Cannabis and psychosis – research findings and commentary (prepared for Fiona Patten MP, Parliament of Victoria)

Joseph M. Boden, PhD

Professor and Director, Christchurch Health and Development Study

University of Otago Christchurch, New Zealand

Research in psychiatric epidemiology began to focus on cannabis and psychosis in the years between 2000 and 2010. However, an early study, known as the "Swedish Conscript Study" [1], was the first to document an association between cannabis use and schizophrenia, using data from 18 years of inductions into national service in Sweden (see Table below for details). What is notable about this study is while it was the first to document this link, and the link was to a diagnosis of schizophrenia, there was no way for the researchers to control for either *prodromal* symptoms (early onset that may be less remarkable in nature, such as "inattentiveness") of schizophrenia, or a predisposition to the illness.

To summarize the studies below, it would appear that those who begin using cannabis at a young age, and more heavily at younger ages are at greater risk of developing symptoms of psychotic illness, or psychosis itself. However, there are several criticisms that have been made of these findings, as well as extensions to the original research itself:

1. The analysis by Fergusson et al used items from the Symptom Checklist 90 [2], which has a "psychoticism" subscale. Fergusson added two items to this from the "paranoia" subscale. While this could still be argued as representing "psychotic symptoms", most of the symptoms reported are mild, and are not represented in other diagnostic tools such as CIDI [3]. A more recent article by Malpas et al [4] suggests that the Positive Predictive Value (PPV) for the Psychosis subscale is very poor (that is, it should not be used to attempt to predict meeting criteria for a psychotic illness at is has low specificity). This casts further doubt on the utility of the findings.
2. These studies are generally unable (with the exception of Caspi et al [5]) to address issues of predisposition to psychotic illness (normally through genetic influences). Caspi's study suggests that the vulnerability to psychotic illness exists only amongst those who have a particular variant (Val/Val) of the COMT gene, which is involved in dopamine regulation. This variant is found in 25% of the population, which shows that it is likely that to develop psychotic illness following cannabis use, a person must: a) be genetically predisposed; b) begin use at an early age (as dopamine regulation is "set" by early adulthood [6]; and c): used heavily at an early age. This implies that the vulnerable group makes up a very small proportion of the population.
3. While the Caspi et al finding has not been fully validated, more recent work has used an approach that involves calculating polygenic risk scores (PRS). PRS [7] is a method of using whole genome sequencing in which a genetic profile is established by comparing cases (in this case, people with psychotic illness) with those without, and identifying a series of genes that differ between these groups. These analyses are done with many hundreds of thousands of DNA samples in order to determine what genetic "fingerprint" a particular illness (such as psychotic illness) might have. A recent study using (PRS) for schizophrenia [8] shows that the cannabis-psychosis link is strong for those with high PRS scores, and very weak for those with PRS scores,

suggesting (as with Caspi et al, above) that the most important factor in determining whether a person develops a psychotic illness following the early and heavy use of cannabis is their genetic susceptibility to a psychotic illness.

One important implication of this line of reasoning is that it is particularly important to restrict the use of cannabis in adolescents (and in particular younger adolescents). However, there is no evidence that prohibition of cannabis has any effect on reducing access to cannabis amongst young people [9].

Table 1 Summary of prospective studies of cannabis use and psychosis (selected findings only)

Study	Sample	Assessment	Outcome Measure	Adjusted association between cannabis and psychosis (95% CI)
Andreasson et al [1]	45,570 male Swedish military conscripts aged 18-21	At 15 year follow-up	Clinical diagnosis of schizophrenia	Highest level of use: Relative risk 2.3 (1.0-5.3)
Arsenault et al [10]	759 members of New Zealand birth cohort	At age 26	DSM-IV criteria for schizophreniform disorder	Cannabis users by age 15: Odds ratio 1.95 (0.76 to 5.01)
Caspi et al [5]	803 members of New Zealand birth cohort	At age 26	DSM-IV criteria for schizophreniform disorder	Participants with Val/Val variant of COMT gene: Odds ratio 10.9 (2.2 to 54.1)
Fergusson et al [11]	1,055 members of New Zealand birth cohort	At age 25	No of psychotic symptoms in past month	Daily cannabis users: Incident rate ratio = 1.77 (1.28 to 2.44)

Ferdinand et al [12]	1,580 Dutch participants followed-up	14 years after first assessment	Psychotic symptomatology as measured by CIDI (presence/absence)	Participants using cannabis 2 years before onset of psychotic symptoms had a hazard ratio of 2.07 (95% CI: 1.20-3.57)
Henquet et al [13]	2,437 German participants aged 14- 24	At baseline and four year follow-up	At least one “broad” or two “narrow” psychosis outcomes	Daily cannabis users: Odds ratio 2.23 (1.30 to 3.84)
Van Os et al [14]	4,104 participants in Dutch general population study	Assessed three times over four years	≥1 positive rating on psychotic symptom items	Highest level of use: Odds ratio 6.81 (1.79 to 25.92)

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