Psychiatria Danubina, 2015; Vol. 27, No. 1, pp 97-100 *View point article*

CANNABIS AND PSYCHOSIS REVISITED

Aleksandar Damjanović[1,2], Maja Pantović[2], Aleksandra Damjanović[3], Bojana Dunjić-Kostić[2], Maja Ivković[1,2], Srđan Milovanović[1,2], Maja Lacković[1,2] & Ivan Dimitrijević[1,2]

[1]School of Medicine, University of Belgrade, Belgrade, Serbia
[2]Clinic for Psychiatry, Clinical Centre of Serbia, Belgrade, Serbia
[3]Pharma Swiss, Belgrade, Serbia

received: 18.8.2014; revised: 17.11.2014; accepted: 16.12.2014

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*

* * * * *

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 (Andreasson 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 sociocultural (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-methyl transferase (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 predilected 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 researh 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-

ral fibres) (Zalesky et al. 2012). Not only that the structural brain abnormalities have been reported in canabis use, but their clinical manifestation in terms of cognitive decline, has also been observed, across almost all domains of cognitive functioning. The impairment has been associated with earlier onset and higher frequency of the use. This is particularly interesting bearing in mind that onset of cannabis use (adolescence and early adulthood), is a period when cannabinoid receptors are still abundant in white matter pathways across the brain. As the cessation of cannabis has not lead to complete recovery of neuropsychological functioning it is reasonable to consider the neurotoxic effects of cannabis on the adolescent brain (Meier et al. 2012). The results indicate that delaying the age at which regular use begins may be beneficial in preventing deeper microstructural alterations in both healthy and those with mental disorders (Zalesky et al. 2012). Nonetheless, it is still, to a certain extent, ambiguous whether exposure to cannabinoids is related to long-term deficits in cognitive functioning (Solowij & Pesa 2012, Solowij et al. 2012).

It could be hypothesized that cannabis is often only an 'entrance' through the door of addiction and heavier drug abuse (Kazuo & Kandel 1984), as well as that it is often abused together with other psychomimetic substances (amphetamines, phenylcyclidine and lysergic aciddiethylamide) (Murray et al. 2003). It is also likely that the individuals who use cannabis at an early age prolong with substance abuse in an early adulthood and later life, which could also be a tributary cause of transient psychotic symptoms (Hall & Degenhardt 2004, Verdoux 2004). Another possibility is that cannabis use is just a marker of poor social and behavioural adjustments at early age, known to predict major psychiatric illnesses, among them schizophrenia (Cannon et al. 2002).

Contrary to this, Arseneault et al. (2002) confirmed cannabis use to be particularly related to the schizophrenia 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 psychotic 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.

Acknowledgements: None.

Conflict of interest: None to declare.

References

1. *Allebeck P, Adamsson C, Engstrom A & Rydberg U: Cannabis and schizophrenia: a longitudinal study of cases treated in Stockholm County. Acta Psychiatrica Scand 1993; 88:21-4.*
2. *Andreasson S, Engstrom A, Allebeck P & Rydberg U: Cannabis and schizophrenia: a longitudinal study of Swedish conscripts. Lancet 1987; 2:1483-6.*
3. *Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE: Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ 2002; 32:1212-3.*
4. *Arseneault L, Cannon M, Witton J & Murray R: Causal association between cannabis and psychosis: examination of the evidence. BrJ Psychiatry 2004; 184:110-7.*
5. *Cannon M, Caspi A, Moffitt TE, Harrington H, Taylor A, Murray RM et al.: Evidence for early, specific, pandevelopmental impairment in schizophreniform disorder: results froma longitudinal birth cohort. Arch Gen Psychiatry 2002; 59:449-57.*
6. *Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H et al.: Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. Biol Psychiatry 2005; 57:1117-27.*
7. *Collip D, Myin-Germeys I & Van Os J: Does the concept of "sensitization" provide a plausible mechanism for the*

putative link between the environment and schizophrenia? Schizophr Bull 2008; 34:220-5.

8. *Degenhardt L, Tennant C, Gilmour S, Schofield D, Nash L, Hall W et al.: The temporal dynamics of relationships between cannabis, psychosis and depression among young adults with psychotic disorders: findings from a 10-month prospective study. Psychol Med 2007; 37:927-34.*
9. *Donoghue K, Doody GA, Murray RM, Jones PB, Morgan C, Dazzan P et al: Cannabis use, gender and age of onset of schizophrenia: data from the ÆSOP study. Psychiatry Res 2014; 215:528-32.*
10. *Fergusson DM, Horwood L J & Swain-Campbell N R. Cannabis dependence and psychotic symptoms in young people. Psychol Med 2003; 33:15-21.*
11. *Hall WD & Degenhardt L: Is there a specific 'cannabis psychosis'? In Castle DJ & Murray RM (eds): Marijuana and madness, 89-100. Cambridge: Cambridge University Press, 2004.*
12. *Hall WD & Degenhardt L: Cannabis use and the risk of developing a psychotic disorder. World Psychiatry 2008; 7:68-71.*
13. *Hambrecht M & Hafner H: Substance abuse and the onset of schizophrenia. Biol Psychiatry 1996; 40:1155-63.*
14. *Hides L, Dawe S, Kavanagh DJ & Young RM: Psychotic symptom and cannabis relapse in recent-onset psychosis. Prospective study. Br J Psychiatry 2006; 189:137-43.*
15. *Kazuo Y & Kandel DB: Patterns of drug use from adolescence to young adulthood: II. sequences of progression. Am J Public Health 1984; 74:668-72.*
16. *Leweke FM, Giuffrida A, Wurster U, Emrich HM & Piomelli D: Elevated endogenous cannabinoids in schizophrenia. Neuroreport 1999; 10:1665-9.*
17. *Ličanin I, Loga S, Cerić I, Masic I, Mataija R, Suljic E et al.: Zloupotreba psihoaktivnih supstanci kod adolescenata u ruralnoj i urbanoj sredini. Med Arh 2002; 56:285-8.*
18. *Linszen DH, Dingemans PM & Lenior ME: Cannabis abuse and the course of recent-onset schizophrenic disorders. Arch Gen Psychiatry 1994; 51:273-9.*
19. *Linszen D &van Amelsvoort T: Cannabis abuse and the courseof schizophrenia. In Castle DJ, Murray RM & D'Souza CD (eds): Marijuana and Madness, 2nd edition, 210-7. Cambridge: Cambridge University Press, 2012.*
20. *Loga S, Loga-Zec S & Spremo M: Cannabis and psychiatric disorders. Psychiatr Danub 2010; 22:296–7.*
21. *Macleod J: Cannabis use and symptom experience amongst people with mental illness: a commentary on Degenhardt et al. Psychol Med 2007; 37:913-6.*
22. *Mannisto P & Kaakkola S: Catechol-O-methyltransferase (COMT): Biochemistry, molecular biology, pharmacology, and clinical efficacy of the new selective COMT inhibitors Pharmacological Reviews 2006; 5:593-628.*
23. *Meier MH, Caspi A, Ambler A, Harrington H, Houts R, Keefe RS et al: Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc Natl Acad Sci USA 2012; 109:E2657-64.*
24. *Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M & Lewis G: Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet 2007; 370:319-28.*
25. *Murray R, Grech A, Phillips P & Johnson S: What is the relationship between substance abuse and schizophrenia? In Murray R, Jones P, Susser E, van Os J, Cannon M (eds): The Epidemiology of Schizophrenia, 317-42. Cambridge: Cambridge University Press, 2003.*
26. *Negrete JC: Cannabis and schizophrenia. Br J Addiction 1989; 84:349-51.*
27. *Patton GC, Coffey C, Carlin JB, Degenhardt L, Lynskey M & Hall W: Cannabis use andmental health in young people: cohort study. BMJ 2002; 325:1195-8.*
28. *Sewell AR, Skosnik PD, Garcia-Sosa I, Ranganathan M & D'Souza DC: Behavioral, cognitive and psychophysiological effects of cannabinoids: relevance to psychosis and schizophrenia. Rev Bras Psiquiatr 2010; 32:S15-S30.*
29. *Solowij N & Pesa N: Cannabis and cognition: short- and longterm effects. In Castle DJ, Murray RM & D'Souza CD (eds): Marijuana and Madness, 2nd edition, 91-102. Cambridge: Cambridge University Press, 2012.*
30. *Solowij N, Yucel M, Lorenzetti V &Lubman D: Does cannabis cause lasting brain damage? In Castle DJ, Murray RM & D'Souza CD (eds): Marijuana and Madness, 2nd edition, 103-13. Cambridge: Cambridge University Press, 2012.*
31. *van Os J, Bak M, Hanssen M, Bijl RV, de Graaf R & Verdoux H: Cannabis use and psychosis: a longitudinal population-based study. Am J Epidemiol 2002; 156:319-27.*
32. *Verdoux H: Cannabis and psychosis proneness. In Castle DJ & Murray RM (eds): Marijuana and madness, 89-100. Cambridge: Cambridge University Press, 2004.*
33. *Verdoux H, Gindre C, Sorbara F, Tournier M & Swendsen J: Cannabis use and the expression of psychosis vulnerability in daily life. Psychol Med 2003; 33:23-32.*
34. *Zammit S, Allebeck P, Andreasson S, Lundberg I & Lewis G: Self-reported cannabis use as a risk factor for schizophrenia: further analysis of the 1969 Swedish conscript cohort. BMJ 2002; 325:1199-201.*
35. *Zalesky A, Solowij N, Yücel M, Lubman DI, Takagi M, Harding IH et al: Effect of long-term cannabis use on axonal fibre connectivity. Brain 2012; 135(Pt 7):2245-55.*

Correspondence:

Professor Ivan Dimitrijević, MD, PhD, Neuropsychiatrist
Clinic for Psychiatry, Clinical Center of Serbia, University of Belgrade
Pasterova 2, 11000 Belgrade, Serbia
E-mail: dr.ivan54@yahoo.com