Psychosis relapse, medication non-adherence, and cannabis

In The Lancet Psychiatry, Schoeler and colleagues present a study describing the mediating effect of medication adherence on the association between continued cannabis use and relapse risk in patients with first-episode psychosis. They have previously reported a relapse rate of 36% in this patient group over a 2-year period. Acknowledging the potential risk of psychosis relapse related to the high proportion of patients continuing cannabis use after the onset of psychosis, the current study investigates the same patient group consisting of 245 patients, obtaining retrospective data on active cannabis use and medication adherence shortly after illness onset, as well as risk of relapse at 2-year follow-up. The authors find that relapse of psychosis associated with continued cannabis use is partly mediated through non-adherence to prescribed antipsychotic medication.

It is well established that cannabis use increases the risk of schizophrenia, not only from the early Swedish conscript studies but also from studies on people who use sinsemilla in London, UK, showing that high potency cannabis increases the risk of schizophrenia. Twin studies from Norway have shown that cannabis increases the risk of psychosis, even when controlling for genetic factors. There has been discussion on the direction of the association, as none of these studies can rule out reverse causality, but it seems reasonable to conclude that cannabis is one of many stressors that can precipitate schizophrenia, at least in susceptible individuals.

The association between cannabis use and psychosis continues to interest clinicians and researchers. Cannabis does not precipitate psychosis in most users. What are the risk factors in the pathway from cannabis use to psychosis? The use of cannabis in patients with psychosis can be divided into three groups: those not using cannabis, those using cannabis with few negative consequences, and those in whom cannabis use is followed by relapse and worsening of the disease. Too little effort has been put into studying people with psychosis who can use cannabis without many negative consequences. Further research should also be put into different variants of cannabis. Strains cultured to produce high content of D-9 tetrahydrocannabinol (THC) are probably associated with higher risk for psychosis than those strains with less THC. In healthy participants, cannabidiol has been shown to inhibit THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. The use of more balanced forms of cannabis could possibly be less detrimental to mental health. Genetic predisposition is one factor that is related to the development of psychosis after the use of cannabis. However, there is still a long way to go in clarifying the interplay between genes and environmental factors in the cannabis-psychosis association. Therefore, we support the request for doing more studies to investigate the possible interaction between polygenic risk score for schizophrenia and cannabis use in causing psychosis. Furthermore, there is a need to examine the use of antipsychotic medication and investigate if some medications are particularly useful for patients with psychotic disorders who intend to continue to use cannabis. In a randomised trial comparing the effects of different antipsychotics, clozapine seemed to stand out in reducing craving for cannabis, a finding that is in need of replication.

Previous research has shown that stopping cannabis use after a first episode of psychosis has beneficial outcomes compared with continued use. A meta-analysis of observational studies published in 2017 compared adherence to antipsychotic medication between cannabis users and non-users, and found that cannabis use increases the risk of non-adherence to anti-psychotic medication and quitting cannabis may help adherence to antipsychotics. In the current study by Schoeler and colleagues, the authors found that adherence to medication was a possible mediator in the association between cannabis use and risk of psychosis relapse when taking potential confounders into account. They found that medication adherence partly mediated the effect of continued cannabis use on outcome, including risk of relapse (proportion mediated=26%, $p_{indirect\, \text{effect}}=0.040$, 95% CI 0.004–0.16), number of relapses (36%, $p_{indirect\, \text{effect}}=0.040$, 0.003–0.14), time to relapse (28%, $p_{indirect\, \text{effect}}=0.051$, –0.53 to 0.001), and care intensity (20%, $p_{indirect\, \text{effect}}=0.035$, 0.004–0.11), but not length of relapse (6%, $p_{indirect\, \text{effect}}=0.35$, –0.030 to 0.09).

Acknowledging the complexity of psychosis relapse prevention, the current findings point to reduction in cannabis use as an intervention target to improve...
medication adherence, thereby preventing psychosis relapse. The understanding of a triangular association of ongoing cannabis use with medication adherence and psychosis relapse may be a step forward in counteracting further psychotic episodes in some patients.

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We declare no competing interests

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10 Foglia E, Schoeler T, Klamerus E et al. Cannabis use and adherence to antipsychotic medication: a systematic review and meta-analysis. *Psychol Med* 2017; published online Feb 09. DOI:10.1017/S0033291717000046.