Práticas e Cuidado: Revista de Saúde Coletiva
ISSN: 2675-7591

LITERATURE REVIEW

THE EFFECTS OF EARLY CANNABIS USE AND THE RISK OF SCHIZOPHRENIA: A NARRATIVE REVIEW

LOS EFECTOS DEL CONSUMO TREMPRANO DE CANNABIS Y EL RIESGO DE ESQUIZOFRENIA: UMA REVISIÓN NARRATIVA

OS EFEITOS DO USO PRECOCE DE *CANNABIS* E O RISCO DE ESQUIZOFRENIA: UMA REVISÃO NARRATIVA

Mariana Silva dos Santos [1]
Fernanda de Moura Soares [2]
Aline Santos Monte [3]

Manuscript received on: July 4, 2022.
Approved on: June 26, 2023.
Published: December 14, 2023.

Abstract
Objective: This article seeks to synthesize the scientific productions on the association between the harmful use of cannabis during adolescence and the risk of schizophrenia. **Methods**: This is a narrative review by searching the Scielo, Pepsic, PNAS and Pubmed databases. Original, review and gray literature articles in English, Spanish and Portuguese were included in the study. The selection of articles, national and international official documents covered the period from 2012 to 2022, excluding articles that did not fit the theme. **Results**: The main evidences support a neurobiological correlation between the problematic use of marijuana and the development of schizophrenia in individuals with genetic predisposition, indicating that there is an influence of genetic and environmental factors, since the chronic use of marijuana can precipitate the emergence of Schizophrenia in genetically vulnerable individuals. **Final considerations**: Although the evidence does not consider a causal relationship between the chronic use of cannabis and the onset of schizophrenia, it is now known that cannabis is a risk factor in this process.

Keywords: Marijuana; Schizophrenia; Genetic predisposition to disease.

Resumen
Objetivo: Este artículo busca sintetizar las producciones científicas sobre la associación entre el uso nocivo de cannabis durante la adolescência y el riesgo de esquizofrenia. **Métodos:** Se trata de una revisión narrativa mediante búsqueda en las bases de datos Scielo, Pepsic, PNAS y Pubmed. Se incluyeron en el estudio artículos originales, de

[1] Specializing in Comprehensive Care for Alcohol and Other Drugs at the School of Public Health of Ceará. Graduated in Psychology from Uninassau. Psychologist at the Municipal Health Department of Caucaia.
ORCID: https://orcid.org/0000-0002-0229-3009 Email: marianast61@hotmail.com
[2] Master in Adult and Child Health from the Federal University of Maranhão. Professor at Christus University Center.
ORCID: https://orcid.org/0000-0002-2837-7489 Email: profa.fernandasoares@gmail.com
[3] Doctorate in Pharmacology from the Federal University of Ceará. Professor at the University of International Integration of Afro-Brazilian Lusofonia.
ORCID: https://orcid.org/0000-0002-2107-1196 Email: alinesmonte@yahoo.com.br

revisión y de literatura gris en inglés, español y portugués. La selección de artículos, documentos oficiales nacionales e internacionales abarcó el período de 2012 a 2022, excluyendo artículos que no encajaban en la temática. **Resultados**: Las principales evidencias sustentan una correlación neurobiológica entre el uso problemático de marihuana y el desarrollo de esquizofrenia en individuos con predisposición genética, indicando que existe una influencia de factores genéticos y ambientales, ya que el uso crónico de marihuana puede precipitar la aparición de esquizofrenia. en individuos genéticamente vulnerables. **Consideraciones finales**: Aunque la evidencia no considera una relación causal entre el uso crónico de cannabis y la aparición de esquizofrenia, ahora se sabe que el cannabis es un factor de riesgo en este proceso.

Palabras claves: Marihuana; Esquizofrenia; Predisposición genética a la enfermidad.

Resumo
Objetivo: O presente artigo busca sintetizar as produções científicas sobre a associação do uso nocivo de cannabis durante a adolescência e o risco de esquizofrenia. **Métodos:** Trata-se de uma revisão narrativa através de busca nas bases de dados Scielo, Pepsic, PNAS e Pubmed. Foram incluídos no estudo artigos originais, de revisão e literatura cinzenta nos idiomas inglês, espanhol e português. Na seleção da amostra optou-se por incluir documentos oficiais nacionais e internacionais, no período de 2012 a 2022, sendo excluídos aqueles que não se encaixavam ao tema. **Resultados:** As principais evidências corroboram para uma correlação neurobiológica entre o uso problemático da maconha e o desenvolvimento de esquizofrenia em indivíduos com predisposição genética, indicando que há influência de fatores genéticos e ambientais, pois o uso crônico da *cannabis* pode precipitar o surgimento de Esquizofrenia em indivíduos vulneráveis geneticamente. **Considerações finais:** Embora que as evidências não considerem uma relação causal entre o uso crônico de *cannabis* e o surgimento de esquizofrenia, hoje sabe-se que *Cannabis* é um fator de risco neste processo.

Palavras-chave: *Cannabis*; Esquizofrenia; Predisposição genética para doença.

INTRODUCTION

Schizophrenia It is a severe mental disorder that affects almost all aspects of mental activity, including distortions of thought, perception, emotions, language, sense of identity, and behavior. The symptoms are associated with varying degrees of persistent social and functional impairments, which cause an extreme distortion of reality[1].

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), in its 5th edition, the lifetime prevalence of schizophrenia ranges from 0.3% to 0.7%. It typically manifests towards the end of adolescence and the beginning of adulthood. The diagnosis requires two or more characteristic symptoms, such as delusions, hallucinations, disorganized speech and/or behavior, negative symptoms

persisting for a period of six months, and prodromal signs of the illness with evident social, occupational, or self-care impairments for six months, including one month of active symptoms[2].

Among the risk factors involved in the development of schizophrenia, genetic factors, environmental influences, and chronic use of psychoactive substances are considered. Individuals with schizophrenia tend to have an increased propensity for drug use. Chronic use of cannabis, among other substances, can be both a triggering factor and a consequence of mental disorders[3,4].

According to the data from the United Nations World Drug Report on non-medical use of cannabis, approximately 209 million people worldwide had a pattern of continuous *cannabis* use, aged between 15 to 64 years. In comparison to adults, the prevalence of *cannabis* use was higher among adolescents. The report emphasizes scientific evidence indicating that early cannabis initiation affects the brain development of young individuals, increases the likelihood of progressing to regular use, and when used frequently, is also associated with an increased probability of depressive disorders, as well as suicidal thoughts and behaviors[5].

In this regard, the literature investigates the association between problematic *cannabis* use and the risk of mental disorders. Chronic cannabis users with a family history of schizophrenia are more susceptible to developing the disorder under certain circumstances. However, it is still unclear whether genetically non-predisposed individuals, who have a pattern of chronic substance use, are directly vulnerable to the disorder and why certain risk factors may precipitate the illness. Therefore, this article aims to synthesize the scientific research on the association between harmful cannabis use during adolescence and the risk of schizophrenia.

METHOD

In order to fulfill the proposed objective, a narrative review was conducted. Narrative review articles are publications intended to describe and discuss the state of the art on a particular subject, essential for contributing to the debate on specific topics, raising questions, and contributing to the updating of knowledge[6]. The

searches were based on the research question: what are the harmful effects of early marijuana use and the risks for schizophrenia?

The process of search and bibliographic selection was conducted in the following databases: Scielo (Scientific Electronic Library Online); Pepsic (Periódicos Eletrônicos em Psicologia); PNAS (National Academy of Sciences) e Pubmed (National Library of Medicine). The following descriptors were used for the sample selection: "marijuana," "early use," "schizophrenia," and "genetic predisposition".

The searches were conducted by one of the authors, without limitations on the study's country or area of knowledge. The study included original articles, review articles, and gray literature in English, Spanish, and Portuguese. The selection of articles and official national and international documents covered the period from 2012 to 2022, with articles not related to the theme being excluded.

RESULTS AND DISCUSSION

After collecting the material and conducting its reading, fourteen bibliographies related to the proposed theme were selected. For data analysis, the main points were extracted, and the topic was divided into three categories: "*Cannabis* use and psychotic symptoms," "Effects of *cannabis* in adolescence," and "*Cannabis* consumption in adolescence and its relationship with schizophrenia".

- The use of cannabis and psychotic symptoms

Regarding the abuse of psychoactive substances such as *cannabis*, there have been long-standing descriptions of acute psychotic disorders associated with drug intoxication. Meta-analysis studies attempt to explain the relationship between the brain and the endocannabinoid system, as well as the risks of heavy *cannabis* use and the occurrence of psychotic symptoms. What is known is that its use can precipitate symptoms of schizophrenia in individuals who have a genetic vulnerability[7,8].

The consumption of these compounds, through *cannabis*, establishes an intimate relationship with the development of psychotic symptoms. Such an association depends on specific factors such as age, duration of exposure, early use, especially during adolescence or even childhood, as well as genetic and environmental factors associated with other factors that are still unknown. Although cannabis use is not a direct causal factor for the development of psychosis, and its consumption does not necessarily always lead to this condition, the possibility of persistent psychotic symptoms appearing in vulnerable patients requires more careful monitoring of these individuals[9].

Consequently, several studies support the relationship between problematic *cannabis* use and the development of mental disorders. As an explanation, it has been analyzed that tetrahydrocannabinol (THC) is responsible for causing dopaminergic dysfunction by increasing the capacity for dopamine synthesis and release. In this regard, patients with psychotic conditions showed an increase in this capacity. As a consequence, substances that increase dopamine release are capable of inducing or exacerbating psychotic symptoms[10].

- The effects of cannabis in adolescence

The evidence indicates that chronic *cannabis* use in adolescence is associated with more severe and persistent negative outcomes compared to use in adulthood. The risk of dependence is 16% in those who initiated *cannabis* use during adolescence and 33% to 50% in daily cannabis users. The symptoms vary and include agitation, euphoria, changes in perception (illusions, feelings of depersonalization, altered perception of time passage, hyperesthesia), anxiety, hallucinations, paranoid ideation, as well as feelings of well-being, relaxation, impaired judgment, compromised short-term memory, attention, motor skills, and reaction time. Intense consumption (or consumption levels higher than usual for the individual) can lead to confusion states or psychotic symptoms. However, there is still no consensus regarding the adverse effects of cannabis consumption[11].

The current hypothesis that the endocannabinoid system is involved in the regulation and release of neurotransmitters suggests that the use of cannabinoids during adolescence may compromise brain development. The earlier the use begins, the greater the adverse effects, exerting a more intense impact on the organism and increasing the likelihood of future psychiatric pathologies. THC is the active ingredient responsible for causing dopaminergic dysfunction and increasing the capacity for dopamine synthesis and release. In this regard, studies have shown that individuals with psychotic conditions exhibited an increase in this capacity; therefore, substances that increase dopamine release are capable of inducing or exacerbating psychotic symptoms[10,12].

The brain is more vulnerable to the effects of cannabis during adolescence than in adulthood. Early onset of use appears to interrupt the cycle of brain development. Around the age of 16, the endocannabinoid system reaches its highest point of density of CB1 neurological receptors, which may lead to a decrease in these receptors, resulting in permanent neuropsychological and neurocognitive deficits. Adolescents who use cannabis heavily show cognitive deficits, including impaired attention, learning, and memory, as well as an inability to change their minds or respond differently. These deficits are similar to those observed in adults, but they are more likely to persist in adolescents and may only recover after long periods of abstinence[13].

A population-based study with 1,574 participants, in which cortical thickness was measured using Magnetic Resonance Imaging, found an association between cannabis use in early adolescence and a reduction in cortical thickness in male participants with a high polygenic risk score. Adults who used *cannabis* since adolescence showed a reduction in neuronal connectivity in prefrontal areas responsible for executive function and inhibitory control, as well as in subcortical networks responsible for habits and routines. The precuneus, a region involved in the integration of various brain functions such as consciousness and alertness, is particularly affected in frequent cannabis users. Long-term cannabis use critically affects the developing brain's white matter, with evidence of damage to axonal connectivity in three fiber tracts: the hippocampus (right fimbria), splenium of the

corpus callosum, and commissural fibers (which connect the two hemispheres of the brain). The damage was more significant with the onset of *cannabis* use at a younger age[14].

The fimbria is a part of the hippocampus involved in memory and learning. These results are consistent with the observation that memory impairment is a common complaint among cannabis users seeking treatment. There have been reports of recovery of hippocampal connectivity after prolonged abstinence. Atypical patterns of orbitofrontal functional connectivity were observed in attention/executive, motor, and reward networks in adolescents who heavily used cannabis. These abnormalities reflect unsatisfactory decision-making capacity and increased impulsivity[15].

- Cannabis use in adolescence and its relationship with schizophrenia

Cannabis use is more common among individuals with schizophrenia. The *cannabis* plant that contains a higher concentration of THC and a lower concentration of cannabidiol may increase the risk of schizophrenia and reduce the age of onset of the disease in genetically vulnerable individuals[16,17].

Cannabis users have a specific variant of the AKT1 gene, which encodes an enzyme responsible for dopamine release in the striatum, thereby increasing the risk for psychosis. According to studies, *cannabis* use during adolescence may contribute to the development of psychosis in adulthood and appears to depend on whether the individual already has a genetic vulnerability to schizophrenia. The striatum corresponds to the brain area rich in dopamine, especially when it receives stimuli. The risk of psychosis among those who have this variant is seven times higher for those who used cannabis compared to those who used it infrequently or never used it[18].

The common cause hypothesis asserts that the explanation is given by the influence of other factors, such as genetic risk, childhood maltreatment, which increase the risk of *cannabis* use and the occurrence of schizophrenia in young individuals. This possibility was considered in some studies by comparing the rate of schizophrenia in people who abuse different drugs[19].

The available evidence indicates a modest contribution of cannabis as a cause of schizophrenia. Several prospective studies have shown a consistent dose-response relationship between cannabis use in adolescence and the risk of psychotic symptoms or schizophrenia[20].

Therefore, the findings are consistent and support the idea that indiscriminate use of *cannabis*, especially among young people, may have future consequences, especially if the individual has a family history of schizophrenia. In individuals with schizophrenia, studies discourage the hypothesis that the association between cannabis and schizophrenic disorders is solely due to self-medication. However, it is still not clear, based on current evidence, whether cannabis use would be responsible for initiating schizophrenic symptoms or causing schizophrenic symptoms in non-vulnerable individuals[20].

CONCLUSION

It can be concluded that cannabis use during adolescence, especially when it occurs intensely and frequently, can trigger symptoms of schizophrenia in individuals with genetic vulnerability.

The brain maturation phase during adolescence is a crucial period for the programming and reprogramming of brain structures, and the interference of any external agent can have serious consequences on its development and disrupt normal functioning, with early cannabis use being one of them.

Therefore, governments, educational, and health services should join efforts to strengthen prevention measures against drug use, especially among adolescents, in order to minimize harm and reduce the risk of severe mental disorders, such as schizophrenia.

REFERENCES

1. Barlow DH, Durand VM. Psicopatologia: Uma abordagem integrada. 7 ed. São Paulo: Cengage Learning; 2016.

2. Associação Americana De Psiquiatria – APA. Manual Diagnóstico e Estatístico de Transtornos Mentais – DSM-V. 5 ed. Trad. Maria Inês Corrêa Nascimento et al. Porto Alegre: Artmed, 2014.

3. Green AI, Tohen MF, Hamer RM, Strakowski SM, Lieberman JA, Glick I et al. First episode schizophrenia-related psychosis and substance use disorders: acute response to olanzapine and haloperidol. Schizophr Res. 2004; 66(2-3):125-35.

4. Organização Mundial Da Saúde. Classificação Estatística Internacional de Doenças e Problemas Relacionados à Saúde. 10 ed. São Paulo: Editora da USP, 2012.

5. United Nations Office on Drugs and Crime. World Drug Report 2022. Nova York: United Nations Publication, Sales No. 22.XI.8, 2022.

6. Rother ET. Revisão sistemática x revisão narrativa. Acta Paul Enferm 2007; 20:v-vi.

7. Silva DAS, De Oliveira NR, Graça MS. A relação entre transtornos mentais e o uso de substâncias psicoativas. Ciência (In) Cena Bahia. 2018;1(6):38-50.

8. Carvalho MTVD. Canabinóides e o seu Prejuízo Mental: Psicoses e Doenças Psiquiátricas do tipo da Esquizofrenia. 2018. Dissertação (Mestrado Integrado em Medicina) - Universidade do Porto, Porto, 2018.

9. D'Souza DC, Radhakrishnan R, Sherif M, Cortes-Briones J, Cahill J, Gupta S et al. Cannabinoids and Psychosis. Curr Pharm Des. 2016;22(42):6380-6391.

10. Barrona, JIB. Psicose e Consumo de Canábis: Causa, Consequência ou Coincidência? 2017. Dissertação (Mestrado Integral em Medicina) - Universidade de Lisboa, Lisboa, 2017.

11.Van Der Pol P, Liebregts N, de Graaf R, Korf DJ, Van Den Brink W, Van Laar M. Predicting the transition from frequent cannabis use to cannabis dependence: a three-year prospective study. Drug Alcohol Depend. 2013;133(2):352-9.

12. Grotenhermen F, Muller-Vahl K. The therapeutic potential of cannabis and cannabinoids. Deutsches Arzteblatt International. 2012;109(29):495-501.

13. Gruber SA, Sagar KA, Dahlgren MK, Racine M, Lukas SE. Age of onset of marijuana use and executive function. Psychol Addict Behav. 2012;26(3):496-506.

14. Volkow ND, Wang GJ, Telang F, Fowler JS, Alexoff D, Logan J et al. Decreased dopamine brain reactivity in marijuana abusers is associated with negative emotionality and addiction severity. The Proceedings of the National Academy of Sciences. 2014;111(30):149-156.

15. Yücel M, Lorenzetti V, Suo C, Zalesky A, Fornito A, Takagi MJ et al. Hippocampal harms, protection and recovery following regular cannabis use. Transl Psychiatry. 2016;6(1):e710.

16. Di Forti M, Sallis H, Allegri F, Trotta A, Ferraro L, Stilo AS et al. Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. Schizophr Bull. 2014; 40(6):1509-17.

17. Myles H, Myles N, Large M. Cannanbis use in first episode psychosis: meta-analysis of prevalence, and the time course of initiation and continued use. Australasian and New Zealand Journal of Psychiatry. 2015; 50(3):208-219.

18.Di Forti M, Lyegbe C, Sallis H, Kolliakou A, Falcone MA, Paparelli A et al. Confirmation that the AKT1 (rs2494732) genotype influences the risk of psychosis in cannabis users. Biol Psychiatry. 2012; 72(10):811-6.

19. Libuy N, Angel V, Ibáñez C. Risk of schizophrenia in marijuana users: Findings from a nationwide sample of drug users in Chile. | National Institute on Drug Abuse (NIDA), 2015.

20. Haney M, Evins AE. Does cannabis cause, exacerbate or ameliorate psychiatric disorders? An oversimplified debate discussed. Neuropsychopharmacology. 2016; 41(2):393-401.