Brief Description of Patient Problem / Setting

During my psychiatry clinical rotation, I encountered a 19-year-old male with a history of Schizophrenia and cannabis use disorder who presented with worsening psychosis after becoming noncompliant with his prescribed antipsychotic medications. Family members reported progressively bizarre behavior, increasing paranoia, social withdrawal, and excessive cannabis use over several months. The patient admitted to frequent daily marijuana use, including high-potency cannabis products, despite prior psychiatric hospitalizations and recommendations to discontinue use. Upon evaluation, he demonstrated severe paranoid delusions and believed that a tracking device had been surgically implanted into his brain to monitor his thoughts and movements.

Schizophrenia is a chronic psychiatric disorder characterized by hallucinations, delusions, cognitive dysfunction, and impaired social and occupational functioning. Emerging evidence suggests that chronic cannabis use, particularly during adolescence and early adulthood, may worsen psychotic symptoms and increase the risk of schizophrenia-spectrum disorders in vulnerable individuals. Young males appear especially susceptible due to neurodevelopmental vulnerability and higher rates of cannabis exposure during late adolescence. During clinical exposure to patients with first-episode psychosis and schizophrenia-spectrum disorders, it became apparent that excessive cannabis use is frequently associated with worsening paranoia, medication noncompliance, recurrent psychotic episodes, and increased psychiatric disease burden. This raises an important clinical question regarding whether chronic cannabis use contributes to increased psychosis severity and higher risk of schizophrenia-related complications in young men.

Search Question: In adolescent and young adult males aged 15–30 years, does chronic cannabis use, compared with little or no cannabis use, increase the risk of developing schizophrenia-spectrum disorders and psychotic symptoms?

Question Type: X Prognosis X Harms

Assuming that the highest level of evidence to answer your question will be meta-analysis or systematic review, what other types of study might you include if these are not available (or if there is a much more current study of another type)? Please explain your choices.

If systematic reviews or meta-analyses were not available, the next highest level of evidence would include large prospective longitudinal cohort studies following cannabis-exposed and non-exposed adolescents and young adults over time to assess the development of schizophrenia-spectrum disorders and psychosis. Case-control studies would also be appropriate to evaluate prior cannabis exposure in individuals with first-episode psychosis compared with matched controls. In the absence of robust cohort data, large population-based registry studies could provide additional evidence regarding long-term psychiatric outcomes associated with cannabis exposure. Randomized controlled trials are not feasible for long-term cannabis exposure due to ethical limitations; however, short-term experimental studies administering THC in controlled settings may help establish acute psychotomimetic effects and biological plausibility.

PICO Search Terms

Population	Intervention	Comparsion	Outcome
Young Adult male	Cannabis usage	Non- cannabis users	Schizophrenia
Male patient between the ages of 15 and 30 years	High-potency cannabis		Psychotic symptoms/psychosis
Male Patients at risk for psychosis			Hospitalization

Search Term Chart

Database	Search terms used	Number of results	filters applied	Notes/ Observations
Pubmed	cannabis AND schizophrenia AND young men AND psychosis risk	65	Last 10 years, English, humans, systematic reviews, meta-analyses, cohort studies	Identified high-quality cohort studies and meta-analyses evaluating the association between cannabis use and increased schizophrenia risk in adolescents and young adults. Strong evidence for dose-dependent psychosis risk with chronic or high-potency cannabis use

Cochrane library	cannabis use AND schizophrenia AND psychosis	20	Last 10 years, English, systematic reviews, meta-analyses	Provided synthesized evidence evaluating the relationship between cannabis exposure and psychosis development. Useful for understanding overall risk trends and causality
CINAHL	young adults AND cannabis AND first episode psychosis	20	Last 10 years, English, cohort studies, systematic reviews	Focused on first-episode psychosis, behavioral risk factors, and adolescent mental health outcomes related to cannabis exposure. Helpful for evaluating early psychiatric presentations and functional outcomes.

Search Strategy

A comprehensive literature search was conducted using PubMed, the Cochrane Library, and CINAHL to identify high-quality evidence evaluating the relationship between cannabis use and schizophrenia-spectrum disorders in young men. Search terms were developed using the PICO framework and included combinations of “cannabis,” “marijuana,” “schizophrenia,” “psychosis,” “first-episode psychosis,” and “young adults.” Boolean operators (AND/OR) were used to refine search results. Filters were applied to include English-language studies published within the last 10 years, prioritizing systematic reviews, meta-analyses, longitudinal cohort studies, and observational studies involving human subjects. Studies were included if they evaluated cannabis exposure and the subsequent development of psychosis or schizophrenia-spectrum disorders. Studies not involving psychotic outcomes or lacking

cannabis exposure data were excluded. This search identified multiple high-quality systematic reviews and longitudinal studies demonstrating a significant association between chronic cannabis use and increased risk of schizophrenia-spectrum disorders, particularly among adolescents and young adult males.

1. Murrie, B., Lappin, J., Large, M., Sara, G., Carter, G., Cotton, S. M., ... & Nielssen, O. (2020). Transition of substance-induced, brief, and atypical psychoses to schizophrenia: A systematic review and meta-analysis. *Schizophrenia Bulletin, 46*(3), 505–516. https://pubmed.ncbi.nlm.nih.gov/31618428/

Abstract : Some people who experience substance-induced psychosis later develop an enduring psychotic disorder such as schizophrenia. This study examines the proportion of people with substance-induced psychoses who transition to schizophrenia, compares this to other brief and atypical psychoses, and examines moderators of this risk. A search of MEDLINE, PsychINFO, and Embase identified 50 eligible studies, providing 79 estimates of transition to schizophrenia among 40 783 people, including 25 studies providing 43 substance-specific estimates in 34 244 people. The pooled proportion of transition from substance-induced psychosis to schizophrenia was 25% (95% CI 18%-35%), compared with 36% (95% CI 30%-43%) for brief, atypical and not otherwise specified psychoses. Type of substance was the primary predictor of transition from drug-induced psychosis to schizophrenia, with highest rates associated with cannabis (6 studies, 34%, CI 25%-46%), hallucinogens (3 studies, 26%, CI 14%-43%) and amphetamines (5 studies, 22%, CI 14%-34%). Lower rates were reported for opioid (12%), alcohol (10%) and sedative (9%) induced psychoses. Transition rates were slightly lower in older cohorts but were not affected by sex, country of the study, hospital or community location, urban or rural setting, diagnostic methods, or duration of follow-up. Substance-induced psychoses associated with cannabis, hallucinogens, and amphetamines have a substantial risk of transition to schizophrenia and should be a focus for assertive psychiatric intervention.

Why I selected this article

I selected this article because it is a high-quality systematic review and meta-analysis that directly evaluates the relationship between substance-induced psychosis and the subsequent development of schizophrenia. This study analyzed data from 50 eligible studies involving more than 40,000 individuals, providing strong evidence regarding the long-term psychiatric outcomes associated with substance-induced psychoses. The article was particularly relevant to my PICO question because it demonstrated that cannabis-induced psychosis had the highest transition rate to schizophrenia compared with other substances, with approximately 34% of individuals later developing schizophrenia-spectrum disorders. The study also highlighted that chronic cannabis exposure in adolescents and young adults may significantly increase psychosis risk and contribute to worsening psychiatric outcomes. I selected this article because it represents one of the highest levels of evidence available and strongly supports the association between excessive cannabis use and increased schizophrenia risk in vulnerable young male populations, closely aligning with my clinical scenario and research question.

2. Patel, R., Wilson, R., Jackson, R., Ball, M., Shetty, H., Broadbent, M., ... & Stewart, R. (2020). The association between cannabis use and schizophrenia: Causative or curative? A systematic review. *Cureus, 12*(7), e9309. https://pmc.ncbi.nlm.nih.gov/articles/PMC7442038/

Abstract: Marijuana is one of the most abused substances in the world. Marijuana is getting legalized around the world. So, it is crucial to understand its effect on our mental health. Its impact on the schizophrenia spectrum needs our special attention. Even though marijuana has been around for a long time, its exact effects are still unknown. Schizophrenia is a chronic illness affecting approximately 20 million people worldwide. Schizophrenia and cannabis seem to have a close relationship, and we want to explore this. We want to know if marijuana is causing, exacerbating, or treating schizophrenia. This systematic review explores this question. We searched online resources like PubMed, PubMed Central, Cochrane Library, and Google Scholar for systematic reviews, traditional reviews, randomized controlled trials, and meta-analysis on cannabis and schizophrenia/ psychosis. We included human studies published in peer-reviewed journals in the English language in the last five years. After reviewing 96 initial results of our search, we excluded 25 duplicates, 29 abstracts, and 18 irrelevant articles. We did a quality assessment for the remaining 24 studies using various quality assessment tools. After the quality assessment, we found 12 articles were of low quality and excluded those. We included the remaining 12 final studies in our systematic review. Out of these 12 studies, five were traditional reviews, two systematic reviews, two meta-analysis, and three observational studies. Six of the articles were on cannabis's effect on just schizophrenia or psychotic disorder. The other six included schizophrenia plus other psychiatric or neurological illnesses. Ten of the studies had data supporting the causative link between cannabis and schizophrenia. Eight records had data supporting the exacerbating effect of marijuana. Six studies had data supporting the therapeutic effect of the cannabidiol (CBD) component of cannabis. From the current data, we can conclude that the tetrahydrocannabinol (THC) component of cannabis can be the main culprit causing psychosis and schizophrenia in the at-risk population. THC can also be the one exacerbating symptoms and causing an adverse prognosis in already diagnosed patients. Even though CBD shows therapeutic effects and THC opposing effects, the data is minimal and low safety and efficacy warrants more research. The relation between cannabis and schizophrenia needs further investigation. We need more case-control studies and clinical trials with a larger population to get conclusive data.

Why we selected this article

I selected this article because it is a comprehensive systematic review that evaluates the complex relationship between cannabis use and schizophrenia-spectrum disorders. The study reviewed multiple forms of high-level evidence, including systematic reviews, meta-analyses, randomized controlled trials, and observational studies, making it highly relevant to my PICO question. This article was particularly valuable because the majority of included studies supported a causative and exacerbating relationship between cannabis use and schizophrenia, especially related to the tetrahydrocannabinol (THC) component of marijuana. The review also demonstrated that chronic cannabis use may worsen psychotic symptoms, contribute to poorer prognosis, and increase psychiatric disease burden in individuals with schizophrenia. Additionally, the article emphasized that adolescents and young adults may represent a particularly

vulnerable population due to neurodevelopmental susceptibility during early brain development. I selected this article because it provides strong evidence supporting the association between excessive cannabis use and increased psychosis risk, closely aligning with my clinical scenario involving a young male patient with schizophrenia and cannabis-induced worsening paranoia and psychosis.

3. Hindley, G., Beck, K., Borgan, F., Ginestet, C. E., McCutcheon, R., Kleinloog, D., ... & Howes, O. D. (2020). Psychiatric symptoms caused by cannabis constituents: A systematic review and meta-analysis. *The Lancet Psychiatry, 7*(4), 344–353. https://pmc.ncbi.nlm.nih.gov/articles/PMC7738353/

Background: Approximately 188 million people use cannabis yearly worldwide, and it has recently been legalized in 11 US states, Canada, and Uruguay for recreational use. The potential for increased cannabis use highlights the need to better understand its risks, including the acute induction of psychotic and other psychiatric symptoms. We aimed to investigate the effect of the cannabis constituent -tetrahydrocannabinol (THC) alone and in combination with cannabidiol (CBD) compared with placebo on psychiatric symptoms in healthy people.

Methods: In this systematic review and meta-analysis, we searched MEDLINE, Embase, and PsycINFO for studies published in English between database inception and May 21, 2019, with a within-person, crossover design. Inclusion criteria were studies reporting symptoms using psychiatric scales (the Brief Psychiatric Rating Scale [BPRS] and the Positive and Negative Syndrome Scale [PANSS]) following the acute administration of intravenous, oral, or nasal THC, CBD, and placebo in healthy participants, and presenting data that allowed calculation of standardised mean change (SMC) scores for positive (including delusions and hallucinations), negative (such as blunted affect and amotivation), and general (including depression and anxiety) symptoms. We did a random-effects meta-analysis to assess the main outcomes of the effect sizes for total, positive, and negative PANSS and BPRS scores measured in healthy participants following THC administration versus placebo. Because the number of studies to do a meta-analysis on CBD's moderating effects was insufficient, this outcome was only systematically reviewed. This study is registered with PROSPERO, CRD42019136674.

Findings: 15 eligible studies involving the acute administration of THC and four studies on CBD plus THC administration were identified. Compared with placebo, THC significantly increased total symptom severity with a large effect size (assessed in nine studies, with ten independent samples, involving 196 participants: SMC 1·10 [95% CI 0·92–1·28], p<0·0001); positive symptom severity (assessed in 14 studies, with 15 independent samples, involving 324 participants: SMC 0·91 [95% CI 0·68–1·14],

p<0·0001); and negative symptom severity with a large effect size (assessed in 12 studies, with 13 independent samples, involving 267 participants: SMC 0·78 [95% CI 0·59–0·97], p<0·0001). In the systematic review, of the four studies evaluating CBD's effects on THC-induced symptoms, only one identified a significant reduction in symptoms.

Interpretation: A single THC administration induces psychotic, negative, and other psychiatric symptoms with large effect sizes. There is no consistent evidence that CBD induces symptoms or moderates the effects of THC. These findings highlight the potential risks associated with the use of cannabis and other cannabinoids that contain THC for recreational or therapeutic purposes.

Why i selected this article : I selected this article because it is a high-quality systematic review and meta-analysis published in *The Lancet Psychiatry* that directly evaluates the psychiatric effects of cannabis constituents, particularly tetrahydrocannabinol (THC). This study was highly relevant to my PICO question because it demonstrated that THC administration significantly increased psychotic symptoms, including hallucinations, delusions, paranoia, and negative psychiatric symptoms compared with placebo. The findings showed large effect sizes for both positive and negative psychotic symptoms, supporting the association between cannabis exposure and worsening psychiatric outcomes. This article was especially important because it helps explain the biological and clinical mechanisms through which cannabis may contribute to psychosis and schizophrenia-spectrum disorders in vulnerable individuals. Additionally, the study highlighted that there was limited evidence that cannabidiol (CBD) consistently reduces THC-induced psychiatric symptoms. I selected this article because it provides strong evidence that THC-containing cannabis products can acutely induce psychotic symptoms and worsen psychiatric disease burden, closely aligning with my clinical scenario involving a young male patient with schizophrenia and severe cannabis-associated paranoia and psychosis.

4. Robinson, T., Ali, M. U., Easterbrook, B., Hall, W., Jutras-Aswad, D., & Fischer, B. (2022). *Risk-thresholds for the association between frequency of cannabis use and the development of psychosis: A systematic review and meta-analysis*. Psychological Medicine, 53(9), 3858–3868. https://doi.org/10.1017/S0033291722000502

Abstract

Background: Epidemiological studies show a dose-response association between cannabis use and the risk of psychosis. This review aimed to determine whether there are identifiable risk-thresholds between the frequency of cannabis use and psychosis development.

Methods: Systematic search of Embase, MEDLINE, PsycINFO, CINAHL, and Web of Science for relevant studies (1 January 2010-26 April 2021). Case-control or cohort studies that investigated the relationship between cannabis use and the risk of psychosis development that reported effect estimates [odds ratios (OR), hazard ratios (HR), risk ratios (RR)] or the raw data to calculate them, with information on the frequency of cannabis consumption were included. Effect estimates were extracted from individual studies and converted to RR. Two-stage dose-response multivariable meta-analytic models were utilized and sensitivity analyses conducted. The Newcastle Ottawa Scale was used to assess the risk of bias of included studies.

Results: Ten original (three cohorts, seven case-control) studies were included, including 7390 participants with an age range of 12-65 years. Random-effect model meta-analyses showed a significant log-linear dose-response association between cannabis use frequency and psychosis development. A restricted cubic-splines model provided the best fit for the data, with the risk of psychosis significantly increasing for weekly or more frequent cannabis use [RR = 1.01, 95% confidence interval (CI) 0.93-1.11 yearly; RR = 1.10, 95% CI 0.97-1.25 monthly; RR = 1.35, 95% CI 1.19-1.52 weekly; RR = 1.76, 95% CI 1.47-2.12 daily].

Conclusion: Individuals using cannabis frequently are at increased risk of psychosis, with no significant risk associated with less frequent use. Public health prevention messages should convey these risk-thresholds, which should be refined through further work.

Why did i select this article I selected this article because it is a high-quality systematic review and meta-analysis that directly answers my PICO question by examining the relationship between cannabis use frequency and the development of psychosis in adolescents and young adults. Unlike broader studies

that only compare “users vs non-users,” this article is especially valuable because it identifies a clear **dose-response relationship**, showing that the risk of psychosis increases as cannabis use becomes more frequent. This is highly relevant to my clinical case of a young male with chronic, daily cannabis use and worsening schizophrenia-spectrum symptoms. The study is strong because it includes both cohort and case-control studies and uses a large pooled sample size, improving the reliability of its findings. It demonstrates that **weekly and daily cannabis use significantly increases psychosis risk**, with daily use showing the highest risk (RR 1.76), while infrequent use shows minimal or no significant increase in risk. This directly supports my PICO comparison between chronic cannabis use and little or no use. I chose this article because it provides clear, clinically meaningful risk thresholds that help translate research into practice. It strengthens the argument that frequent cannabis use is not just associated with psychosis, but that there is a measurable increase in risk based on use patterns. This is important for counseling patients, especially adolescents and young adults, on the psychiatric risks of regular cannabis use and its role in worsening or precipitating schizophrenia-spectrum disorders.

Clinical bottom line

Current high-quality evidence from systematic reviews, meta-analyses, and cohort studies demonstrates that chronic cannabis use, particularly frequent or high-potency THC exposure, is associated with an increased risk of psychosis onset and worsening schizophrenia-spectrum disorders in adolescent and young adult males. Cannabis use is consistently linked to earlier onset of psychosis, more severe positive symptoms (such as paranoia and hallucinations), and greater overall psychiatric disease burden in both first-episode and established schizophrenia. A key finding from dose-response meta-analyses is a clear frequency-dependent risk. Infrequent cannabis use shows little to no significant increase in psychosis risk, while weekly use is associated with a moderate increase and daily use confers the highest risk, supporting a threshold effect for clinically meaningful exposure. Evidence also shows that cannabis-induced psychosis carries a substantial risk of transition to schizophrenia, highlighting its role in long-term disease progression. Experimental studies further support biological plausibility by demonstrating that THC can acutely induce psychotic symptoms in healthy individuals. Overall, the evidence supports a strong, dose-dependent association between cannabis use and schizophrenia-spectrum disorders, particularly in young males during neurodevelopmental vulnerability periods. While confounding factors limit definitive causal inference, cannabis remains a significant modifiable risk factor. Clinically, this underscores the importance of routine screening, patient education on dose-related risk, and counseling for cessation in individuals at risk for psychosis.