Cannabis and Psychosis: An Overview of The Relationship
Cannabis e Psicose: Uma Visão Geral da Relação

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The relationship between the recreational use of cannabis and psychosis has been an area of great interest, research and debate, mainly concerning the impact of cannabis on the development of primary psychotic disorders (PPD), namely schizophrenia spectrum disorders. Psychotic symptoms or transient psychotic experiences may occur after an intoxication with cannabis, without configuring a full-blown psychotic episode. In these situations, the insight is usually preserved, and the symptoms generally resolve spontaneously and completely in less than 24 hours. If these symptoms persist beyond the period of intoxication and a complete psychotic episode develops, then it is usually named cannabis-induced psychotic disorder (CIPD). Tetrahydrocannabinol (THC) is the cannabinoid found in cannabis plants and its derivatives that seems to be the main responsible one to induce acute dose-dependent psychotic episodes. Psychotic episodes induced by cannabis happen more frequently in patients consuming more potent cannabis (with higher THC concentrations) and may occur in individuals without a personal or family history of psychotic disorder. Those psychotic episodes may have schizophrenia-like symptoms and may last for days or even weeks after abstinence. Theoretically, no prodromal symptoms would be found in these cases and there should be a complete return to the previous level of functioning, but in clinical practice it doesn’t always happen that way. It is often challenging to clarify whether a psychotic episode, which develops in a patient that is actively consuming cannabis, is a CIPD, or a first episode psychosis (FEP) or a subsequent acute decompensation of a PPD instead. Patients frequently maintain cannabis consumption even after the psychotic episode development, which makes this distinction even more challenging because it is not possible to assess the presence or absence of psychotic symptoms during a consistent abstinence period. For the diagnosis of CIPD according to the DSM-5, the presence of a PPD must be excluded, the symptoms must exceed what would be expected in an intoxication, and the duration of the psychotic episode should not exceed a maximum of 4 weeks after the last cannabis use. Clinically, when observing patients in a cross-sectional manner and trying to distinguish CIPD from a primary psychotic disorder with comorbid cannabis use disorder (CUD), the former shows a higher prevalence of affective symptoms (namely depression), psychomotor agitation and anxiety symptoms. Furthermore, in CIPD, when compared to a PPD with comorbid CUD, insight is less disturbed, there is a quicker remission of positive symptoms, the prevalence of negative symptoms is lower, and the presence of family history of psychosis is rarer. The role of cannabis consumption in the etiopathogenesis and precipitation of PPD, namely schizophrenia, remains a subject of intense debate and controversy in the scientific community. What is known, having been replicated numerous times, is that individuals presenting a FEP or diagnosed with schizophrenia report having used cannabis much more often than the general population. It is also well established that schizophrenia spectrum disorders are much more frequent in individuals with a history of cannabis use than in individuals who have never used it. Furthermore, cannabis consumption is associated to a 1.4 to approximately 4x higher risk of developing schizophrenia. This risk is as higher as more intense, frequent and
severe the use of cannabis is, and it also seems to be higher if the patient started using cannabis earlier in the life.\textsuperscript{12,13} The onset of cannabis use usually precedes the appearance of psychotic symptoms, and a FEP arises earlier, at younger ages, in cannabis users versus non-users.\textsuperscript{8,12} Adding to these epidemiological associations, it has also been demonstrated that patients with PPD who use cannabis have a worse prognosis, show worse adherence to antipsychotic treatment, present more frequent decompensations and hospitalizations, and show more intense positive psychotic symptoms.\textsuperscript{14,15} Importantly, discontinuing and maintaining abstinence from cannabis in patients with schizophrenia seems to reduce the risk of a poor prognosis, and increase adherence to treatment, to an equivalent degree of individuals who have never used it.\textsuperscript{11,14}

Although these data show a consistent epidemiological association between cannabis use and the development of PPD, a biological causal link has not yet been clearly established. It is not yet possible to declare with certainty that cannabis use biologically predisposes or contributes to the development of schizophrenia or other PPD in the future.\textsuperscript{2,10}

To explain the (at least epidemiologic) association between these two phenomena, there are various hypotheses:

- The “common vulnerability” hypothesis, which postulates that the factors (genetic, developmental, psycho-social) that grant vulnerability and greater risk to an individual to develop a PPD, are the same ones that make that same individual more vulnerable to use cannabis and other psychoactive substances. According to this hypothesis, cannabis use can be considered a predictor for the onset of a PPD in the future, as it is a manifestation of a common underlying vulnerability.\textsuperscript{2,10}

- The “self-medication” hypothesis, which postulates that patients with schizophrenia, for example, use cannabis to alleviate symptoms that are already part of disorder manifestations, namely anxiety during the prodromal phase or secondary to psychotic symptoms.\textsuperscript{2,10,11}

- Finally, the hypothesis that seems more plausible and to better explain the association between cannabis use and psychosis, is the one postulating that cannabis consumption (especially if intense and initiated prematurely), is a late environmental factor that, in genetically vulnerable individuals, and adding to other risk factors, contributes to the development of PPD, and often triggers the FEP. Nevertheless, it’s not possible to clarify the burden of cannabis use in the etiopathogenesis of psychotic disorders compared to other possible risk factors.\textsuperscript{2,10,11}

Cannabis use is neither a sufficient nor a necessary factor for the development of PPD and therefore most individuals who use cannabis will not develop a disease such as schizophrenia. However, cannabis use may be a determinant in the etiology, age of onset and prognosis of PPD, being a potentially controllable risk factor. Therefore, the prevention and treatment of cannabis use and CUD, with psychosocial and psychopharmacologic interventions, is probably an intervention with great impact in the natural course of psychotic disorders.