Cannabis Use as a Risk Factor for the Development of Schizophrenia

Introduction

Mental disorders refer to conditions in which patients exhibit altered behavior and thought processes, emotional instability and limited social capacity; different illnesses being presented with different combinations of symptoms. Psychotic disorders, of which schizophrenia is the most studied, are considered by the field of psychiatry to be one of the more severe forms of mental illness. (Radhakrishnan, Wilkinson and D'Souza, 2014). Schizophrenia, a heterogenous condition of which the etiology is unclear, is a psychotic disorder featuring 'positive' symptoms (such as hallucinations, delusions and loss of contact with reality), 'negative' symptoms (such as diminished social capacity, lack of energy and decreased motivation) and cognitive dysfunction (Khan et al., 2015). The fact that schizophrenic patients often struggle to live independently, the fact that management of the illness (including a range of anti-psychotic drugs) is plagued with numerous side-effects and has proven unable to rid patients of negative and cognitive symptoms, as well as the fact that schizophrenia causes increased mortality (Os and Kapur, 2009); all make the goal of prevention and identification of susceptible individuals crucial.

Through rigorous research some risk factors were identified as increasing the risk of the development of schizophrenia, many of which are not capable of modification; such as the male gender, positive family history of schizophrenia and genetic polymorphism (Picchioni and Murray, 2007). One potential factor that arose, and sparked much controversy, was the use of cannabis as a preventable risk factor for schizophrenia. Cannabis, a drug that until recently was considered illegal in most parts of the world, is nevertheless one of the most commonly used drugs in today's society (Radhakrishnan, Wilkinson and D'Souza, 2014), especially among teenagers and young adults.

The topic of cannabis use, specifically during adolescence, and its connection to schizophrenia as an avertible risk factor will be related to the clinical history of a 25-year-old male acquaintance of mine, who for the sake of confidentiality will be referred to as "Patient X". Since the age of 14, "Patient X" has admitted to smoking cannabis with his friend groups on an almost daily basis. He stated that he used to be "a social butterfly", and thrived off social interaction, but noticed that skill diminish as he grew older. He struggled to maintain social connections and became distant from many of his friends. He detailed that he begun to experience hallucinations, which today he could recognize as the first stages of schizophrenia, but which at the time he attributed to stress and consequently ignored. At the age of 23 he was diagnosed with schizophrenia after attacking his father, because he suffered from the delusion that his father was "out to get him". "Patient X" attributes his schizophrenia to his habit of cannabis use. By reviewing current literature, this report will explore the potential link between cannabis and schizophrenia.

Literature review

Cannabis, a highly popular recreational drug, is a plant composed of various cannabinoids; different regions containing different compositions. (Radhakrishnan, Wilkinson and D'Souza, 2014). Delta-9-tetrahydrocannabinol (THC), the main component of cannabis, has been shown to induce symptoms similar to those seen in schizophrenia, such as reduced cognitive capacity, decreased motivation and psychotic episodes (Volkow et al., 2016); and this has helped to place cannabis use under suspicion as a risk factor.

Various biological hypotheses were proposed to explain the relationship between cannabis use and schizophrenia. The first suggested that in the population there are certain people who were genetically susceptible to developing schizophrenia, and that cannabis use functioned as a trigger for the onset of the disease. Schizophrenia is hypothesized to be a disease of dopamine dysregulation (Khan et al., 2015); and so one of the genes that was studied was Catechol-O-methyltransferase (COMT), an enzyme that participates in the breakdown of dopamine in the pre-frontal cortex (Radhakrishnan, Wilkinson and D'Souza, 2014). Various studies have found an association between polymorphisms of COMT (differing in their rate of enzymatic activity), cannabis use and the development of schizophrenia; however, these studies seem to disagree on which allele is implicated with the disease, making it difficult to draw definitive conclusions. (Caspi et al., 2005; Costas et al., 2011).

Another biological plausibility that was considered was that cannabis use during adolescence disrupted normal brain development and thus induced schizophrenia. The endocannabinoid system appears to be involved in numerous neuro-developmental processes, which reach their peak at adolescence. The introduction of exogenous cannabis during this period may irreversibly affect these processes and lead to lasting neurological damage (Malone, Hill and Rubino, 2010; Volkow et al., 2016). One longitudinal study found a direct link between earlier cannabis use and decreased cognitive functioning (Fontes et al., 2011), which appears to support the theory that individuals are more vulnerable to the effects of cannabis during adolescence. Due to the fact that brain structure is often altered in patients suffering from schizophrenia (Khan et al., 2015), brain imaging was also used as a tool in multiple studies to assess the link between cannabis use and psychosis. The volume of the brain appears to be diminished in patients with schizophrenia (See Figure 1), and these studies demonstrated that adolescents who smoke cannabis exhibited a reduction in grey matter volume (Johnston et al., 2012) similar to those seen in schizophrenia. Furthermore, cannabis smoking teens exhibited an imbalanced cortical maturation (Epstein and Kumra, 2015) and alterations in the neural matrix (Gilman et al., 2014) when compared to their peers who did not use cannabis; findings that were mostly consistent to those found in schizophrenia patients. (Khan et al., 2015). These results seem to highlight the effects of cannabis on the developing brain and strengthen the association with the development of schizophrenia. Despite the fact that many studies support this theory, others seem to dispute it: one review found that the association between cannabis and altered brain morphology was weak and the temporal sequence (cannabis use prior to development of schizophrenia) could not be determined (Malchow et al., 2013), while another study found that after controlling for confounding factors (i.e. alcohol abuse and gender) there was no significant change in brain morphology between the study and control groups (Depue et al., 2015). This hypothesis, therefore, is yet to be confirmed.

Another theory which might explain the link between cannabis and schizophrenia is slightly different than those previously indicated; it is possible that patients who are in the first stages of schizophrenia (but are unaware of it) are more susceptible to cannabis use as a form of "self-medication", meaning that it is schizophrenia which leads to higher cannabis use in

adolescence rather than the other way around. One cohort study which seems to support this theory demonstrated that individuals who were at high genetic risk for schizophrenia were more prone to early cannabis abuse, but not to other substances like smoking and alcohol (Hiemstra et al., 2018). Yet, other studies refute this hypothesis by presenting an age dependent relationship between the onset of cannabis use and the onset of schizophrenia; smoking cannabis at an earlier age seemed to expedite the commencement of psychotic symptoms (Large et al., 2011; Ron et al., 2011; Dragt et al., 2012). These findings would suggest a unidirectional relationship between cannabis and schizophrenia, however they cannot rule out the “self-medication” theory entirely.

While many theories exist, which appear to be contradictory on the pathophysiology of the association between cannabis and psychotic disorders, one finding that is generally agreed is that there is a dose dependent relationship between these two factors. A 35-year cohort study found that chronic and heavy cannabis use increased the risk of schizophrenia by a significant margin (Manrique-Garcia et al., 2012) and several review articles have backed this claim (Radhakrishnan, Wilkinson and D’Souza, 2014; Khan et al., 2015; Marconi et al., 2016). A dose dependent relationship would also contribute to the notion that cannabis use is a causal and preventable risk factor for the development of schizophrenia and give merit to the idea of limiting access to it, especially for adolescents, as a measure of prevention.

Discussion

“Patient X” was diagnosed with schizophrenia at the age of 23 because his symptoms, that included delusions of persecution, auditory hallucinations and social withdrawal, were compatible with how medicine defines schizophrenia today. However, the truth is that schizophrenia is very poorly understood and unclearly defined. While it is considered a mental illness, it has many physical symptoms: such as increased mortality rates at younger ages (Os and Kapur, 2009) and reduced grey matter volumes (as seen in neuroimaging) (Khan et al., 2015). Furthermore, while is it is generally accepted that abnormal dopamine synthesis is associated with the disease (Khan et al., 2015), it is unknown how exactly this may cause the symptoms associated with schizophrenia. Some people have psychotic episodes and heal completely, while others do not. (Os and Kapur, 2009). Bearing that in mind, it is very difficult for research to move forward and identify risk factors for the disease when there is still considerable uncertainty regarding the definition of the disease itself. Research attempting to understand the underlying pathophysiology of schizophrenia is sparse, and accordingly it may be advisable for future research to focus on this goal specifically.

Cannabis use and its link to the development of schizophrenia have been studied extensively. Some studies suggest that in patients who are genetically susceptible to schizophrenia, cannabis use may act as a trigger for the onset of the disease. Susceptibility is often determined through family history of mental illness, specifically of psychotic diseases. “Patient X” has no family history of psychosis he could mention. He did mention he had an aunt who suffered from depression, but he was unable to clarify whether she had self-diagnosed herself or if she had been diagnosed by a professional, and I therefore chose to disregard this detail. Regardless, based on family history alone it is unlikely that Patient X was susceptible to schizophrenia and that it was his use of cannabis that had instigated the illness. Nonetheless, genetic mutation may occur randomly and therefore it is difficult to determine whether this is true for “Patient X”.

“Patient X” however firmly believes that his chronic cannabis use is the direct cause for the development of his illness. Research suggests that his belief may have some merit. The available literature seems to support the theory that a dose dependent relationship exists between the level of cannabis use and the development of psychosis disorders (Manrique-Garcia et al., 2012; Radhakrishnan, Wilkinson and D’Souza, 2014; Khan et al., 2015; Marconi et al., 2016). This means that heavier, more frequent use of cannabis is often associated with earlier progression and deteriorating prognosis. “Patient X” admits to almost daily marijuana use over a period of at least 9 years, and this could - according to available data - be linked to his condition. However, it is important to mention that available research often did not address certain confounders. For example: Manrique-Garcia et al (2012) used military conscripts for their study population, but the military is a framework which is associated with periods of severe stress which could in and of themselves directly affect the risk of schizophrenia. Accordingly, while it is possible that “Patient X”’s heavy cannabis use is associated with the disease, it is important to take this association at no more than face value.

The age of cannabis use may also play a significant role in its association to psychosis. “Patient X” begun smoking marijuana at 14 years of age, meaning he was undergoing puberty. Research suggests that adolescence is a period in a person’s life that is associated with many neurological changes (Malone, Hill and Rubino, 2010), and that the process of these changes could have been disrupted or altered due to cannabis use, resulting in brain volume irregularities. This type of brain alteration could only be viewed through neuroimaging, which unfortunately has never been performed on “Patient X”. If, hypothetically, his neuroimaging was to show changes related to schizophrenia - such as the thinning of grey matter - then that would not in itself be sufficient to prove or disprove this theory; firstly, because other studies have shown the relationship between cannabis use and brain volume alterations to be weak to non-existent, and secondly, because “Patient X” has already gone through puberty and has schizophrenia and so it would be impossible to discern whether these changes resulted from the cannabis use in adolescence or from the disease itself. Therefore, while this theory is potentially persuasive, there is unfortunately a paucity of evidence required to support it, and in any event not in “Patient X's” case specifically.

A few studies suggest that cannabis using teens, who are either in high risk for developing schizophrenia or in the early phases of the disease, use cannabis specifically as a form of self-medicating. “Patient X” contested this theory and argued that the primary cause for his drug use was peer pressure, and that he only smoked the drug in order to be “a part of the gang”. While he did find the effects of smoking cannabis enjoyable, he did not feel he that he needed to smoke. While there is some evidence to support “Patient X”’s conclusion, there are others who dispute it. It is generally unclear whether cannabis use is the cause of schizophrenia or vice versa, and it is impossible to reach a conclusion today based on “Patient X”’s history alone. “Patient X”’s cannabis abuse seems to have occurred prior to his condition manifesting itself, but it is very possible that he was in the early stages of the disease and was as yet unaware of the fact.

Conclusion

Schizophrenia is a multifactorial disease that is still largely mis-understood. It is defined today as a specific combination of symptoms: positive symptoms, negative symptoms and cognitive symptoms, which may vary from case to case. While there have been many studies performed

to try and deduce risk factors and identify susceptible individuals, there do not seem to be any conclusive answers on the topic. By reviewing the relevant literature, both current and historical, this report has attempted to overview the link between cannabis use and schizophrenia and to identify a mechanism by which this association may exist. While various mechanisms were suggested, studies often contradicted each other. This report related this information to “Patient X” and attempted to understand whether there is a credible connection between his heavy cannabis use and his schizophrenic condition. While studies do seem to suggest an association between cannabis use and the development of schizophrenia, there is clearly insufficient information available today to establish it as a fact. More research is obviously required on this topic if definitive conclusions are to be reached.