The Environment and Schizophrenia: The role of Cannabis Use

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Introduction

That cannabis is a cause of poor outcome in existing psychotic illness is generally accepted, in Europe at least (Linszen et al. 1994; Van Os et al, 2002). However, whether cannabis can precipitate schizophrenia in those with genetic liability, was, until recently, more controversial. Cannabis use has been rising, and the age of initiation of use falling, in many European countries, with 5-15% of young people being regular cannabis users in countries such as Holland (Monshouwer et al. 2005). Since much recent evidence suggests that liability to schizophrenia is a dimensional phenomenon with a distribution in the population (Rutter 2003), if cannabis use carried an increase in risk for schizophrenia, this would clearly be of public health concern. Reports of exposure to tetrahydrocannabinol, the principal psychoactive component of cannabis (D'Souza et al. 2004), as a possible cause for schizophrenia, date back to the early 1960s (Zal'Tsman & Lenskii, 1962), and in 1987 a methodologically superior study demonstrated a convincing dose-response relationship between early cannabis use and later admission for schizophrenia in young men (Andreasson et al. 1987). However, it was not until after 2000 that the issue was seriously considered (Arseneault et al. 2004; Smit et al. 2004).

Is the reported association between cannabis and schizophrenia true?

Is the association due to chance?

All published prospective studies examining the association between cannabis and psychosis outcomes are considered in table 1 (Arseneault et al. 2002; Fergusson et al. 2003; Henquet et al. 2005; Stefanis et al. 2004; Van Os et al. 2002; Weiser et al. 2002; Zammit et al. 2002). It can be seen that, in spite of differences in definition (some studies focused on the narrow outcome of schizophrenia, others on the wider outcome of psychotic symptoms) and other differences between studies such as length of follow-up, baseline cannabis use consistently increased the risk for the psychosis outcome at follow-up. In order to obtain a pooled effect size from these studies,

meta-analysis of the odds ratios of the individual studies was carried out using STATA, version 8.0 (StataCorp 2002), using a random effects model with weighting according to the inverse of error variances. The pooled estimate for development of psychosis associated with prior cannabis use was an odds ratio (OR) of 2.1 (95% CI: 1.7-2.5; test for heterogeneity: Q= 5.0, p=0.54). This held regardless of whether only studies using the narrow clinical outcome were used (OR=2.37, 95% CI: 1.7-3.3; test for heterogeneity: Q=1.5, p=0.47) or whether studies using the broad outcome of psychotic symptoms were considered (OR=1.9, 95% CI: 1.5-2.5; test for heterogeneity: Q=2.4, p=0.49). The results of this meta-analysis show that the association between cannabis and later psychosis outcome is consistent, and although a relative risk of around 2.0 is not a very large effect size, cannabis use is extremely prevalent in young people (i.e. the age group most at risk of psychosis), making this a very relevant finding.

Is the association confounded?

As longitudinal studies clearly are dependent on observational designs, confounding may be an issue (Macleod et al. 2004). For example, cannabis use may be associated with use of amphetamines and, independent of that association, amphetamines may be associated with the psychosis outcome. However, all the studies in table 1 attempted to adjust for confounding factors, and although effect sizes were reduced, the effect of cannabis persisted after adjustment for factors such as: age, sex, social class, ethnic group, family history of psychiatric illness, urbanicity, and use of other drugs. Therefore, although confounding due to unmeasured factors can never be ruled out in observational studies, it is unlikely, given the large number of confounders adjusted for in attempts to "explain away" observed cannabis associations, that the reported association between cannabis and psychosis is entirely due to confounding factors (Fergusson et al. 2005).

Is the association the result of reverse causality?

Reverse causality refers to the fact that individuals with expression of vulnerability to psychosis, such as social anxiety or the softest expressions of subtle psychosis-like experiences, may be more likely to start using cannabis so as to "self-medicate" their distress. This is a plausible hypothesis and must be examined before it can be concluded that cannabis contributes causally to the risk of psychosis. Studies have attempted to deal with this issue in different ways. A Dutch cohort study excluded, at baseline, all individuals who had ever had any psychosis-like experience and examined, in the remaining 80% of the sample, the effect of baseline cannabis on psychosis at follow-up. Despite exclusion of the 20% with any sign of psychosis liability, an association with psychosis at follow-up was still evident (Van Os et al. 2002). In a birth cohort study from New Zealand, an association was shown between cannabis use at age 15 years and schizophrenia symptoms at age 26 years. When psychosis liability at age 11 years was adjusted for, this association remained significant (Arseneault et al. 2002). A third longitudinal study used statistical modeling in an attempt to distinguish between causal and self-medication hypotheses, and reported that the data were more compatible with a causal rather than a non-causal explanation (Fergusson et al. 2005). Finally, a cohort study from Greece examined the self-medication hypothesis, by testing whether subtle psychotic experiences with distress would have stronger associations with cannabis use than psychotic experiences without distress. The authors, however, found stronger associations between cannabis and psychotic experiences in the absence of distress, making self-medication unlikely (Stefanis et al. 2004).

Nevertheless, psychosis liability by itself may well explain part of the association between cannabis and psychosis. For example, Henquet and colleagues examined whether individuals with expression of psychosis liability but who had never used cannabis, would be more likely to start using cannabis over the follow-up period. They found that psychosis liability predicted future cannabis use, although the effect size was small and statistically imprecise. However, the authors also found an association the other way round: cannabis use at baseline predicted onset of psychotic symptoms over the follow-up period (Henquet et al. 2005). A recent Dutch study

replicated these results reporting similar, bidirectional associations that were statistically precise (Ferdinand et al. 2005). Therefore, both the self-medication hypothesis and the causal hypothesis may be true. In fact, such a bidirectional relationship between risk factor and disease is not unusual for psychiatric disorders such as psychotic illness (Van Os and Sham 2003).

Is the association between cannabis and psychosis causal?

Causality is generally thought to be plausible if studies i) report an association between the exposure and the outcome consistently and with a strong effect size, ii) show dose-response relationships between the exposure and the outcome, iii) show the exposure precedes the outcome and iv) there is a plausible biological mechanism linking the exposure and the outcome. With the exception of a large effect size, the studies in table one fulfill criteria i-iii. Of note is that with regard to the temporal order issue, three studies have shown that in particular cannabis use at an earlier age (early adolescence) increases the risk for later psychosis outcomes (Arseneault et al. 2002; Stefanis et al. 2004; Van Os et al. 2002). This observation is of interest with regard to criterion (iv) of biological plausibility, as cannabis interacts with endocannabinoid systems that are involved in neurodevelopment. In rats, chronic cannabinoid treatment during puberty induces behavioural and cognitive changes that are not encountered if animals are exposed to cannabis in adulthood (Schneider and Koch 2003), and may result in shaping adult risk for psychotic disorder (Veen et al. 2004). Another plausible biological mechanism that may explain the association between cannabis and psychosis is that of dopamine sensitisation, induced by regular cannabis use, whereby individuals become progressively more vulnerable to dopamine induced perceptual and cognitive aberrations that may progress to full-blown psychotic symptoms (Howes et al. 2004). Nevertheless, while both these mechanisms are plausible, much more evidence is required before the biological mechanisms linking cannabis consumption with psychosis can be established.

What type of cause is cannabis?

Clearly not all patients with psychotic illness have been exposed to cannabis and not all cannabis users develop psychosis. Thus, cannabis is neither a necessary nor a sufficient cause; it must be a component cause (Rothman 1986), i.e. it is co-dependent on some other factor in order to have causal influence on risk for psychosis (Degenhardt and Hall 2002; Degenhardt et al. 2003). Several studies suggest that one factor that cannabis can combine with in order to exert causal influence is genetic liability to psychosis. There are two ways to measure genetic liability to psychosis: directly and indirectly, and studies with both measures provide growing evidence than an underlying mechanism of gene-environment interaction explains the association between cannabis and psychosis.

Studies with indirect measures of genetic risk

McGuire and colleagues found that the relatives of patients with acute psychosis who tested positive for cannabis had a ten times higher morbid risk for schizophrenia than relatives of patients who tested negative (McGuire et al. 1995). Similarly, Verdoux and colleagues, in an elegant momentary assessment study of cannabis and psychotic experiences in the flow of daily life (Verdoux et al. 2003), found that the risk of developing cannabis-induced psychotic experiences was much higher in individuals with evidence of psychosis liability (measured by a psychosis proneness scale shown to be sensitive to familial transmission of psychosis liability (Hanssen et al. 2005)). Henquet and colleagues reported that the 3.5 year risk of developing broadly defined psychotic symptoms was 21% in young people using cannabis in the absence of psychosis liability, but 51% in those who had both cannabis use and psychosis liability (Henquet et al. 2005), and similar findings were reported in another cohort study (Van Os et al. 2002). In an interesting experimental study, D'Souza and colleagues showed that patients with schizophrenia appeared to be more sensitive to cannabis-induced cognitive impairments and showed greater increases in psychotic symptoms than well controls (D'Souza et al. 2005).

Studies with direct measures of genetic risk

The above studies all concur in showing moderation of cannabis-induced risk for psychosis by underlying liability, presumably of genetic origin. A recent study by Caspi and colleagues, using data from the New Zealand birth cohort sample cited earlier (Arseneault et al. 2002), showed that a functional polymorphism in the catechol-O-methyltransferase (COMT) gene moderated the effect of adolescent cannabis use on risk for adult psychosis. Individuals homozygous for the COMT valine^{158} allele, were most likely to exhibit psychotic symptoms and to develop schizophreniform disorder, after adolescent exposure to cannabis. However, adolescent cannabis use had no such adverse influence on individuals with two copies of the methionine allele (Caspi et al. 2005). Also, cannabis use by itself was not associated with either the COMT valine or methionine allel, suggesting that underlying gene-environment correlation could not explain the findings.

Conclusion

The observed deleterious effect of cannabis use on the prognosis of patients with psychotic disorder may involve the same mechanism as the observed deleterious effect of cannabis use on the prognosis of individuals with high levels of liability to psychosis. Further study of gene-environment interactions is likely to help elucidate the exact role of cannabis in the onset and the persistence of psychotic disorders but there is an urgent need for human and animal studies examining the biological mechanisms involved.

Table 1. Prospective studies examining associations between cannabis use and psychosis outcomes

Reference	Study design (age at baseline)	Subjects (N)	Defenition of cannabis use	Outcome	Odds Ratio (95% CI)	Adjustment
Zammit et al., 2002	conscript cohort (18-20 yrs)	50053	lifetime use of cannabis > 50 times at baseline	schizophrenia	3.1 (95% CI 1.7-5.5)	diagnosis at baseline, IQ, social integration, disturbed behavior, cigarette smoking, place of upbringing
Van Os et al., 2002	population-based (18-64 yrs)	4045	lifetime use of cannabis at baseline	psychotic symptoms	2.8 (95% CI 1.2-6.5)	age, sex, ethnic group, single marital status, level of education, urbanicity, discrimination
Weiser et al., 2002	population-based (16-17 yrs)	50413	lifetime use of any drugs (principally marijuana) at baseline	schizophrenia	2.0 (95% CI 1.3-3.1)	IQ, social functioning, non-psychotic disorder
Arseneault et al., 2002	birth cohort (15-18 yrs)	759	lifetime use of cannabis by age 15	schizophreniform disorder	3.1 (95% CI 0.7-13.3)	sex, social class, psychotic symptoms prior to cannabis use
Fergusson et al., 2003	birth cohort (18-21 yrs)	1011	DSM-IV cannabis dependence at baseline	psychotic symptoms	1.8 (95% CI 1.2-2.6)	preceeding psychotic symptoms, use of other substances, mental health, social, family and individual factors
Stefanis et al., 2004	birth cohort (19 yrs)	3500	lifetime use of cannabis	positive and negative psychotic symptoms	4.3 (95% CI 1.0-17.9)	other drug use, depressive symptoms, sex, schoolgrade
Henquet et al., 2005	population-based (14-24 yrs)	2437	lifetime use of cannabis at baseline	psychotic symptoms	1.7 (95% CI 1.1-2.5)	age, sex, socioeconomic status, urbanicity, trauma, predisposition for psychosis, other drug use, tobacco, alcohol

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