinski D, Claussen V, Spuluk FV, Korte F: **Effects of delta-9-tetrahydrocannabinol in man**. *Psychopharmacologica* 1967, **11**:184-188.
- F1000Prime RECOMMENDED**
6. D'Souza DC, Cho H-Y, Perry EB, Krystal JH: **Cannabinoid 'model' psychosis, dopamine interactions and implications for schizophrenia**. In *Marijuana and Madness*. Edited by Castle DJ, Murray RM. Cambridge: Cambridge University Press; 2004:142-165.
 7. Huestis MA, Gorelick DA, Heishman SJ, Preston KL, Nelson RA, Moolchan ET, Frank RA: **Blockade of effects of smoked marijuana by the CB1-selective receptor antagonist SR141716**. *Arch Gen Psychiatry* 2001, **58**:322-328.
- F1000Prime RECOMMENDED**
8. Verdoux H, Gindre C, Sorbara F, Tournier M, Swendsen J: **Cannabis use and the expression of psychosis vulnerability in daily life**. *Psychol Med* 2003, **33**:23-32.
- F1000Prime RECOMMENDED**
9. Negrete JC: **Cannabis and schizophrenia**. *Br J Addiction* 1989, **84**:349-351.
- F1000Prime RECOMMENDED**
10. Linszen DH, Dingemans PM, Lenior ME: **Cannabis abuse and the course of recent-onset schizophrenic disorders**. *Arch Gen Psychiatry* 1994, **51**:273-279.
- F1000Prime RECOMMENDED**
11. Linszen D, van Amelsvoort T: **Cannabis abuse and the course of schizophrenia**. In *Marijuana and Madness, 2nd edition*. Edited by Castle DJ, Murray RM, D'Souza CD. Cambridge: Cambridge University Press; 2012:210-217.
 12. Zammit S, Moore THM, Lingford-Hughes A, Barnes TRE, Jones PB, Burke M, Lewis G: **Effects of cannabis use on outcomes of psychotic disorders: a systematic review**. *Br J Psychiatry* 2008, **193**:357-363.
- F1000Prime RECOMMENDED**
13. Solowij N, Pesa N: **Cannabis and cognition: short- and long-term effects**. In *Marijuana and Madness, 2nd edition*. Edited by Castle DJ, Murray RM, D'Souza CD. Cambridge: Cambridge University Press; 2012:91-102.
 14. Solowij N, Yucel M, Lorenzetti V, Lubman D: **Does cannabis cause lasting brain damage?** In *Marijuana and Madness, 2nd edition*. Edited by

- Castle DJ, Murray RM, D'Souza CD. Cambridge: Cambridge University Press; 2012:103-113.
15. Castle DJ, Solowij N: **Acute and subacute psychomimetic effects of cannabis in humans.** In *Marijuana and Madness*. Edited by Castle DJ, Murray RM. Cambridge: Cambridge University Press; 2004:41-53.
 16. Morgan VA, Waterreus A, Jablensky A, Mackinnon A, McGrath JJ, Carr V, Bush R, Castle D, Cohen M, Harvey C, Galletly C, Stain HJ, Neil AL, McGorry P, Hocking B, Shah S, Saw S: **People living with psychotic illness in 2010: The second Australian national survey of psychosis.** *ANZ J Psychiatry* 2012, **46**:735-752.
 17. Moore E, Mancuso S, Slade T, Galletly C, Castle D: **The impact of alcohol and illicit drugs on people with psychosis: The second Australian national survey of psychosis.** *ANZ J Psychiatry* 2012, **46**:864-878.
 18. Spencer C, Castle D, Michie P: **Motivations that maintain substance use among individuals with psychotic disorders.** *Schizophr Bull* 2002, **28**:233-247.
 19. Macleod J: **Cannabis use and symptom experience amongst people with a mental illness: a commentary on Degenhardt et al.** *Psychol Med* 2007, **37**:913-916.
 20. Henquet C, van Os J, Kuepper R, Delespaul P, Smis M, a Campo J, Myin-Germeys I: **Psychosis reactivity to cannabis use in daily life: an experience sampling study.** *Br J Psychiatry* 2010, **196**:447-453.
- F1000Prime RECOMMENDED**
21. Lubman D, King J, Castle DJ: **Treating comorbid substance use disorders in schizophrenia.** *Int Rev Psychiatry* 2010, **22**:191-201.
 22. James W, Castle DJ: **Addressing cannabis use in people with psychosis.** In *Marijuana and Madness, 2nd edition*. Edited by Castle DJ, Murray RM, D'Souza CD. Cambridge: Cambridge University Press; 2012:225-233.
 23. Häfner H, Maurer K, Löffler W, Riecher-Rössler A: **The influence of age and sex on the onset and early course of schizophrenia.** *Br J Psychiatry* 1993, **162**:80-86.
- F1000Prime RECOMMENDED**
24. Kuepper R, van Os J, Lieb R, Wittchen H-U, Hofer M, Henquet C: **Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study.** *BMJ* 2011, **342**:1-8.
 25. Andreason S, Allebeck P, Engstrom A, Rydberg U: **Cannabis and schizophrenia: a longitudinal study of Swedish conscripts.** *Lancet* 1987, **ii**:1483-1485.
- F1000Prime RECOMMENDED**
26. Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE: **Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study.** *BMJ* 2002, **325**:1212-1213.
- F1000Prime RECOMMENDED**
27. Zammit S, Arseneault L, Cannon M, Murray RM: **Does cannabis cause schizophrenia?** In *Marijuana and Madness, 2nd edition*. Edited by Castle DJ, Murray RM, D'Souza CD. Cambridge: Cambridge University Press; 2012:169-183.
 28. Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H, Taylor A, Arseneault L, Williams B, Braithwaite A, Poulton R, Craig IW: **Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism of the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction.** *Biol Psychiatry* 2005, **57**:1117-1127.
- F1000Prime RECOMMENDED**
29. Di Forti M, Henquet C, Verdoux H, Murray RM, van Os J: **Which cannabis users develop psychosis?** In *Marijuana and Madness, 2nd edition*. Edited by Castle DJ, Murray RM, D'Souza CD. Cambridge: Cambridge University Press; 2012:137-143.
 30. Arseneault L, Cannon M, Witton J, Murray R: **Cannabis as a potential causal factor in schizophrenia.** In *Marijuana and Madness*. Edited by Castle DJ, Murray RM. Cambridge: Cambridge University Press; 2004:101-118.
 31. Jablensky A, Sartorius N, Ernberg G, Anker M, Korten A, Cooper JE, Day R, Bertelsen A: **Schizophrenia: manifestations, incidence and course in different cultures.** *Psychol Med Monograph* 20 1992.
- F1000Prime RECOMMENDED**
32. Hall W, Degenhardt L: **What are the policy implications of the evidence on cannabis and psychosis?** In *Marijuana and Madness, 2nd edition*. Edited by Castle DJ, Murray RM, D'Souza CD. Cambridge: Cambridge University Press; 2012:55-65.