CANNABIS AND PSYCHOSIS REVISITED

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SUMMARY

The association between cannabinoids and psychosis has been known for almost a thousand years, but it is still speculated whether cannabis use may be a contributory cause of psychosis, that is, whether it may precipitate schizophrenia in those at risk. In this paper, we will briefly present the data from individual longitudinal studies in the field, together with the factors that are considered important for the association of cannabis abuse and occurrence of schizophrenia and prevention opportunities in the target population.

The reviewed studies clearly suggest that cannabis abuse predicts an increased risk for schizophrenia, particularly in young adults. They underline both the need to create adequate prevention measures and consequently avoid the occurrence of the disease in the young at risk. Particular attention should be additionally devoted toward encouraging the young presenting with psychotic symptoms to stop or, at the very least, reduce the frequency of cannabis abuse. The issues are undoubtedly to be addressed by the health care system in general.

Key words: schizophrenia – cannabis – psychosis

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INTRODUCTION

The association between cannabinoids and psychosis has been known for almost a thousand years. However, it is still speculated whether cannabis use may precipitate psychosis in those at risk. Given that substance abuse is frequent among patients with schizophrenia, and that recent studies indicate that the abuse could pose a contributory factor to the occurrence of the disease (Fergusson et al. 2003), the summary of the recent findings on the linkage between psychosis and cannabis is rightfully considered to be a "hot topic". An increasing rate of cannabis abuse among the young, particularly in developed countries (Hall & Degenhardt 2008), underlines the importance of the issue, importantly in the aspect of prevention. In this paper, we will briefly present the data from the individual longitudinal studies in the field, together with the factors that are considered important for the association of cannabis use and occurrence of schizophrenia. We will also present prevention opportunities in the target population.

LONGITUDINAL STUDIES - CONTEMPORARY RESEARCH FRAMEWORK

A large number of studies deal with the link between psychosis and cannabis abuse. One of the strongest evidence for that was given by the Swedish cohort study, which included a significant number of participants (50,465), over a 15 years period (Andreason et al. 1987). The study pointed out that people who abuse cannabis by the age of 18 are at a 2.4 times greater risk for developing psychosis later in life. This was confirmed by the results from the region of the Southern Balkans, which, in addition to this, spoke in favour of the substance abuse being more frequent among adolescents in urban than in rural areas (Licanin et al. 2002, Loga et al. 2010). A longitudinal study of van Os et al. (2002) reported that the cannabis use predicted an elevated risk of developing psychotic symptoms in previously healthy individuals, over a short term follow-up period. Moreover, the risk has appeared to be even greater in those who have reported a higher frequency of the cannabis abuse. This has indicated the dose-dependent relationship of cannabis and psychotic symptoms, even when controlled for the confounding factors (drug use, psychopathology). Cannabis has proven to lead not only to development of the psychotic symptoms in healthy individuals, but also predict schizophrenia in those at risk for psychotic symptoms.

The general population birth cohort study from New Zealand examined the relationship of cannabis and the presence of psychotic symptoms in early adulthood, controlling the potential reverse causation for several confounding factors, including previous psychotic symptoms (Fergusson et al. 2003). As it was previously argued that the pre-existing psychotic symptoms could lead to the cannabis dependence, controlling such factors elucidated the temporal linkage of cannabis and psychotic symptoms. The study clarified the association of the cannabis dependence disorder and the later onset of psychotic symptoms, with the risk of the psychotic symptoms being even more increased at earlier age.
Despite the higher risk for developing psychotic symptoms at earlier age, after controlling for a number of confounding factors (anxiety disorder, behavioural problems, childhood abuse, academic achievement, previous psychotic symptoms) it has been revealed that the association continued to be strong and significant, in late adolescence. The same has been further supported by the recent meta-analysis of Moore et al. (2007), which confirmed increased, frequency-dependent risk of developing psychosis in those who used cannabis.

According to Arseneault et al. (2004), the cannabis use is not enough for the occurrence of the psychotic symptoms, but it might be an important element in the environmental interaction with an already vulnerable brain. The damaging effects of cannabis are not expressed in all individuals who used it, but those who do experience them are of particular importance at both clinical and population level.

**PLAUSIBLE ETHIOPATHOLOGICAL LINK**

Establishing disease causality in the research and clinical practice is not an easy task, particularly in the mental health field. Factors relevant to ascertain this link include temporality, strength and direction of the relationship, reliability, specificity, consistency, experimental support, and biological plausibility (Sewell et al. 2010). Some authors consider the temporal association to be one of the most important factors, and the evidence from the experimental studies favours this view.

The previously presented longitudinal studies sustain the idea of the chronological precedence of the cannabis use in adolescence compared to schizophrenia in later life. It was revealed that this association remains even after controlling for many of the factors thought to predict or contribute to development of schizophrenia. They included not only the biological (low IQ, gender, age, previous psychotic symptoms), but also the socio-cultural (place of upbringing, cigarette smoking, ethnic group, level of education, unemployment, single marital status) and the behavioural markers (disturbed behaviour, poor social integration) of the susceptibility to psychosis (Arseneault et al. 2004). However, it has been noted in clinical practice that the cannabis consumption may precede, but also co-occur or follow the onset of schizophrenia.

For more than 20 years, the studies have been dealing with cannabis preceding the onset of the psychotic symptoms. Allebeck et al. (1993) found that cannabis abuse had preceded the onset of the psychotic symptoms, by at least one year in almost 70% of patients with schizophrenia, while other authors report even higher rates (Linszen et al. 1994). Not only that cannabis has been linked to the onset of psychosis, but it has also been linked to the earlier age of onset and a more abrupt onset of the psychotic symptoms in schizophrenic patients (Linszen et al. 1994, Hambrecht et al. 1996). A more recent study of Donoghue et al. (2014) that has examined the interaction effect of gender and cannabis use on age of onset of schizophrenia has found that cannabis use is in connection with earlier age of onset of schizophrenia, as well as that the gender difference in age of onset is reduced among cannabis users. The additional verification of the causality of this relationship is offered by the presence of a dose-dependent relationship between the cannabis use and schizophrenia (Zammit et al. 2002, Fergusson et al. 2003), and idiosyncrasy of the outcome (Arseneault et al. 2002). It is argued whether the risk for schizophrenia predisposes to cannabis use, making the link between them just an alongside phenomenon of a joint susceptibility for both psychosis and cannabis. Although this might be the case, the majority of the longitudinal studies, as we have mentioned it before, have controlled this reverse causality confirming the temporal link of cannabis and psychosis (Macleod et al. 2007, Collip et al. 2008, Moore et al. 2007).

The biological plausibility of the link between cannabis and schizophrenia could be anticipated in the effects of cannabinoids on the neurotransmitter pathways and the neurodevelopmental trajectories known to be involved in the onset of schizophrenia and the schizophreniform disorders. To support the fact, we offer the results of three recent studies as an explanation. Elevated levels of anandamide, an endogenous cannabinoid agonist, have been found in the cerebrospinal fluid of patients with schizophrenia (Leweke et al. 1999). In addition, an interaction has been noticed between the cannabis use and the catechol-O-methyltransferase (COMT) polymorphism, a methylation enzyme important for the metabolism of dopamine (Mannisto & Kaakkol 2006, Caspi et al. 2005). This was further confirmed by both retrospective (Hall & Degenhardt 2004) and prospective studies on the exacerbation of symptoms during the regular cannabis use (Degenhardt et al. 2007, Hides et al. 2006).

The findings suggest that some individuals are simply more predisposed to the damaging qualities of cannabis. This was further enlightened by the data regarding the general population, confirming that the propensity to psychosis and the psychosis-like symptoms correlated to the frequency of the cannabis abuse (Verdoux et al. 2003). Apart from the data on the general population, the similar was confirmed on those with schizophrenia, where the cannabis use lead to more severe psychotic symptoms and a less favourable course, regardless of the staging of the disorder (Negrete 1989, Linszen et al.1994, Linszen et al. 2012). One of the problems in establishing the clear link between cannabis and schizophrenia might be the fact that negative and cognitive symptoms of schizophrenia are poorly addressed by both research and treatment. Cannabis can cause short-term disturbances in memory, attention, and executive functions. The research has found microstructural alterations in the white matter of the developing brain, associated with long-term cannabis use (impaired axonal connectivity in fornix, splenium of the corpus callosum and commissu-
underlying the cannabis related onset of psychosis and to clarify the biological pathways individual susceptibility to the cannabinoid-related factors that trigger the onset of the psychotic symptoms. Further studies of this factor is neither essential nor sufficient to lead to schizophrenia or other psychiatric outcomes. This suggests a longitudinal temporal relationship between cannabis and schizophrenia, rather than the poor pre-morbid functioning (Patton et al. 2002). Altogether, the association between frequency of the cannabis use and schizophrenia adheres some, but not all, of the usual reference points for causality. However, not all individuals using cannabis develop schizophrenia, nor all those who present with symptoms of schizophrenia have a history of cannabis use. Therefore, it is probable that the cannabis use is a tributary cause interacting with other factors and consequently leading to schizophrenia or other psychiatric disorders. However, it is crucial to underline that this factor is neither essential nor sufficient to lead to the onset of the psychotic symptoms. Further studies are necessary to elucidate the factors that trigger individual susceptibility to the cannabinoid-related psychosis and to clarify the biological pathways underlying the cannabis related onset of psychosis (Sewell et al. 2010).

CONCLUSION

The reviewed studies clearly suggest that cannabis abuse predicts an increased risk for schizophrenia, particularly in young adults. In addition, they underline the need to look at the problem taking into account two perspectives. On one hand, there is a need to create adequate measures to prevent the onset disease in the young at risk. Secondly, if the disorder is already present, how are we to prevent those who bear it to relapse? The issues are undoubtedly to be addressed by the health care system in general, using the basic concept of prevention – education, targeting the young and underlying possible consequences of the cannabis abuse (addiction, academic decline, social isolation, depression, and psychosis). The cannabis abuse can precipitate the positive symptoms of schizophrenia, relapse, need for in-patient treatment, and finally unfavourable outcome of the disease. Those who have already developed psychosis are not to be ignored in psycho-education, by any of the involved in caregiving. Particular attention is to be devoted to encouraging the young presenting with psychotic symptoms to discontinue or, at the very least, reduce the frequency of the cannabis (ab)use.

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References

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