Cannabis use and a causal link to schizophrenia and psychosis in adolescents: a review

The use of marijuana in youth has been well documented in Canada, with 25% of Ontario high school students reporting to have used it at least once, and 5% of Nova Scotia high school students who have reported to use it on a daily basis (Canadian Public Health Association, 2012). The prevalence of cannabis among youth is alarming when considering the increasing amount of evidence showing that brain development and its vulnerability to exogenous cannabinoids is most critical during the perinatal and pubertal period (Sundram, 2006). The proposed changes to the brain include synaptic pruning, neuronal development and the rearrangement of neural networks. As a result of these neuroanatomical changes, a link between the use of cannabis in youth and the development of psychosis has been proposed in those predisposed to the disease. Research resolving the correlation between these two occurrences has been well documented in human and animal models; however the focus of this review paper is to amalgamate the literature studying human adolescents only.

Various types of neuroanatomical changes have been studied in adults who began smoking cannabis at their adolescence. In a study conducted by Yucel et al. (2008) looking at 15 male heavy cannabis smokers (> 5 joints daily for >10 years), it was found that the participants had an approximate 12% reduction of hippocampal and 7% reduction of amygdala volume compared to the controls. Previous research has shown that a reduction in, or the abnormality of the left hippocampus in particular has been linked to the occurrence of psychotic symptoms (Rais et al., 2008). Consistent with this notion, the study correlated the use of cannabis and positive psychotic symptoms, which may reflect a pre-existing disposition to psychosis in these individuals.

The prefrontal cortex has also been implicated in schizophrenia and psychotic symptoms, specifically with regard to dopamine regulation. The dopamine hypothesis of schizophrenia outlines that an excess of dopamine is related to the positive symptoms of schizophrenia, and the deficiency of dopamine is related to the negative symptoms (Davis et al., 1991). THC has been found to cause insult to the brain and can result in a disturbance in the CB1 receptors which lead to the cascade of events responsible for glutamate and GABA release (Bosong & Niesink, 2010). However, the changes that result in this neuroanatomical rewiring is dependent on many factors, such as age of initiation of cannabis smoking, the duration, and where exactly in the neural development the individual is in during the smoking of cannabis. Many longitudinal studies regarding the development of psychosis and schizophrenia in individuals with early onset and longstanding cannabis use have been conducted. By the time of publication in 2011, Casadie, Fernandes, Murray, & Di Forti ascertained that at least 10 longitudinal studies following cannabis use as a risk factor in schizophrenia. Among the most famous was a study following Swedish army conscripts for 15 years. Over the duration of the study, the researchers analyzed 45 570 people (males) and had concluded that individuals showed a dose-response relationship wherein those who had smoked cannabis by the age of conscription (18) had doubled the risks of developing schizophrenia (Andreasson, Allebeck, Engstrom, & Rydberg, 1987). When a follow up analysis was conducted, it was seen that heavy users were found to have six times greater likelihood of being diagnosed with schizophrenia than non-users (Zammit, Allebeck, Andreasson, Lundberg, & Lewis, 2002).

This early and thorough study laid the groundwork for many similar studies conducted over the last 10 years, only a few of which will be discussed here. One of the more recent studies, conducted by Henquet et al. (2005) followed 2437 German individuals aged 14-24 years. The evidence by the researchers ascertained that there was a steady, but not drastic dose-dependent relationship between cannabis and psychosis. Cannabis users with a predisposition to psychosis had a significantly increased occurrence of psychosis after a four year follow up study. 17.4% of individuals had a single lifetime experience of a psychotic symptom, and 7.1% reported two or more psychotic symptoms. This was true even when other such as age, gender, and other mental illnesses were adjusted for. Similar to the Swedish conscripts study, strong evidence for cannabis use at a younger age correlated with higher than average psychotic episodes or schizophrenic characteristics. The possibility for extraneous factors, such as...
socioeconomic status and the possible propensity of younger subjects to use cannabis for a longer duration must also be considered (Konings, Henquet, Maharajh, Hutchinson, & Van Os, 2008).

Critics of the correlation between cannabis use and schizophrenia have also noted the possibility for a reverse causal relationship, or self-medicating; such that individuals who were more predisposed to schizophrenia were more likely to use cannabis as a result. However, as determined by the study by Henquet, et al. (2005), a predisposition to psychosis was not a reliable predictor in later cannabis use. The use of cannabis has been consistently shown to precede psychotic symptoms, even in individuals who did not have any previous experience with psychotic like experiences (Kuepper, et al., 2011).

However, minor causative factors of cannabis and schizophrenia have also been established (Arseneault, 2002), approximately 8% of those with schizophrenia report cannabis use (Arseneault, 2004). Veen et al. and Zammit et al. have noted that dose, gender and age of onset for the disease also appeared to have a causal relation to the drug (as cited Sundram, 2006).

A major negative aspect to the longitudinal studies mentioned in this paper, as well as the many other that studied cannabis and psychosis is that they are rife with variables that were uncontrollable. Because of the unethical consequences and illegality of creating a contrived human study, many other confounding factors are unavoidable. One of the most important variables that could not be controlled is the content of the cannabis smoked, exactly frequency and the stage of brain development in the individual. Although many studies did attempt to control for other variables, it is nearly impossible in naturalistic observation studies.

Despite this inability to perfectly control for confounds, a large body of animal and human based evidence has shown that cannabis may cause an exacerbation of psychotic-like symptoms, and may help develop a higher likelihood of developing a psychotic disorder. (Kuepper, et al., 2011). Further research must be conducted in order to further determine the strength, if any, causal relationships between cannabis and schizophrenia.

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