Clearing the smoke: What do we know about adolescent cannabis use and schizophrenia?

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While cannabis has been used as a recreational drug in many cultures around the world for centuries, it is only recently that we have begun to understand the biology of how this drug affects the brain. The discovery of the primary components of the endocannabinoid system (the cannabinoid CB1 and CB2 receptors and the endogenous ligands anandamide and 2-arachidonoylglycerol) in the late 1980s and early 1990s allowed for discrete and focused research to occur. In the last 25 years, it has been determined that many of the prototypical effects of cannabis use (increased feeding, sedation, reduced anxiety, reduced blood pressure) mimic the actions of endocannabinoid signalling.[1] That being said, many of the effects of cannabis remain a mystery.

The past few decades have been rife with debate regarding the safety and medical utility of cannabis, little of which has actually been rooted in scientific evidence. The extremes of these opinions state that cannabis is a completely innocuous and harmless substance, or that it is a highly dangerous drug whose use provokes a series of adverse health complications. While both of these opinions are for the most part inaccurate, these unfortunately are the types of debates that often occur in a political sphere and can have substantial impact on policy decisions. The need for evidence-based decisions to guide cannabis access is imperative given that in the states of Colorado and Washington recreational sale of cannabis is now legal and that in Canada there is currently substantial revision and overhaul occurring with the medical marijuana program. While many conditions, including lung cancer and cardiac arrthymias, have been at the forefront of the cannabis safety debate for some time, interestingly the discussion has predominantly moved to psychiatry — specifically the association between adolescent cannabis use and the development of schizophrenia.

The first study that brought this association to the forefront of the research community was a paper published in *Lancet* in 1987 that demonstrated a significant association between cannabis use and the development of schizophrenia in a 15-year longitudinal study of more than 45 000 healthy Swedish army conscripts.[2] Individuals who consumed a high level of cannabis (defined as use of cannabis on more than 50 occasions by the age of 18 years) had a greater risk of schizophrenia developing. This finding was interesting, as several historical reports had documented psychotic-like reactions to cannabis, suggesting that there may be a basis for associating cannabis use with the development of schizophrenia. In the decades that followed, several other reports confirmed this association (see the reviews by Malone and colleagues,[3] D'Souza and colleagues[4] and Arsenault and colleagues[5]); that is, when examined retrospectively, individuals in whom schizophrenia had developed exhibited a higher level of cannabis use, often during adolescence. Based on this association, several schools of thought formed: 1) cannabis causes schizophrenia, 2) cannabis acts as a specific risk factor for provoking schizophrenia, and 3) cannabis is used as self-medication.

So what does the science actually tell us? First, the hypothesis that cannabis can cause schizophrenia *de novo* is essentially without evidence. Although it is true that administration of very high doses of tetrahydrocannabinol (THC), the psychoactive constituent of cannabis, to healthy individuals can produce psychotic-like symptoms transiently,[6] these symptoms subside very quickly and are not representative of a *bona fide* psychiatric condition. More so, within the Western world, cannabis use went from essentially nonexistent before the 1950s to extremely prevalent in the 1960s and 1970s. Despite this dramatic shift in cannabis use at a societal level, the prevalence of schizophrenia has largely remained stable.[7]

With respect to the self-medication hypothesis there is conflicting evidence. Several reports have documented that cannabis consumption in people with schizophrenia is associated with a reduction in negative and cognitive symptoms (although this is often coupled with a significant increase in positive symptoms[8–11]). The argument is that since conventional antipsychotic medications do not manage negative symptoms well, cannabis is an adjunct that patients use to

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J Psychiatry Neurosci 2014;39(2):75-7.

DOI: 10.1503/jpn.140028

attenuate their negative symptoms. Consistent with this, there are significantly higher rates of cannabis use in people with schizophrenia than in the general population.[12] The major problem with this hypothesis is that both prospective and retrospective studies have reliably found that cannabis use typically precedes the onset of clinical symptoms, arguing against the hypothesis that this association is purely driven by the attempt to manage symptoms.[13]

The most parsimonious hypothesis is that cannabis acts as a specific risk factor that can provoke the onset of a psychotic episode in individuals who are already vulnerable to schizophrenia developing.[7] This hypothesis explains not only why an association between cannabis use and schizophrenia exists, but also why this association is moderate, at best, at a population level.

Assuming that the association between cannabis and psychosis is exclusively mediated by a unique sensitivity to the adverse effects of cannabis in individuals vulnerable to schizophrenia, the question of why adolescence is a period of unique vulnerability arises. Interestingly, several lines of evidence suggest that adolescence may be a specific period for sensitivity to cannabis.

First, the endocannabinoid system is important for cortical development, neuronal migration, connectivity and synaptogenesis.[14] During adolescence, many brain regions undergo dramatic levels of growth and synaptic remodelling, of which the prefrontal cortex (PFC) is probably the most robust.[15] Interestingly, the PFC is rich in cannabinoid receptors[16] and is one of the brain regions most heavily implicated in schizophrenia.[17] Animal studies examining the effects of adolescent exposure to THC have demonstrated that this manipulation can have significant effects on the morphology and function of the maturing PFC.[18–20]

In addition, cannabinoids are known to provoke dopamine (DA) release,[21] and this effect is amplified in individuals with schizophrenia or individuals who have first-degree relatives with schizophrenia.[22] During adolescence, the dopaminergic system in the PFC undergoes a transitory shift in functionality where the ability of DA to modulate interneuron populations emerges.[23] Therefore, the ability of cannabinoids to enhance DA signalling may have differential effects on a brain in development as opposed to a mature brain where the DA system is established.

Furthermore, the endocannabinoid system itself undergoes dramatic ontogenetic changes during adolescence where the expression of the CB1 receptor increases from early life, peaks just at the onset of adolescence and declines throughout aging.[24,25] As such, adolescence represents a period of heightened CB1 receptor density and possibly functionality, meaning that the effects of cannabis on a brain at this period could be fundamentally different than the effects on a mature brain.

Taken together, there are compelling biological explanations for how cannabis exposure during adolescence could have adverse effects on brain development, particularly that of the PFC. However, in the majority of teenagers who use cannabis, schizophrenia does not develop, suggesting that there must be additional factors that render the brain of a high-risk adolescent exquisitely sensitive to the effects of cannabis. Specific gene polymorphisms, such as ones within the *COMT* or *AKT1* genes seem likely candidates,[26–28] although a single polymorphism is unlikely to explain this association. Elucidating these factors should be a major focus of ongoing research.

Where does this knowledge take us and how does it inform the cannabis debate? What can be said is that the extreme opinions on this subject are not rooted in science. There is little evidence that, at a population level, cannabis use during adolescence is a primary contributing factor in the development of psychiatric illness. In fact, it has even been suggested that at a societal level, the prevention of 3000–4000 adolescents from consuming cannabis may prevent only 1 case of psychosis from emerging.[29] At the same time, however, there is evidence that in high-risk populations, cannabis can be highly adverse, so arguments claiming that cannabis is innocuous are equally flawed. Health Canada has recently compiled a document reviewing the science regarding the potential benefits and adverse effects of cannabis for an array of medical conditions, including psychiatric illnesses, to provide an evidence-based compendium for physicians and medical practitioners (www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/marihuana/med/infoprof-eng.pdf). Ideally, documents such as this will be used to guide and influence policy decisions and regulatory warnings regarding the accessibility of cannabis to the public as well as consider the age of the individual (as well as family history and risk factors) before access to cannabis is granted. More so, once a diagnosis of schizophrenia is present, cannabis use is clearly adverse and is related to medication nonadherence,[30] accelerated grey matter loss[31] and worse long-term prognosis.[32] As such, regardless of age, any individual with a diagnosis of schizophrenia should be warned of these nontrivial issues, and the contraindication of cannabis with this condition should be given substantial consideration.

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