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CANNABIS AND THE RISK OF REHOSPITALIZATION IN PATIENTS WITH SCHIZOPHRENIA: AN OVERVIEW

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ABSTRACT

Schizophrenia is a chronic psychiatric disorder characterized by a course marked by recurrent relapses and frequent rehospitalizations, leading to progressive impairment in psychosocial functioning and a substantial burden on patients, their families, and healthcare systems. Among the recognized poor prognostic factors, cannabis use plays a prominent role because of its high prevalence among individuals with schizophrenia and its impact on the course of the illness. Numerous longitudinal studies and several meta-analyses have shown that continued cannabis use is associated with an increased risk of relapse, poorer treatment adherence, worsening psychotic symptoms, and more frequent rehospitalizations. The proposed mechanisms primarily involve the effects of Δ9-tetrahydrocannabinol (THC) on the endocannabinoid system, dopaminergic neurotransmission, and neurodevelopmental processes in vulnerable individuals. Although uncertainties remain regarding the contribution of confounding factors, such as the use of other substances and the initial severity of the illness, the available evidence suggests that cannabis is a modifiable factor that may adversely influence the prognosis of schizophrenia. This article provides an overview of the current knowledge regarding the impact of cannabis on the risk of rehospitalization and discusses its main implications for clinical practice.

KEYWORDS : Schizophrenia; Cannabis; Rehospitalization; Relapse; THC; Treatment adherence.

INTRODUCTION

Schizophrenia is a chronic and severe psychiatric disorder affecting approximately 24 million people worldwide **(1),(2)**. It is one of the leading causes of disability among young adults and

is characterized by profound disturbances in perception, thinking, emotions, and behavior **(3)**. Despite significant advances in understanding its pathophysiology and the development of new therapeutic strategies, its course remains frequently marked by relapses and repeated hospitalizations, which adversely affect functional outcomes and quality of life **(5)**.

Rehospitalization is a major indicator of the clinical course of schizophrenia. It generally reflects a psychotic relapse requiring intensive psychiatric care but also results from the complex interplay of several risk factors, including poor treatment adherence, psychosocial difficulties, substance use disorders, and psychiatric comorbidities **(6),(7),8)**. Each episode of rehospitalization is associated with increased healthcare costs, disruption of continuity of care, and a greater risk of long-term functional deterioration **(7),(8)**.

Among the psychoactive substances used by patients with schizophrenia, cannabis occupies a unique position. It is the most commonly used illicit substance in this population, with a prevalence far exceeding that observed in the general population **(9),(10),(11)**. Cannabis use has attracted growing interest in psychiatry because of accumulating evidence suggesting its involvement not only in triggering psychotic disorders in vulnerable individuals but also in worsening the clinical course of patients already diagnosed with schizophrenia **(12),(13),(14)**.

Over the past two decades, advances in our understanding of cannabinoids, the increasing availability of high-potency cannabis products containing elevated concentrations of Δ9-tetrahydrocannabinol (THC), and the expansion of cannabis legalization policies in several countries have intensified interest in the psychiatric consequences of cannabis use **(15),(16)**. Longitudinal studies have shown that patients who continue to use cannabis regularly experience more severe psychotic symptoms, a poorer response to antipsychotic treatment, reduced treatment adherence, and a higher risk of relapse **(17),(18),(19)**. These findings raise important questions regarding the impact of cannabis use on the risk of rehospitalization, a key indicator of disease severity and clinical outcome.

However, interpreting the available evidence remains challenging. Published studies differ in their diagnostic criteria, methods of assessing cannabis use, duration of follow-up, and adjustment for potential confounding factors, including the concomitant use of other substances, socioeconomic characteristics, and the baseline severity of schizophrenia **(20)**. Despite this heterogeneity, several systematic reviews and meta-analyses consistently support an association between persistent cannabis use and an increased risk of relapse and rehospitalization **(21)**.

The aim of this article is to provide an overview of the current evidence regarding the relationship between cannabis use and rehospitalization in patients with schizophrenia. It first

outlines the main epidemiological findings, then examines the pathophysiological mechanisms that may explain this association, and finally discusses the evidence from clinical studies and its implications for psychiatric practice.

1. Cannabis and Schizophrenia: A Common Comorbidity

Substance use disorders are among the most common comorbidities in patients with schizophrenia **(22),(23),(24)**. Among these substances, cannabis occupies a prominent position because of its high prevalence and its potential impact on the course of the illness **(25)**. Epidemiological data indicate that patients with schizophrenia use cannabis far more frequently than the general population, with lifetime prevalence rates generally ranging from 25% to 45%, depending on the populations studied and the diagnostic criteria applied **(9),(22),(23)**. This prevalence is even higher among younger individuals, men, and patients experiencing a first episode of psychosis **(26),(27)**.

Several hypotheses have been proposed to explain this strong association. The self-medication hypothesis suggests that some patients use cannabis to reduce anxiety, improve mood, alleviate certain negative symptoms of schizophrenia, or lessen the adverse effects of antipsychotic medications **(28),(29)**. Although this theory may explain some clinical situations, it does not account for all observations, particularly the fact that cannabis use often precedes the onset of the first psychotic symptoms **(30),(31)**.

Another hypothesis is based on the existence of a shared vulnerability to both schizophrenia and substance use disorders. Genetic factors, neurodevelopmental abnormalities, early-life trauma, family dysfunction, socioeconomic disadvantage, and exposure to environments that facilitate substance use may simultaneously increase the risk of developing schizophrenia and engaging in addictive behaviors **(32),(33).**This interaction between individual vulnerability and environmental factors is now widely recognized as a key component in the pathophysiology of psychotic disorders **(34)**.

From a clinical perspective, patients with schizophrenia who use cannabis often exhibit a distinctive profile. They are generally younger at diagnosis, experience an earlier onset of illness, display greater impulsivity, use other psychoactive substances—particularly tobacco and alcohol—more frequently, and demonstrate poorer adherence to treatment **(35),(36)**. These characteristics may influence clinical outcomes independently of cannabis use itself, highlighting the need for cautious interpretation of study findings **(17),(35)**.

Nevertheless, studies published in recent years suggest that persistent cannabis use remains associated with a poorer prognosis even after adjustment for these potential confounding

factors **(37)**. Patients who continue to use cannabis experience more frequent relapses, a greater number of hospitalizations, a less favorable response to treatment, and more severe impairment in psychosocial functioning **(13),(37)**. These findings have led researchers to consider cannabis not only as a common comorbidity but also as a potentially modifiable factor influencing the course of schizophrenia **(14),(21),(37)**.

2. Neurobiological Basis of Cannabis Use in Schizophrenia

The association between cannabis use and the course of schizophrenia is supported by complex pathophysiological mechanisms involving the endocannabinoid system, dopaminergic pathways, excitatory and inhibitory neurotransmission, as well as genetic and neurodevelopmental factors. Although these mechanisms have not yet been fully elucidated, experimental and clinical evidence suggests that cannabis—particularly preparations rich in Δ9-tetrahydrocannabinol (THC)—may exacerbate the neurobiological abnormalities already present in individuals with schizophrenia.

2.1. The Endocannabinoid System

The endocannabinoid system is a neuromodulatory network widely distributed throughout the central nervous system. It plays an essential role in regulating cognition, emotion, memory, learning, reward processing, and the stress response **(38),(39)**. The system primarily consists of cannabinoid receptors CB1 and CB2, endogenous cannabinoids—notably anandamide and 2-arachidonoylglycerol (2-AG)—as well as the enzymes responsible for their synthesis and degradation **(40),(41)**.

CB1 receptors are particularly abundant in the prefrontal cortex, hippocampus, basal ganglia, and cerebellum, brain regions involved not only in cognitive and emotional functions but also in the pathophysiology of schizophrenia **(42)**. Activation of these receptors modulates the release of several neurotransmitters, including glutamate, γ-aminobutyric acid (GABA), and dopamine **(43)**.

Several studies have demonstrated alterations in the endocannabinoid system among patients with schizophrenia, including changes in CB1 receptor expression and endocannabinoid concentrations **(44),(45)**. This dysregulation may contribute to the abnormalities in neurotransmission observed in schizophrenia and may partly explain these patients' increased vulnerability to the effects of cannabis **(46),(47)**.

2.2. The Role of THC in the Exacerbation of Psychotic Symptoms

Δ9-Tetrahydrocannabinol (THC) is the principal psychoactive constituent of cannabis. By binding to CB1 receptors, THC alters the activity of several neural circuits involved in the regulation of thought, emotion, and perception **(48)**.

One of the best-established mechanisms involves its effect on dopaminergic neurotransmission. THC indirectly increases dopamine release within the mesolimbic pathway, whose hyperactivity is considered a central mechanism underlying the positive symptoms of schizophrenia, including hallucinations, delusions, and disorganized thinking **(49),(50).**

In genetically susceptible individuals, this increase in dopaminergic activity may promote the onset of psychotic episodes or accelerate the occurrence of relapses **(51),(52)**. In patients with established schizophrenia, repeated cannabis use may further exacerbate pre-existing neurobiological abnormalities and compromise long-term clinical stability **(31),(52)**.

Furthermore, the average THC content of cannabis products available on the market has increased substantially over the past few decades. High-potency cannabis products are now widely available and appear to be associated with a greater risk of psychosis, relapse, and hospitalization than products containing lower concentrations of THC **(53),(54)**.

2.3. Cannabidiol (CBD)

Unlike THC, cannabidiol (CBD) does not possess psychotomimetic properties. Several studies have suggested that CBD may exert anxiolytic, anti-inflammatory, and potentially antipsychotic effects **(55),(56).**

CBD acts through complex mechanisms, including indirect modulation of cannabinoid receptors, increased anandamide concentrations, and interactions with the serotonergic and glutamatergic systems **(57),(58)**. Several clinical studies have reported modest improvements in psychotic symptoms among patients receiving CBD as an adjunct to antipsychotic treatment **(59)**.

However, most cannabis products used for recreational purposes have a very high THC-to-CBD ratio. The progressive decline in the CBD content of illicit cannabis preparations may contribute to increasing their psychotogenic potential and may partly explain the higher risk of psychotic decompensation observed among regular cannabis users **(15),(58)**.

2.4. Genetic Vulnerability and Neurodevelopmental Factors

Not all cannabis users develop schizophrenia, highlighting the importance of individual vulnerability. Genetic studies suggest that certain polymorphisms involved in dopaminergic

neurotransmission, the endocannabinoid system, and neurodevelopment may influence susceptibility to the psychotomimetic effects of THC **(60),(61).**

Furthermore, adolescence represents a critical period of brain development. Early exposure to cannabis may disrupt synaptic maturation and neuroplasticity, thereby increasing the risk of psychotic disorders in genetically or biologically predisposed individuals **(62),(63)**. This hypothesis is supported by several studies showing that cannabis use initiated before the age of 16–18 years is associated with an earlier onset of schizophrenia and a more severe clinical course **(30),(63)**.

2.5. From Biological Mechanisms to Rehospitalization

The neurobiological effects of cannabis have direct clinical consequences. By exacerbating psychotic symptoms, impairing cognitive functioning, and reducing judgment and insight, cannabis use may compromise treatment adherence and increase engagement in high-risk behaviors **(64)**. This combination of effects contributes to a higher likelihood of relapses requiring hospitalization **(64)**.

It is also likely that these biological mechanisms interact with psychosocial factors such as social isolation, socioeconomic disadvantage, limited family support, and the concurrent use of other psychoactive substances **(37),(64)**. Therefore, the risk of rehospitalization is unlikely to result from a single mechanism but rather from a complex interaction between biological vulnerability, addictive behaviors, and the psychosocial environment **(32),(64)**.

3. Influence of Cannabis on the Clinical Course of Schizophrenia

- **Worsening of Positive Symptoms**

Beyond its neurobiological effects, clinical evidence indicates that cannabis use influences several aspects of the course of schizophrenia. Longitudinal studies consistently show that patients who continue to use cannabis regularly experience a less favorable clinical course than either non-users or those who discontinue cannabis use **(65),(66)**.

The most consistent findings concern positive symptoms. Cannabis users are more likely to experience hallucinations, delusions, disorganized thinking, and episodes of psychomotor agitation requiring hospitalization **(67)**. Several prospective studies further suggest that these episodes tend to be more severe, occur more frequently, and respond less favorably to antipsychotic treatment than in non-users **(68)**.

- **Negative Symptoms and Overall Functioning**

Findings regarding negative symptoms are more heterogeneous. Although some earlier studies suggested that cannabis might transiently alleviate negative symptoms or improve

subjective well-being, more recent evidence does not support a sustained beneficial effect **(69),(70)**. Instead, chronic cannabis use appears to be associated with progressive deterioration in psychosocial functioning, including impaired social relationships, occupational instability, poorer independent living skills, and reduced quality of life **(71)**.

Several longitudinal investigations have also demonstrated that continued cannabis use is associated with poorer global functioning, even after adjustment for illness severity and other potential confounding factors **(71)**.

- **Cognitive Impairment**

Cognitive impairment represents one of the strongest predictors of long-term disability in schizophrenia. Deficits in attention, working memory, executive functioning, verbal learning, and processing speed substantially affect patients' functional recovery **(72),(73)**.

Cannabis use may further aggravate these impairments through its effects on hippocampal and prefrontal cortical function **(72)**. Although some studies have reported inconsistent findings, the overall evidence suggests that persistent cannabis use is associated with greater cognitive dysfunction, particularly among patients with early-onset or heavy cannabis exposure **(74)**. These cognitive deficits may compromise insight, reduce adherence to treatment, and indirectly increase the likelihood of psychotic relapse and rehospitalization **(74)**.

- **Treatment Adherence**

One of the principal mechanisms linking cannabis use to poor clinical outcomes is reduced treatment adherence. Patients who continue to use cannabis are more likely to discontinue antipsychotic medication, miss scheduled follow-up appointments, and show lower engagement in psychosocial rehabilitation programs **(75),(76),(77)**.

Poor adherence has consistently been identified as one of the strongest predictors of psychotic relapse and rehospitalization **(75),(77)**. Several mediation analyses further suggest that treatment non-adherence explains part—but not all—of the association between cannabis use and adverse clinical outcomes **(75)**. This indicates that cannabis probably contributes to relapse through multiple complementary biological and behavioral mechanisms rather than through reduced adherence alone **(75)**.

Overall, the available evidence supports the conclusion that continued cannabis use adversely affects multiple dimensions of schizophrenia, including symptom severity, cognitive functioning, psychosocial recovery, and treatment adherence. These combined effects contribute substantially to the increased risk of relapse and rehospitalization observed among regular cannabis users **(64)**.

4. Cannabis and the Risk of Rehospitalization: A Critical Review of the Evidence

4.1. Longitudinal Studies: A Consistent Association with Relapse

Rehospitalization is one of the principal indicators of prognosis in schizophrenia. It generally reflects a psychotic relapse requiring inpatient psychiatric care but also results from the complex interplay of multiple clinical, therapeutic, and psychosocial factors **(78)**. Each subsequent hospitalization is associated with progressive deterioration in personal, social, and occupational functioning, increased healthcare costs, and reduced quality of life **(78),(79)**. In this context, identifying modifiable factors influencing the risk of rehospitalization is essential for optimizing long-term outcomes in patients with schizophrenia.

Among these modifiable factors, cannabis use has attracted considerable attention because of its high prevalence among patients with schizophrenia and its potential impact on illness progression **(9),(25)**. Over the past two decades, numerous prospective cohort studies have investigated this relationship. Although methodologies differ, their findings consistently suggest that persistent cannabis use is associated with an increased risk of psychotic relapse and subsequent rehospitalization **(80)**.

Longitudinal studies provide the strongest evidence for evaluating the temporal relationship between cannabis exposure and adverse clinical outcomes. Patients who continue to use cannabis after the diagnosis of schizophrenia generally experience a shorter time to relapse, more frequent psychotic exacerbations, and a greater number of psychiatric readmissions than patients who discontinue cannabis use or have never used cannabis **(80),(81)**.

Evidence from first-episode psychosis cohorts is particularly compelling. Continued cannabis use during the early years following diagnosis has consistently been associated with poorer clinical stability, higher relapse rates, and increased rehospitalization, whereas sustained cannabis abstinence is associated with outcomes approaching those observed in non-users **(81)**. These findings support the hypothesis that early interventions targeting cannabis cessation may improve the long-term prognosis of schizophrenia.

Despite these consistent observations, variability in effect sizes remains across studies owing to differences in study design, follow-up duration, definitions of cannabis exposure, and adjustment for potential confounders **(80)**. Nevertheless, the convergence of findings across diverse populations strengthens the evidence supporting a detrimental effect of persistent cannabis use.

4.2. Evidence from Meta-Analyses

Systematic reviews and meta-analyses provide the highest level of evidence currently available. Overall, these studies consistently demonstrate that persistent cannabis use is

associated with increased risks of psychotic relapse, worsening positive symptoms, treatment failure, and psychiatric rehospitalization **(83)**.

Several meta-analyses have also identified a dose–response relationship. Daily cannabis use and consumption of high-potency cannabis preparations rich in THC appear to confer substantially greater risks than occasional use **(53),(82)**. Conversely, cannabis discontinuation is associated with progressive improvement in clinical stability and lower relapse rates, reinforcing the concept that cannabis represents a potentially modifiable prognostic factor **(14),(82)**.

Nevertheless, evidence synthesis also highlights several methodological limitations. Included studies differ in the definition of cannabis exposure, assessment methods, duration of follow-up, and outcome measures, contributing to statistical heterogeneity **(17),(83)**. Despite these limitations, the remarkable consistency of findings across independent investigations considerably strengthens the robustness of the observed association.

4.3. Factors Modulating the Risk of Rehospitalization

Current evidence suggests that cannabis rarely acts as an isolated determinant of rehospitalization but rather interacts with several biological, therapeutic, and psychosocial factors **(21),(64)**.

Treatment adherence remains the most consistently identified mediator. Cannabis users are significantly more likely to discontinue antipsychotic medication, miss psychiatric appointments, and disengage from psychosocial interventions **(77)**. Although impaired adherence explains an important proportion of relapse risk, several prospective studies demonstrate that cannabis remains independently associated with relapse after statistical adjustment for adherence, suggesting additional underlying mechanisms **(13),(84)**.

Characteristics of cannabis exposure also appear important. Earlier age at initiation, higher frequency of use, longer duration of exposure, and consumption of high-potency THC products have all been associated with progressively poorer outcomes **(15),(63)**.

Polysubstance use further complicates interpretation. Concurrent tobacco, alcohol, stimulant, or other illicit drug use is common among cannabis users with schizophrenia and may amplify relapse risk, complicate treatment, and reduce adherence **(22),(84)**.

Psychosocial determinants—including socioeconomic disadvantage, unemployment, homelessness, limited family support, and poor access to mental health services—also contribute substantially to rehospitalization risk **(6),(85)**. Overall, current evidence supports a multifactorial model in which cannabis interacts with several individual and environmental vulnerabilities rather than acting as a single independent causal factor.

4.4. Limitations of the Available Evidence

Despite the consistency of available findings, several limitations deserve consideration. Most published studies remain observational, precluding definitive causal inference **(17),(21)**.

Cannabis exposure is frequently assessed through self-report, introducing potential recall bias and underestimation of actual consumption **(17),(82)**. Furthermore, relatively few investigations precisely quantify THC concentration, CBD content, cumulative exposure, or changes in cannabis potency over time **(53),(54)**.

Residual confounding also remains possible despite multivariable adjustment, particularly regarding illness severity, medication adherence, socioeconomic factors, and concurrent substance use **(21),(84)**.

Finally, most evidence originates from Europe, North America, and Australia. Data from Africa, the Middle East, and other low- and middle-income countries remain scarce, limiting generalizability across different healthcare systems and sociocultural settings **(21),(85)**.

4.5. Implications for Psychiatric Practice

Current evidence supports systematic screening for cannabis use during routine assessment of all patients with schizophrenia, particularly adolescents, young adults, and individuals experiencing first-episode psychosis **(21),(64)**.

Management should integrate optimized antipsychotic treatment with addiction-focused interventions and psychosocial rehabilitation **(77),(86)**. Psychoeducation, motivational interviewing, cognitive behavioral therapy, family interventions, and relapse prevention programs have demonstrated benefits in reducing cannabis use and improving treatment engagement **(88)**.

Long-acting injectable antipsychotics may further improve adherence among selected patients with co-occurring substance use disorders and may contribute to reducing relapse and rehospitalization **(89),(90)**.

Overall, early identification of cannabis use combined with multidisciplinary management currently represents the most promising strategy for reducing rehospitalization and improving long-term functional recovery in schizophrenia **(21),(86),(90)**.

CONCLUSION

The available evidence consistently indicates that cannabis use is associated with a less favorable clinical course of schizophrenia. Patients who continue to use cannabis regularly are at greater risk of psychotic relapse, worsening psychotic symptoms, poorer treatment adherence, and more frequent rehospitalizations. Although the current evidence does not

always allow for the establishment of a definitive causal relationship, the consistency of the findings strengthens the hypothesis that cannabis has a detrimental impact on the course of schizophrenia.

This issue is of particular importance in the context of the increasing potency of cannabis products and the growing normalization of cannabis use in certain populations. Systematic screening for cannabis use, early identification of high-risk patients, and the implementation of integrated management strategies are essential to improving clinical and functional outcomes in patients with schizophrenia.

Finally, large-scale prospective studies incorporating detailed characterization of cannabis use patterns and long-term follow-up are needed to better understand the mechanisms linking cannabis use to rehospitalization and to identify the most effective interventions for preventing relapse.

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