

Marijuana use and the risk of schizophrenia

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Abstract— *To review the literature on the association between cannabis use as a triggering factor for schizophrenia in individuals with a predisposition to psychosis who used cannabis and to verify the relationship with the pathogenesis.*

I. INTRODUCTION

Schizophrenia is classified in the Diagnostic and Statistical Manual of Mental Disorders - DSM-5 (APA, 2014) within the Spectrum that can have a variation within a limit of commitment and intensity. Thus, schizophrenia is defined through multiple symptoms such as delusions, grossly disorganized or catatonic behavior, hallucinations, and negative symptoms. In addition, moments of symptom reduction are interspersed, with apathy, social isolation and difficulties in expressing emotions.

Cannabis has psychoactive substances such as cannabidiol (CBD) and tetrahydrocannabinol (THC), which generate a direct influence on the Central Nervous System (CNS), being classified as disturbing it. Its acute use can generate in the person a state similar to that of the psychotic, such as affective blunting, agitation, confusion in thoughts and hallucinations. Some authors defend that these symptoms are restricted to cannabis psychosis, that is, symptoms that occur only in the specific use of the drug. Other authors defend the direct influence of the substance on the development of schizophrenia, being considered one

of the risk factors for this disorder. The onset of schizophrenia occurs in youth and the use of cannabis is more intense between the ages of 15 and 20, coincidentally, being an additional point for analyzing the manifestation of symptoms (FITAS, 2012).

Among the various studies carried out in the area of chemical dependence and the relationship with the advent of schizophrenia, some authors believe that schizophrenia could be triggered by substance abuse, at least in subjects who have a predisposition, while others believe that patients with schizophrenia would use drugs to avoid the discomfort of disease symptoms or pharmacological treatment (HAMBRECHT; HAFNER, 2000). The hypothesis is unanimous that the comorbidity can generate a worsening of the prognosis and cause difficulty in the treatment, which can lead the schizophrenic subject to suicidal ideation.

OBJECTIVE

To review the literature on the association between cannabis use as a triggering factor for schizophrenia in individuals with a predisposition to psychosis who used cannabis and to verify the relationship with the pathogenesis.

II. METHOD

The methodology used was bibliographic research in the SciELO, Virtual Health Library (VHL) and Pubmed databases on the topic in question. As inclusion criteria, studies published in Portuguese, English and Spanish in the last fifteen years were used, with the following descriptors: schizophrenia and cannabis. The exclusion criteria used were articles published for more than fifteen years, which were in languages other than Portuguese, English and Spanish, and which were not in accordance with the topic in question.

SCHIZOPHRENIA

Schizophrenia affects just under 1% of the population at some point in their lives. A systematic review showed that incidence rates ranged from 7.7 to 43.0 per 100,000, a fivefold difference. A survey carried out by Kirkbride et al. (----) evaluated the incidence of psychosis in three English cities as part of the large AESOP (Etiology and Ethnicity of Schizophrenia and Other Psychoses) study.

The peak incidence for schizophrenia in males was between 20 and 24 years, but 29 to 32 years in females. Schizophrenia in females appears on a flatter curve later than in males. Thus, this study confirms earlier evidence of an earlier age of onset of schizophrenia in males.

The risk factors for the disorder are diverse and divided into two main groups: biological and social. First-

degree biological relatives have a 10 times greater risk of developing the disease than the general population. Studies have also indicated other risk factors such as pregnancy and childbirth complications, exposure to influenza during various epidemics of the disease, maternal starvation during pregnancy, Rhesus factor incompatibility, and an excess of winter births in the etiology of the disorder.

Given the early development of the disease, the financial expense is significant and long-lasting. It is estimated that the financial cost of the disease in the United States is greater than that of all types of cancer combined. A relevant fact, with regard to the social sphere, indicates that 15 to 45% of North Americans living on the streets have a diagnosis of schizophrenia. (KAPLAN, 2017).

The pathological mechanism of schizophrenia is not fully understood and current antipsychotics are characterized by severe limitations: these treatments are effective for only about half of patients and involve serious neurological and metabolic side effects, in addition to being able to lead to sexual dysfunction or agranulocytosis. ; KONDEJ; KACZOR; 2018).

THE INTERFERENCE CAUSED BY CANNABIS IN THE APPEARANCE OF THE PATHOLOGY

By collecting information, it was observed that there is a relationship between the etiopathogenesis of schizophrenia and the use of Cannabis, in which one of the authors studied emphasizes the greater probability of developing the pathology in people who daily use the substance with higher concentration. of THC (JUNIOR, 2019). Tetrahydrocannabinol, THC, is considered a psychoactive substance located in cannabis-type plants. This substance can increase the subject's anxiety levels, as well as affect their ability to learn, develop psychotic symptoms, cause tachycardia and sedation effects (BAU; PARISE; AVIZ, 2021).

This substance is undergoing studies, not being proven or fully defined all the symptoms that the use of cannabis can generate, however, when there is an increase in the levels of the substance in the body, the mental effects can be accentuated (JUNIOR, 2019).

Schizophrenia is treated as a pathology that results from or has the ability to intensify due to the use of cannabis, however, it occurs in predisposed people (BAU; PARISE; AVIZ, 2021).

The use of marijuana interferes with the development of the pathology and causes difficulty in treatment, which causes neurological changes in the person. According to Oliveira and Moreira (2007) apud Bau, Parise and Aviz (2021), cannabis is seen as a disturber of the Central Nervous System (CNS), generating in the person the

lack of spatial orientation, changes in any of the five senses, memory and causing you to become dependent on the substance. This is all due to the compounds identified in cannabis, generating a feeling of well-being in the individual.

RISK BEHAVIORS OF INDIVIDUALS WHO USE CANNABIS

The symptoms of schizophrenia together with the effects of the drug can generate mental confusion in the subjects, considering the appearance of behaviors that put these people at risk. As it is a disorder that has different phases, the symptoms can be both positive and negative, it is understood that risk behaviors can be presented in two moments, however, manifested in different circumstance (BAU; PARISE; AVIZ, 2021).

Among the various characteristics that schizophrenia has, negative symptoms are identified. At this stage, the subject tends to isolate himself from his support network and from society, which favors the development of depressive conditions. Despite this, depression can occur at all stages of the disease (MOGADOURO et al., 2009 apud BAU; PARISE; AVIZ, 2021). It is observed in the analyzed articles that, regarding the possibilities of suicide in individuals with schizophrenia, it is common to happen in depressive symptoms. It was noted that there is a contradiction between one of the articles that brings the perspective that the patient with schizophrenia does not necessarily use the drug due to chemical dependence, however, for the relief of their own symptoms, even in the search to reduce the discomfort of the side effects of the drugs. (TRINADE; SANTOS; OLIVEIRA, 2019).

It was observed, on the other hand, through another article, that the use of cannabis may be related to the attempt to reduce negative symptoms and may also be the cause (OLIVEIRA; MOREIRA, 2007 apud BAU; PARISE; AVIZ, 2021). Research has shown that high levels of CB1 receptors in the CNS, including the anterior cingulate cortex, have been described in schizophrenic people (ZAVITSANOU; GARRICK; HUANG, 2004 apud BAU; PARISE; AVIZ, 2021). According to Oliveira and Moreira (2007) apud Bau, Parise and Aviz (2021), the anterior cingulate cortex is fundamental for cognition, especially with regard to attention and motivation. The changes that marijuana generates in the CNS are related to the negative symptoms of schizophrenia.

Thus, it was observed that schizophrenic people who use cannabis or other substances to relieve negative symptoms, and those who manifest such symptoms by using the drug frequently, tend to be more likely to present risk behaviors, which can cause suicide. The existence of depressive symptoms is the fundamental cause of

reintegration in schizophrenia and is more closely related to mortality and morbidity (MOGADOURO et al., 2009 apud BAU; PARISE; AVIZ, 2021). Therefore, the patient who presents a depressive condition in addition to the diagnosis of schizophrenia and makes the conciliation with the use of cannabis, may have high possibilities of suicide due to feelings of hopelessness in association with risk behaviors, leading to an overdose, for example.

The use of drugs in general (marijuana, cocaine, crack) can induce the patient to have an increase in symptoms, such as delusions, fear, hallucinations and a feeling of persecution. In addition to having been found that drug use generates a feeling of self-sufficiency and self-confidence in these subjects (TRINTADE; SANTOS, OLIVEIRA, 2019).

Taking into account the behaviors and symptoms, it can be taken into account that the individual with schizophrenia, when using drugs, increases the possibilities of developing suicidal ideation, based on the assumption that in a moment of hallucination in which the subject imagines that he is being chased, he runs the risk of crossing a street without noticing if a vehicle is coming, throwing himself from somewhere that is high in the quest to escape from the person he is chasing, or even feeling self-confident to commit some illicit act, putting his life endangered (BAU; PARISE; AVIZ, 2021).

It has been proven that the abusive use of marijuana can worsen psychotic symptoms in patients with schizophrenia (OLIVEIRA; MOREIRA, 2007 apud BAU; PARISE; AVIZ, 2021). Even so, some changes were identified regarding how cannabis works effectively in the person's CNS. Some studies point out that the substance intensifies and affects positive symptoms, while others show the existence of functional interactions between cannabinoids and dopamine, that is, drugs that cause dopaminergic D2 receptor blockade reduce the positive symptoms of the disease (OLIVEIRA; MOREIRA, 2007 apud BAU; PARISE; AVIZ, 2021).

Among the consequences that drug use has on the subject, it is possible to find, through one of the studies, that they suffer fatal accidents more frequently, with the probability that a part of the accidents is due to suicides that have not been explained. Even though there is no specific information about the risk behaviors that an individual with schizophrenia

who uses cannabis can develop, it is confirmed that the drug can interfere with the treatment of these people. Thus, when treatment is not taken seriously, the consequences can be fatal (BAU; PARISE; AVIZ, 2021).

RELATIONSHIP BETWEEN CANNABIS USE AND SCHIZOPHRENIA

Some studies suggest that exposure to substances such as cannabis accounts for the increased prevalence of schizophrenia, in a causal relationship, that is, substance abuse would trigger schizophrenia, at least in predisposed individuals (MUESER et al., 1990).

Andreasson et al. (1987) carried out a study in which the hypothesis of a case-control causal model was investigated, in which 50,000 young people were followed up over a period of 15 years. This study suggested a positive and dose-dependent correlation between early initiation of marijuana use and later diagnosis of schizophrenia in young men. Zammit et al. (2002), after a review of this study, found that for subjects who used marijuana alone, the dose-response relationship remained significant with a 1.5-fold increased risk. For people who had used marijuana more than 50 times, the risk rose to 3.1 times.

After the year 2000, the causal model gained strength (ARSENEAULT et al., 2004; SMIT; BOLIER; CUIJPERS, 2004), probably due to advances in the neurobiology of the endocannabinoid system. From that year on, systematic reviews of the epidemiological studies published until then began to assess the strength of the evidence for the predominance of the causal model.

In 1993, a Swedish study investigated 112 patients diagnosed with schizophrenia and marijuana use. In 69% of patients, marijuana abuse had occurred at least one year before the onset of psychotic symptoms. The disease preceded use in only 11% of cases (ALLEBECK; ADAMSSON; ENGSTROM, 1993). In 1994, a Dutch study showed that in 23 of the 24 cases studied, marijuana use had preceded the onset of the first psychotic symptoms by at least one year (LINSZEN; DINGEMANS; LENIOR, 1994).

A Dutch study followed 4045 subjects without psychosis and 59 subjects with psychotic symptomatology, assessed at baseline, through the first and third years. After adjusting for confounders, cannabis users at baseline were approximately three times more likely to manifest psychotic symptoms at follow-up. A dose-response relationship was found, with an OR of 6.8 (95% CI: 1.8-25.9) associated with the highest level of cannabis use.

The relationship between cannabis use and psychotic symptoms was more evident in cases with more severe symptoms. Cannabis-using individuals with psychotic symptoms at baseline had a higher risk of developing schizophrenia compared to non-using individuals. The attributable risk, that is, the percentage of cases that would be preventable if consumption were eliminated, was estimated at 13% for psychotic symptoms

and 50% for psychotic disorders requiring psychiatric treatment.

A German study evaluated the relationship between cannabis use and psychotic symptoms in individuals with a predisposition to psychosis, who used cannabis for the first time in adolescence. In this study, 2437 individuals from the general population, aged between 14 and 24 years, with and without risk factors for psychosis, were followed for four years. In view of this study, there was an increase in the risk of psychosis depending on the dose, in individuals exposed to cannabis, with an OR of 1.53 (95% CI: 1.1-2.1) in individuals with consumption greater than five times at the beginning of the study. However, predisposition to psychosis was not found to be a predictive factor for cannabis use, which suggests that consumption leads to psychotic symptoms and not the other way around.

Semple, McIntosh, and Lawrie (2005) performed a systematic review of the literature and included in the meta-analysis only those studies that clearly examined the association between marijuana use and schizophrenia or schizophrenic psychosis, but not with psychotic symptoms. These authors found that marijuana use was a risk factor and tripled the chance of developing schizophrenia.

Arseneault et al. (2004) showed that marijuana use doubled the risk for schizophrenia and estimated that the abolition of marijuana use would bring about an approximately 8% reduction in the incidence of schizophrenia.

Henquet et al. (2005) gathered seven prospective studies published between 2002 and 2005 that examined the association between marijuana use and the development of psychosis and submitted them to a meta-analysis study. The result revealed that there was a positive association between the two factors with a relative risk of around 2. Although the authors acknowledged that this value was not that high, they argue that, as marijuana use is quite prevalent in the young population, which is the group at greatest risk for developing psychosis, the data became quite relevant.

It is understood that the neurodevelopmental characteristic during adolescence may be vulnerable to the effects of cannabis consumption. Consumption aggravates psychotic symptoms in individuals at risk for schizophrenia, possibly inducing dysfunctions in the most relevant neurotransmitter systems, such as GABAergic and dopaminergic transmission (PAROLARO, 2010). Another 2000 epidemiological study in a German-influenced region of 1,500,000 people found that thirteen percent of 232 patients diagnosed with schizoid disorder had a history of cannabis abuse, which was twice the rate of matched normal controls. (HAMBRECHT; HÄFNER, 2000)

Despite studies, the correlation between cannabis use in adolescence and later development of schizophrenia is not conclusive. The pathogenic process is complex, it is likely that it depends on the existence of certain genes, on their activation or inactivation, on their interactions that can be influenced by non-genetic environmental factors.

III. CONSIDERATIONS

Schizophrenia is a multifactorial disorder, reflecting the interaction between vulnerability and contributing environmental factors. Although the factors that make the brain at the time of maturation “vulnerable” to substances such as THC are still unknown, it is reasonable to consider this substance as part, an integral “knot” of a complex interactive of pathophysiological factors. In it, changing any part of the system can lead to malfunction of the entire array. The disturbance is not found in one or several “nodes”, but possibly in the interaction between them.

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