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REVIEW ARTICLE

Impact of Substance-Induced Psychosis on Adolescents

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ABSTRACT: Cannabis exposure during adolescence, the critical period of neurodevelopment, causes profound and often permanent neurobiological changes with negative long-term implications. These include reduced educational attainment, depression, anhedonia, anxiety, impulsive behavior, and problems with memory and attention. This review explores the effect of substance-induced psychosis (SIP) on adolescents, in particular adolescent cannabis users, who have an 8-fold higher incidence of psychosis than non-users, a vulnerability not seen in adults. Cannabis' influence on the endocannabinoid system (ECS) is of key importance for adolescents as CB1 receptor expression peaks between ages 14-17, increasing the tetrahydrocannabinol (THC) induced disruption of the endocannabinoid system. This has a profound effect on synaptic pruning and global excitation-inhibition balance, directly impacting brain development, in particular, dopaminergic systems. SIP remains challenging to diagnose due to overlap with other psychotic disorders, and misdiagnosis is common, with 25% of people diagnosed with PPD in emergency departments having SIP. Both SIP and schizophrenia's symptoms include ideas of reference, persecutory delusions, and auditory hallucinations. Positive and negative psychotic symptoms caused by persistent cannabis use disorders increase in severity over time. Cannabis users exhibit poorer symptomatic outcomes than those who use other illicit substances. They have an earlier age of onset of psychosis and poorer social functioning than alcohol misusers. Cannabis induced psychotic disorders have a higher risk of conversion to schizophrenia than alcohol induced psychosis. Meta-analysis reveals that cannabis-induced psychosis (CIP) had the highest rate of progression to schizophrenia (34%) than all other substances, while alcohol had the lowest (9%).[1] Cognitive behavioral therapy (CBT), motivational interviewing (MI), contingency management (CM), rewards programs, and familial involvement are effective when treating adolescents with cannabis use disorders. The Adolescent Community Reinforcement Approach (A-CRA) is also an effective treatment for cannabis abstinence. Recreational Cannabis use (CU) in adolescents could be reduced by banning cannabis marketing, limiting retail expansion, and increasing its price and legal age of purchase. Adolescents can access support through rehabilitation centers offering cannabis detoxification and non-pharmacological treatments. Given the impact on neurodevelopment and high psychosis conversion rates, protecting adolescents from CU during this critical developmental window represents a public health priority.

KEYWORDS: Translation Medical Sciences, Disease Detection and Diagnosis, Psychiatry, Substance Use.

Introduction

292 million people worldwide used illicit drugs in 2022, which has risen by 20% since 2012. Cannabis remains the most widely used drug across all ages, making up 78% of global illicit drug use, with 228 million users in 2022.[1,2] While cannabis usage rates appear stable in American adolescents (25.8% in 12th graders in 2024,[3] tetrahydrocannabinol (THC) potency has increased from 4% in 1995 to 15-20% today,[4] increasing the exposure for adolescents. Additionally, recreational cannabis use is now legalized in multiple areas, including Canada, Uruguay, and 27 jurisdictions in the US.[2] Daily cannabis users are now more common in the USA than daily alcohol users, and while the median drinker uses alcohol on 4-5 days per month, the median cannabis consumer uses the drug on 15-16 days per month.[5]

This widespread use is of particular concern for adolescents, who face unique neurodevelopmental vulnerabilities during a critical period of brain maturation. Illicit substance use may have longitudinal effects, including psychosis, defined as the presence of delusions, which are fixed false beliefs, and[6] hallucinations, which are sensory perceptions that occur in the absence of an actual external stimulus.[7] Substance-induced psychosis (SIP) is when substances such as cannabis, stimulants, or alcohol contribute to the onset of these psychotic symptoms.[7]

Cannabis intoxication behaves in a dose-responsive manner, meaning greater consumption results in greater intoxication and the potential for greater long-term side effects.[8] As shown in Figure 1, earlier initiation of cannabis is linked to a greater likelihood of developing psychosis; the cumulative incidence of psychotic disorders was eight times higher among adolescents who used cannabis than those who had not. Comparatively, Figure 1 displays a smaller difference in cumulative psychotic disorder incidence between young adults who had used cannabis and those who did not.[9] This age-dependent vulnerability demonstrates the significance of focusing on the adolescent demographic, as CU during this time period is a far stronger predictor of psychotic disorders for them than for adults. Early diagnosis and intervention are necessary to prevent disruption of the endocannabinoid system and subsequent long-term cognitive symptoms and psychiatric disease.

Cannabis use, however, is not the sole cause of SIP, as substances like alcohol and psychostimulants can also cause this. Social impacts of SIP include reduced educational attainment and employment acquisition. This review article analyzes the

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current academic literature on SIP, the biological influences on the brain, and long-term social implications with a particular focus on CU. In addition, this article provides a critical analysis of the current difficulties in the field of diagnosing SIP, the impacts of different substances on SIP severity, and treatment and intervention.

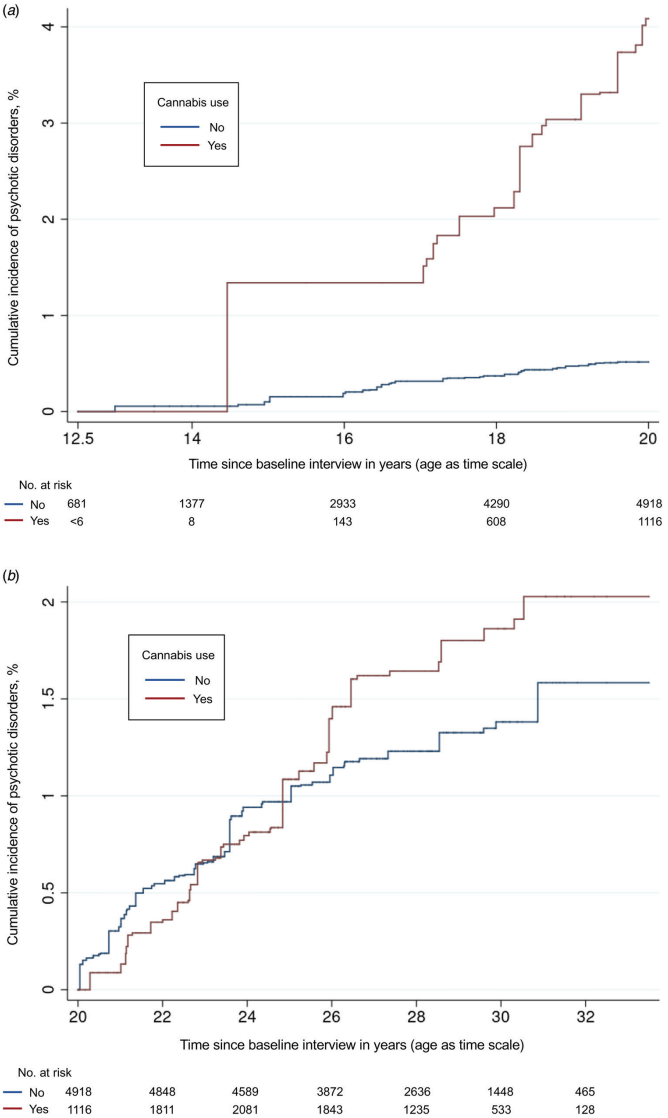

Figure 1: Comparative longitudinal study displaying that CU at adolescence is associated with a greater risk of developing psychotic disorders.[9] 15–20-year-olds using cannabis were associated with increased cumulative psychotic incidence than those not using it. This difference was less significant in 20–32-year-olds.

Biological Influences of THC on the Adolescent Brain:

To understand why adolescents show this increased vulnerability to psychosis, we must understand the normal function of the endocannabinoid system (ECS) and how THC disrupts this. The ECS plays a key role in memory, learning, reward, and pain pathways in the brain and consists of cannabinoid receptors and endocannabinoids (eCBs). There are two subtypes of cannabinoid receptors known as cannabinoid receptor type 1 (CB1R) and cannabinoid receptor type 2 (CB2R). CB1Rs are the most abundant G-protein-coupled receptors in the brain, with their highest density found in the hippocampus, basal ganglia, cerebellum, and neocortex.[10] Their expression peaks between ages 14-17, an age also associated with intensive synaptic pruning, a key neurodevelopmental process which removes weak synaptic connections. This "use it or lose it" process peaks between 16 and 20, especially in prefrontal brain regions associated with executive function and emotional regulation, which show up to a 40% reduction in synaptic density. THC exposure during this period leads to excessive pruning via overactivation of the ECS, potentially explaining the long-term cognitive effects of adolescent CU.[11]

The main role of the ECS is the regulation of neurotransmission via retrograde transmission at the synapse; this function is impaired by THC exposure. Figure 2 shows how, in normal ECS functioning, eCBs regulate the release of GABA and glutamate neurotransmitters, fine-tuning the activity of their synapses and consequently the balance of excitation and inhibition within the brain. Figure 3 shows how THC acts as a partial agonist of CB1R, subsequently leading to chronic downregulation of CB1R and significant disruption to the ECS.[12] This disruption reduces sensitivity to stress and reward[13], and also the release of GABA and glutamate. Glutamate is an excitatory neurotransmitter, meaning it makes neurons more likely to fire. GABA is an inhibitory neurotransmitter, meaning it causes neurons to be less likely to fire. Overstimulation of the ECS by THC creates an imbalance of excitatory-inhibitory neurotransmission in the brain by reducing inhibition more than excitation.[12]

Rodent studies have shown that this excitatory-inhibitory imbalance increases psychosis-like behaviours.[12] As shown in Table 1, CU in adolescence has numerous neurological effects. Reduced GABA release due to THC disinhibits dopaminergic neurons, as the neurons that would normally suppress their activity become less active. This reduces the amount of cortisol released in response to tension, which heightens feelings of bliss.[13] The disruption of these dopamine pathways (Figure 4) increases susceptibility to addiction and psychosis.[12] Early exposure to THC in adolescence results in a reduced release of dopamine in adulthood in response to stress and psychostimulants[14], showing the lifelong impact on brain function, CU in adolescence can cause this. Crucially, while the ECS normally functions at a synapse level over a timeframe of minutes, THC activates the ECS across the whole brain for hours at a time, preventing it from performing its normal role.

Table 1: Summary of the impact of adolescent THC exposure. Various neurotransmitter systems are affected during THC exposure, which increases the risk of psychosis.

Neurotransmitter	Consequences of adolescent THC exposure
Glutamate (excitatory)	Reduced executive function and increased risk of psychosis.
GABA (inhibitory)	Anxiety
Dopamine	Decreased cortisol, heightened feelings of bliss, increased susceptibility to addiction and psychosis
Endocannabinoids	Reduced sensitivity to stress and reward

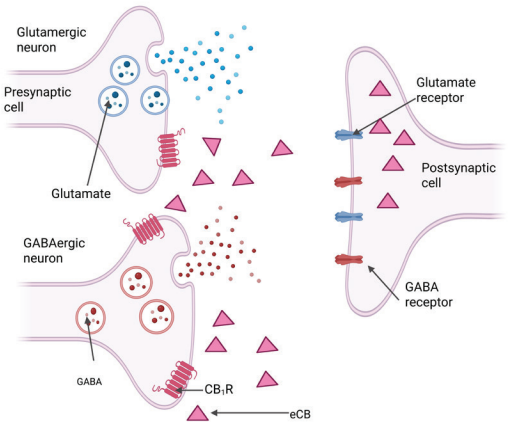

Figure 2: Normal Synaptic Transmission.[12] In the absence of cannabis, normal functioning of the ECS occurs. eCBs regulate the release of GABA and glutamate neurotransmitters, which create an excitatory-inhibitory balance in neurotransmission.

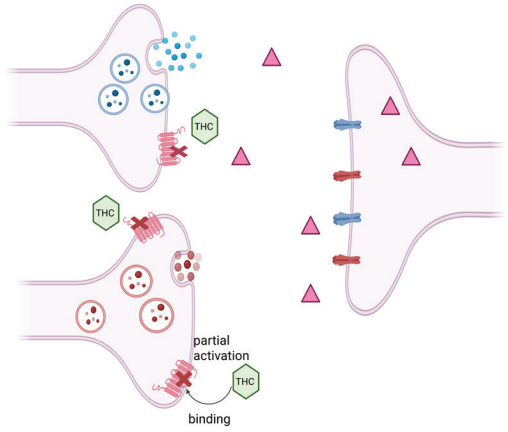

Figure 3: Effects of adolescent CU.[12] THC acts as a partial agonist of CB1R, downregulates CB1R, and reduces the release of GABA and glutamate. THC overstimulates the ECS, causing an excitatory-inhibitory imbalance.

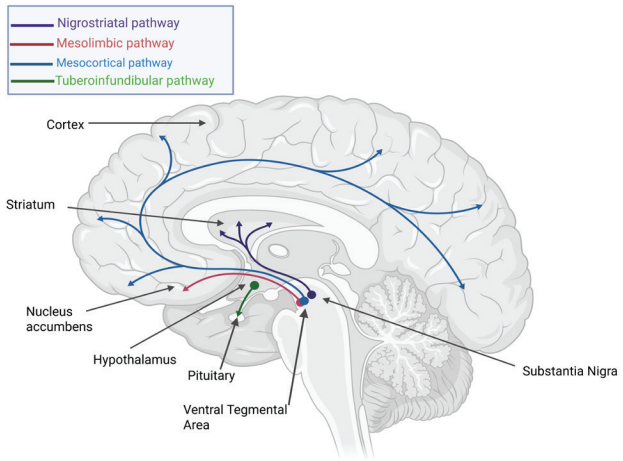

Figure 4: Dopamine pathways in the brain. THC exposure during adolescence disrupts dopamine pathways in the brain, which increases the risk of addiction and psychosis.

Long-term social implications:

Adolescent cannabis users are likely to suffer from poor cognitive function, showing problems with memory, attention, educational attainment, and,[15,16] impulsive behaviours.[15] A meta-analysis showed that CU in adolescence increased the relative risk of depression (37%), suicidal ideation (50%). In addition, the risk of suicide attempts was 3.46 times higher.[13] Regular CU in adolescence can also cause anhedonia and anxiety.[16] Persistent CU can result in increased criminal and risk-taking behaviors among adolescents.[17] Adolescents aged 14-15 display more evident increases than adults, proving that CU has a greater effect on younger demographics. However, in countries where cannabis remains illegal, this increased likelihood of criminal behavior may be due to regular users becoming connected to the illegal drug market and drug traders through their attempts to get access to cannabis. The user may then be influenced by people in the market who encourage participation in violent crimes.[17]

Studies show that CU lowers IQ and the ability for sustained focus.[18] This inhibition affects school performance and educational attainment. Adolescents who use cannabis tend to also be high-school dropouts and have lower attainment rates in their careers and education.[19] This highlights the need to reduce CU in adolescents through effective early diagnosis and intervention. The earlier the intervention, the lower the risk of experiencing significant adverse financial, health, and education outcomes.

Difficulty Diagnosing:

Given the significant neurobiological influence of CU in adolescence and its long-term social implications, accurate and early diagnosis of SIP is crucial. However, there are some limitations in diagnostic criteria and the overlap between SIP and schizophrenia, which can make diagnosis challenging. There are only minor changes between the current Diagnostic and Statistical Manual of Mental Disorders (DSM)-V criteria for SIP and the previous DSM-IV criteria for SIP. The DSM-V criteria now specify that individuals must have one or both of the following symptoms: delusions and/or hallucinations. It also now stipulates that the disturbance present in the individual must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.[7] Due to the DSM-V criteria being more recent, the literature exploring its limitations is sparse. For this article, the DSM-IV criteria will be evaluated instead, which are relevant to the DSM-V as well.

The DSM-IV requires four criteria for an SIP diagnosis, as shown in Table 2. Diagnosing SIP can be uncertain, partly due to the current discrepancies in the DSM-IV criteria.

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Table 2: DSM-IV criteria for SIP.[20] The DSM-IV criteria require clinicians to assess whether hallucinations or delusions were present near or during a period of cannabis intoxication before diagnosing SIP. An SIP diagnosis also requires symptoms to persist in the absence of delirium, and these symptoms should not be better explained by a non-substance-induced psychotic disorder.

Criterion	Description
A	Prominent hallucinations or delusions (patients must lack the insight that substances cause their hallucinations).
B	i) symptoms from criterion A occurred during or within a month of intoxication or withdrawal ii) The disturbance is not caused by using medication
C	A non-substance-induced psychotic disorder cannot better explain the disturbance. Evidence of a non-substance-induced psychosis may include symptoms which manifest before the onset of substance use (or medication use), remain for a significant amount of time after acute withdrawal or severe intoxication has stopped or having symptoms over what would be predicted given the type, amount or duration of substance use. In addition, evidence such as a history of multiple non-substance-related episodes could rule out SIP.
D	The disturbance occurs not only during delirium.

Problems with diagnostic criteria:

In criterion A, the term 'prominent' is ambiguous, as there is no description of what severity or duration of symptoms would be considered 'prominent.' Criterion A's lack of information about other psychotic symptoms, including negative symptoms and disorganized speech, is an issue, as negative symptoms are common in SIP patients.[20]

Criterion A only lists hallucinations and delusions narrows the range of symptoms present in SIP and thus fails to account for the frequent discovery of many other symptoms in SIP. Criterion B's failure to focus on the criterion of withdrawal and intoxication also causes confusion. Psychotic episodes linked to SUD are not included in the SIP criteria if there is no intoxication. This disregards tolerance that is built by persistent substance use, which means individuals have a lower likelihood of being intoxicated. All these issues contribute to the underreporting of SIP, highlighting the need for improved criteria for increased accuracy in diagnosing.[20]

In emergency departments, when there is uncertainty, psychotic disorders tend to be reported as primary psychotic disorder (PPD) rather than SIP,[21] highlighting that a large proportion of patients fail to be diagnosed with SIP at the start of hospitalization as a result of the imprecision of DSM IV. As SIP is underreported, clinicians fail to identify and treat many adolescents with SIP, which may contribute to continuing CU into adulthood due to their increased dependence. Furthermore, failure to receive treatment correlates with poorer clinical and educational outcomes as cannabis use in adolescents interferes with the ECS during peak brain maturation.

There are currently different definitions for substance-induced psychosis across DSM-V and the International Classification of Diseases (ICD). A key difference between DSM 5 and ICD 10/11 is that DSM-V requires only the presence of psychotic symptoms after substance use for diagnosis, whereas ICD 10 and ICD 11 believe the sole presence of psychotic symptoms is not enough for a diagnosis. In ICD-10 and ICD-11, the symptoms should be significantly more severe than what is expected in the intoxication or withdrawal of the particular substance and dosage used.[22] These inconsistencies across criteria may cause underdiagnosis or misdiagnosis of SIP, highlighting the need for a standardized definition.

Overlap with schizophrenia:

When diagnosing SIP, we must consider not only the diagnostic requirements but also the similarities between SIP and schizophrenia. Schizophrenia is defined as "a heritable, complex, multi-dimensional syndrome with varying degrees of psychotic, negative, cognitive, mood, and motor manifestations,"[23] specifically two or more of the following symptoms: hallucinations, disorganized speech, delusions, and grossly disorganized or catatonic behavior for at least 6 months. At least one of the symptoms present must be delusions, hallucinations, or disorganized speech.[7] Symptoms that overlap between schizophrenia and substance-induced psychosis are ideas of reference, persecutory delusions, and auditory hallucinations.[24] Cannabis-induced psychosis (CIP) and schizophrenia possess overlapping genetic risk factors,[25] so accurate diagnosis cannot be made solely by looking at the individual's genes. Heritability estimates reveal 11% of the variance in lifetime CU is explained by measured genetic variants.[26] This overlap is problematic because the similarities between schizophrenia and CIP often make a differentiated diagnosis difficult. Individuals with schizophrenia may use illicit substances as well, thus further blurring the lines between schizophrenia and CIP.

Studies show that in emergency departments, 25% of people diagnosed with PPD had substance-induced psychosis.[21] The dangers of misdiagnosing SIP as PPD include the added burden of stigma, a low chance of clinicians correcting the diagnosis in the future,[21] with only 15% of misdiagnoses corrected within 6 months,[27] unmerited hospitalizations, and incorrect medication being prescribed. The misdiagnosis can lead to the use of antipsychotic medication and increase the risk of developing side effects like tardive dyskinesia, neuroleptic malignant syndrome, and diabetes.[21]

Treatments for adolescents with SIP, who are incorrectly diagnosed with schizophrenia, would focus on alleviating psychotic symptoms rather than specific treatments that address the root cause of their psychosis, that is, their substance use. Ineffective treatments stemming from an inaccurate diagnosis are particularly harmful for adolescents whose positive life outcomes depend on early detection and treatment. To maximise treatment impacts, it is important to identify the drug of choice. Common culprits of SIP are cannabis, alcohol, and psychostimulants, especially as these substances are known to impair critical neurological developments occurring during adolescence. The specific psychotic trajectories of CU, psychostimulants, and alcohol can also be compared to gain a better understanding of their impact and treatment.

Comparison with other illicit substances:

Persistent cannabis use disorder (CUD) is correlated with positive and negative symptoms, which worsen over time. CUD is the only substance use disorder in which symptomatic and functional decline occurs from year 1 to year 2 in a 2-year follow-up, compared with alcohol use disorder (AUD)

and psychostimulant use disorder. Even cannabis users who comply with medication have a greater likelihood of having a poor symptomatic outcome than other substance misusers. Continuing to use cannabis after the development of first-episode psychosis (FEP) can cause symptom levels to increase. In addition, there is a dose-dependent relation between psychotic symptoms and CU, meaning that the greater the amount consumed, the more severe the psychotic symptoms will be. The gradual decline in the condition of cannabis misusers may stem from intense, persistent CU and low compliance with medication at the beginning of the psychotic disorder.[8] This worsening trajectory highlights the significance of early interventions for cannabis users.

Psychostimulants can also induce SIP, and their addictive properties may make cessation difficult. In the prospective longitudinal cohort study by Plamondon, there was a higher rate of addiction in the 24th month among cocaine and amphetamine users when compared to cannabis and alcohol users. These findings indicate that stopping psychostimulant use may be more challenging than cessation of alcohol or cannabis. In this study, participation selection bias was reduced as it ensured that all consenting and qualified individuals within established catchment areas were able to take part. However, a limitation of this study is that it did not possess objective methods of assessing substance use, such as urine tests.[8]

Psychostimulant misusers with FEP tend to have higher rates of unemployment than FEP patients who use cannabis.[8] It is clear that psychostimulants have harmful effects on individuals and should receive intervention as early as possible. The impact of stimulant use on psychotic symptoms was less dose-dependent than cannabis, and it possessed differing trajectories for occasional and persistent use. Even though both cannabis and stimulant use affect dopaminergic transmission, which dysregulates and influences psychotic symptoms and psychotic relapse, CU appears to be involved to a lesser degree than stimulant use. Due to the direct effect on dopaminergic transmission, even the occasional use of stimulants is enough to aggravate the psychotic symptoms and psychotic relapse. The severity of psychotic symptoms achieved by occasional use of psychostimulants can only be matched by CU if it is frequent.[28] By focusing on alcohol use in comparison to CU, we can discern that different substances have trends and trajectories and better understand the need for stricter cannabis regulation.

Alcohol vs Cannabis:

Cannabis induces over-activation of the endocannabinoid system by cannabinoid receptor type 1 agonists such as THC. Chronic over-activation of endocannabinoids during adolescence changes brain maturation and can have a lasting impact on the adult brain.[29] Alcohol consumption increases the sensitivity of the mesocorticolimbic dopamine network, which consists of the mesolimbic and mesocortical dopamine pathways in the brain. This may lead to an increase in positive symptoms.[30]

CIP and alcohol-induced psychosis display differences in clinical characteristics in adolescents. These fundamental differences underlie distinct clinical trajectories. CU is correlated with more severe positive psychotic symptoms compared to alcohol, which has a greater association with anxiety.[31] CIP displays a higher conversion rate to schizophrenia than alcohol-induced psychosis.[22,32] A Scottish register-based cohort study of 3486 patients diagnosed with SIP in Scottish hospitals found CIP had a 21.4% risk of conversion to schizophrenia compared to alcohol-induced psychotic disorders with a 10.4% risk.[33] However, the data did not contain drug screening confirmation, and the data were collected from 1997 to 2012, meaning it may not be an accurate reflection of current substance use trends and treatment approaches.

In a Finnish register-based cohort study of 18,478 SIP cases, the risk of conversion to schizophrenia was significantly higher for CIP(46%) than for alcohol-induced psychosis(5%).[34] While both studies show a higher transition rate from CIP to schizophrenia, they are retrospective and therefore are more susceptible to bias than prospective studies. In the Finnish study, only 0.7% of 18,478 cases were diagnosed with CIP compared to 85.4% diagnosed with alcohol-induced psychosis. Cannabis is illegal in both Finland and Scotland. The large difference between alcohol-induced psychosis and CIP suggests the results are confounded by underreporting out of fear of facing legal repercussions. This selection bias from illegal cannabis status would artificially inflate relative risk ratios while underestimating absolute CIP prevalence. Prospective studies with biological verification remain urgently needed.

Those who misuse alcohol have a lower risk of showing symptoms found in schizophrenia, such as paranoia, hallucinations, and negative symptoms, than cannabis-induced psychotic disorder. Cannabis misusers have an earlier age of onset of psychosis and a shorter period of experiencing illness,[35] but their symptoms deteriorate over time[8]. In contrast, alcohol misusers usually have a later age of onset with higher anxiety levels and,[31] higher hospitalization rates.[35] Despite this, they have better social functioning than cannabis users.[31] These dissimilarities highlight the importance of substance-specific approaches in the treatment and interventions of SIP in adolescents.

Treatment, Early Detection, and Intervention:

The difficulty in diagnosing CIP, along with the detrimental effects of substance use at the peak of brain maturation in adolescents, creates a call to action to reduce CUD rates. Psychological interventions combined with social interventions have shown promise for adolescents with CUDs. Adolescent CU often manifests as a social behavior encouraged by peers, and therefore, interventions such as MI, CM with rewards for not using cannabis would be effective. Combining motivational enhancement therapy (MET) and CBT with a rewards program led to longer periods of cannabis abstinence in adolescents. Familial involvement in treatments also proved beneficial for adolescents. Interventions for young adults should involve building resilience to pain, protective circles of peers, and training for better coping skills.[36]

A-CRA is another effective method for reducing CU in adolescents by providing cannabis users with problem-solving,

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communication, anger management, and relapse prevention skills through 19 procedures. An added benefit of A-CRA is that it is more cost-effective than CBT and MET.[37] In addition, having brief check-up sessions improved abstinence rates, highlighting the importance of follow-up meetings over many years. Clinicians should design interventions so that they capture the interest of the age group they are targeting. For example, using computerized or mobile programs appeals to young adults to strengthen motivation and allow self-monitoring.[36] CUD interventions should be designed and selected for each demographic to address the different challenges each age group faces when attempting abstinence.

When considering pharmacological interventions, there are no FDA-approved medications for CUD, and off-label psychotropic medications have had minimal benefits, such as mitigating withdrawal symptoms. However, medications to ease prolonged withdrawal symptoms when utilized in combination with counselling and social support have proved to be beneficial.[36] Furthermore, early detections and interventions are extremely beneficial for adolescents as this improves clinical and functional outcomes.

Prevention – Canada and solutions:

There are solutions to the problem of increasing CUDs that do not involve banning cannabis entirely. Cannabis-related ED visits declined in Canada following the legalization of recreational cannabis with tight retail regulations. However, it increased at the time of cannabis commercialisation.[38] This suggests that to minimize the increase in cannabis use following the legalization, cannabis marketing should be banned, and the expansion of retail stores selling cannabis should be prevented.

Additionally, increasing the price of cannabis could deter people from purchasing cannabis regularly, which reduces its accessibility by making it unaffordable for many. Studies have proved this by the high tax on cigarettes, which serves to decrease cigarette purchases and use. Adolescents are two to three times more reactive to changes in the pricing of cigarettes than the overall population.[39] This suggests that raising the price of illicit substances has the most significant impact on adolescents, as they are likely to have low-paid or part-time jobs. In Canada, the legal age for purchasing cannabis is 18; therefore by raising the legal age to 21, will prevent many adolescents from being able to purchase cannabis. By increasing the age of initiation of cannabis, neurological developments will not be affected as much, which could improve educational outcomes for many adolescents.

Support for Adolescents with CUD:

Adolescents struggling with drug addiction can get help through rehabilitation centers. There is a range of different rehabilitation centers, each targeted at dealing with a specific substance. These rehabilitation centers could create a sheltered, supportive environment in which adolescents with CUDs undergo a cannabis "detox" while participating in counselling, yoga, and meditation. A recent study from Andra Pradesh has displayed an increase in cognitive function among young adults with CUDs after they participated in non-pharmacological rehabilitation such as meditation, group counselling, physical activities, and yoga during periods of cannabis abstinence.[40]

Online programs targeting CUDs are increasingly present in Austria, Belgium, the Czech Republic, Spain, the UK, Sweden, Germany, the Netherlands, and Estonia. Examples of these programs include VALIC, CANreduce, and SIBRT. In addition, Belgium, Romania, and the UK now have cannabis-specific clinics which offer clinical assessments, detoxification, short-term and long-term rehabilitation to improve treatment outcomes such as cannabis abstinence and increase the likelihood of psychosis remission. They also aim to lower levels of CU and increase contentment with life. However, there are few cannabis-specific clinics targeted at adolescents, and in-person clinics have limited coverage as they only offer face-to-face treatments in some cities.[41]

Barriers that prevent participation in treatments for CUDs include fear of stigma, believing these treatments are not needed, feeling unmotivated to attempt abstinence, and poor mental health. Other reported barriers include finding it hard to admit they need support, limited treatment availability, worries about confidentiality, cynicism about the treatment's effectiveness, and a desire to be self-sufficient.[42] To further support adolescents, we must encourage them to seek help for their CU. By displaying posters with contact information for rehabilitation programs in public places that adolescents frequent, such as schools, gyms, and shopping centers, we can ensure that they know help is available. Individual schools should ensure that students struggling with drug addiction have a non-judgmental, trusted adult they can look to for support, such as a guidance counsellor. Increasing the support available for substance use in primary care settings would allow for earlier detection and interventions.[43]

■ Discussion

This review has demonstrated the mechanistic pathways linking adolescent CU to psychosis, with 25-46%[1] of patients with SIP from cannabis showing conversion to schizophrenia, far over other substances. While previous work has focused on adult populations, this review explains some of the unique vulnerabilities in adolescents that heighten their risk in a manner qualitatively different from adults. The significant biological influence of adolescent CU on the brain through the binding of THC to CB1Rs in the ECS. This binding dysregulates neurotransmission and lowers stress and reward sensitivity. Because CB1R expression peaks during adolescence, THC has a greater impact on adolescents than on other age groups. Specifically, THC lowers eCB levels in the ECS and reduces the release of GABA and glutamate, creating an excitatory-inhibitory imbalance which increases the risk of developing psychosis. Dopamine pathways are also disrupted, increasing vulnerability to addiction. These effects have long-term ramifications, including poorer cognitive function, educational attainment, and increased risk of depression, which can negatively impact the life outcomes of adolescent cannabis users.

The DSM-IV criteria have limitations that make diagnosing CIP challenging. Its limitations include its dismissal of psychotic symptoms when the individual has insight and a lack of information about negative symptoms, withdrawal, and intoxication. SIP has overlapping symptoms with schizophrenia, such as ideas of reference, persecutory delusions, and auditory hallucinations. These facts make it difficult to differentiate between the disorders and provide accurate diagnoses.

By comparison with alcohol, this review identifies that CU has a more detrimental effect on clinical and functional outcomes, while alcohol use has a clearer link to anxiety. Psychotic symptoms associated with CUD get worse over time, and CUD had the greatest severity of positive symptoms, while AUD had the least. Cannabis users tended to have an earlier age of onset of psychosis than alcohol users, although they experienced shorter periods of illness and fewer hospitalisations. CIP was more likely to convert to schizophrenia than alcohol induced psychosis. Despite these findings from Finnish and Scottish cohort studies being significant, the studies are retrospective, so the data is more vulnerable to bias than if they were prospective. The studies found many fewer CIP than alcohol-induced psychosis diagnoses, which may be due to underreporting out of fear of legal repercussions, as cannabis is illegal in both countries. Different substances have different trends and trajectories. Cannabis users have a poorer symptomatic outcome than other substance users, although psychostimulant use has lower rates of abstinence than cannabis. However, the study that identified this finding is limited by its lack of objective methods to measure substance use. Cannabis users' exacerbation of psychotic symptoms over time can be attributed to persistent, severe CU and non-compliance with medication at the start of psychosis.

Different demographics benefit from different treatments and interventions to promote abstinence from cannabis use. Off-label psychotropic medications do not have significant benefits, and there is no FDA-approved medication for CUD. A combination of MET, CBT, and a rewards program, as well as familial involvement in treatment, proved to be most effective for adolescents. Computerized programs that allow self-monitoring also appealed to this group. Abstinence rates improved when follow-up check-up sessions were incorporated into treatment. The legalisation of cannabis in Canada with tight regulations was not associated with large increases in CU, yet cannabis commercialisation was. Increasing the legal age of cannabis purchase from 18 to 21 in Canada would reduce the number of adolescents who use cannabis and increase the age of initiation for many.

This review has numerous limitations that should be acknowledged. Firstly, the rapidly evolving landscape of cannabis product development and its use and regulation creates a moving target. Studies performed on adolescent CU even 5-10 years ago may have limited relevance to an adolescent population now using cannabis concentrates of 60-90% THC. Geographical variation in legality and regulation also creates different exposure contexts that may not be comparable. Studies linking substance use to psychosis have mostly focused on adult populations who have differing neurobiology from adolescents, meaning findings may not be directly applicable. The heterogeneity of cannabis products encompassing diverse cannabinoid compounds, consumption methods, and usage habits complicates the interpretation of studies that typically specify cannabis use only. Finally, the absence (for ethical reasons) of any causal studies or trials of CU makes untangling premorbid vulnerability from the effects of cannabis difficult. In addition, cannabis users often use other psychoactive drugs, which analysts struggle to control for. Future research utilizing techniques such as Mendelian randomization may overcome some of these causal limitations, though it should also be noted that the Bradford Hill criteria for causation are largely met.

Conclusion

Adolescent CU has significant neurobiological effects, causing long-term social implications and increased risk of psychosis. By focusing on early detection and intervention, clinical and functional outcomes can be significantly improved. CB1R expression peaks in adolescence, making CU during this period particularly harmful, partly due to excessive synaptic pruning as well as negative cognitive effects that persist into adulthood.

Many critical research questions are outstanding, ranging from causality to biomarker development to the lack of specific treatment offered to affected adolescents. The unique vulnerability of adolescents to the increased potency of THC and the trend towards reduced regulation of their sale to adolescents represents a potential health crisis. Immediate action through information campaigns, adolescent access restriction, and investment in treatment infrastructure and research should be prioritized.

Future research should aim to perform longitudinal studies on the treatment outcomes of adolescents with CIP to identify interventions to maintain long-term cannabis abstinence. In addition, there should be more cannabis-specific rehabilitation clinics tailored to the adolescent population. Countries offering face-to-face support should increase their national coverage to maximise their impact on adolescents by making treatment easily accessible. Policymakers should aim to regulate CU by limiting retail expansion of recreational cannabis, banning cannabis marketing, raising the legal age of purchase, and increasing its price in countries where it is legal.

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References

1. Murrie, B.; Lappin, J.; Large, M.; Sara, G. Transition of Substance-Induced, Brief, and Atypical Psychoses to Schizophrenia: A Systematic Review and Meta-Analysis. *Schizophr. Bull.* **2020**, *46* (3), 505–516. https://doi.org/10.1093/schbul/sbz102.
2. *UNODC World Drug Report 2024: Harms of world drug problem continue to mount amid expansions in drug use and markets*. United Nations : Information Service Vienna. https://unis.unvienna.org/unis/en/pressrels/2024/uniscp1177.html (accessed 2025-01-25).

DOI: 10.36838/v7i10.99

3. *Reported use of most drugs among adolescents remained low in 2024.* National Institutes of Health (NIH). https://www.nih.gov/news-events/news-releases/reported-use-most-drugs-among-adolescents-remained-low-2024 (accessed 2025-06-02).
4. Abuse, N. I. on D. *Cannabis Potency Data | National Institute on Drug Abuse (NIDA)*. https://nida.nih.gov/research/research-data-measures-resources/cannabis-potency-data (accessed 2025-06-02).
5. Caulkins, J. P. Changes in Self-Reported Cannabis Use in the United States from 1979 to 2022. *Addiction* **2024**, *119* (9), 1648–1652. https://doi.org/10.1111/add.16519.
6. Kapur, S. Psychosis as a State of Aberrant Salience: A Framework Linking Biology, Phenomenology, and Pharmacology in Schizophrenia. *Am. J. Psychiatry* **2003**, *160* (1), 13–23. https://doi.org/10.1176/appi.ajp.160.1.13.
7. Glasheen, C.; Batts, K.; Karg, R.; Hunter, D. Impact of the DSM-IV to DSM-5 Changes on the National Survey on Drug Use and Health.
8. Ouellet-Plamondon, C.; Abdel-Baki, A.; Salvat, É.; Potvin, S. Specific Impact of Stimulant, Alcohol and Cannabis Use Disorders on First-Episode Psychosis: 2-Year Functional and Symptomatic Outcomes. *Psychol. Med.* **2017**, *47* (14), 2461–2471. https://doi.org/10.1017/S0033291717000976.
9. McDonald, A. J.; Kurdyak, P.; Rehm, J.; Roerecke, M.; Bondy, S. J. Age-Dependent Association of Cannabis Use with Risk of Psychotic Disorder. *Psychol. Med*. **2024**, *54* (11), 2926–2936. https://doi.org/10.1017/S0033291724000990.
10. Zhang, M.; Chen, T.; Lu, X.; Lan, X.; Chen, Z.; Lu, S. G Protein-Coupled Receptors (GPCRs): Advances in Structures, Mechanisms and Drug Discovery. *Signal Transduct. Target. Ther*. **2024**, *9* (1), 88. https://doi.org/10.1038/s41392-024-01803-6.
11. Germann, M.; Brederoo, S. G.; Sommer, I. E. C. Abnormal Synaptic Pruning during Adolescence Underlying the Development of Psychotic Disorders. *Curr. Opin. Psychiatry* **2021**, *34* (3), 222–227. https://doi.org/10.1097/YCO.0000000000000696.
12. Bara, A.; Ferland, J.-M. N.; Rompala, G.; Szutorisz, H.; Hurd, Y. L. Cannabis and Synaptic Reprogramming of the Developing Brain. *Nat. Rev. Neurosci.* **2021**, *22* (7), 423–438. https://doi.org/10.1038/s41583-021-00465-5.
13. Fischer, A. S.; Tapert, S. F.; Lee Louie, D.; Schatzberg, A. F.; Singh, M. K. Cannabis and the Developing Adolescent Brain. *Curr. Treat. Options Psychiatry* **2020**, *7* (2), 144–161. https://doi.org/10.1007/s40501-020-00202-2.
14. Bloomfield, M. A. P.; Ashok, A. H.; Volkow, N. D.; Howes, O. D. The Effects of Δ9-Tetrahydrocannabinol on the Dopamine System. *Nature* **2016**, *539* (7629), 369–377. https://doi.org/10.1038/nature20153.
15. Lorenzetti, V.; Alonso-Lana, S.; Youssef, G.; Verdejo-Garcia, A.; Suo, C.; Cousijn, J.; Takagi, M.; Yücel, M.; Solowij, N. Adolescent Cannabis Use: What Is the Evidence for Functional Brain Alteration? *Curr. Pharm. Des.* **2017**, *22* (42), 6353–6365. https://doi.org/10.2174/1381612822666160805155922.
16. Bloomfield, M. A. P.; Hindocha, C.; Green, S. F.; Wall, M. B.; Lees, R.; Petrilli, K.; Costello, H.; Ogunbiyi, M. O.; Bossong, M. G.; Freeman, T. P. The Neuropsychopharmacology of Cannabis: A Review of Human Imaging Studies. *Pharmacol. Ther.* **2019**, *195*, 132–161. https://doi.org/10.1016/j.pharmthera.2018.10.006.
17. Fergusson, D. M.; Horwood, L. J.; Swain-Campbell, N. Cannabis Use and Psychosocial Adjustment in Adolescence and Young Adulthood. *Addiction* **2002**, *97* (9), 1123–1135. https://doi.org/10.1046/j.1360-0443.2002.00103.x.
18. Trezza, V.; Cuomo, V.; Vanderschuren, L. J. M. J. Cannabis and the Developing Brain: Insights from Behavior. *Eur. J. Pharmacol.* **2008**, *585* (2–3), 441–452. https://doi.org/10.1016/j.ejphar.2008.01.058.
19. Volkow, N. D.; Baler, R. D.; Compton, W. M.; Weiss, S. R. B. Adverse Health Effects of Marijuana Use. *N. Engl. J. Med.* **2014**, *370* (23), 2219–2227. https://doi.org/10.1056/NEJMra1402309.
20. Mathias, S.; Lubman, D. I.; Hides, L. Substance-Induced Psychosis: A Diagnostic Conundrum. *J. Clin. Psychiatry* **2008**, *69* (3), 358–367. https://doi.org/10.4088/JCP.v69n0304.
21. Schanzer, B. M.; First, M. B.; Dominguez, B.; Hasin, D. S.; Caton, C. L. M. Diagnosing Psychotic Disorders in the Emergency Department in the Context of Substance Use. *Psychiatr. Serv.* **2006**, *57* (10), 1468–1473. https://doi.org/10.1176/ps.2006.57.10.1468.
22. Tandon, R.; Shariff, S. M. Substance-Induced Psychotic Disorders and Schizophrenia: Pathophysiological Insights and Clinical Implications. *Am. J. Psychiatry* **2019**, *176* (9), 683–684. https://doi.org/10.1176/appi.ajp.2019.19070734.
23. Tandon, R.; Nasrallah, H.; Akbarian, S.; Carpenter, W. T.; DeLisi, L. E.; Gaebel, W.; Green, M. F.; Gur, R. E.; Heckers, S.; Kane, J. M.; Malaspina, D.; Meyer-Lindenberg, A.; Murray, R.; Owen, M.; Smoller, J. W.; Yassin, W.; Keshavan, M. The Schizophrenia Syndrome, circa 2024: What We Know and How That Informs Its Nature. *Schizophr. Res.* **2024**, *264*, 1–28. https://doi.org/10.1016/j.schres.2023.11.015.
24. Dawe, S.; Geppert, L.; Occhipinti, S.; Kingswell, W. A Comparison of the Symptoms and Short-Term Clinical Course in Inpatients with Substance-Induced Psychosis and Primary Psychosis. *J. Subst. Abuse Treat*. **2011**, *40* (1), 95–101. https://doi.org/10.1016/j.jsat.2010.08.002.
25. Keramatian, K.; Levit, A. Caring for Youth with Co-Occurring Substance Use and Severe Psychiatric Disorders: Diagnostic Challenges and Clinical Implications. *J. Can. Acad. Child Adolesc. Psychiatry* **2023**, *32* (3), 202–208.
26. Pasman, J. A.; Verweij, K. J. H.; Gerring, Z.; Stringer, S.; Sanchez-Roige, S.; Treur, J. L.; Abdellaoui, A.; Nivard, M. G.; Baselmans, B. M. L.; Ong, J.-S.; Ip, H. F.; van der Zee, M. D.; Bartels, M.; Day, F. R.; Fontanillas, P.; Elson, S. L.; de Wit, H.; Davis, L. K.; MacKillop, J.; Derringer, J. L.; Branje, S. J. T.; Hartman, C. A.; Heath, A. C.; van Lier, P. A. C.; Madden, P. A. F.; Mägi, R.; Meeus, W.; Montgomery, G. W.; Oldehinkel, A. J.; Pausova, Z.; Ramos-Quiroga, J. A.; Paus, T.; Ribases, M.; Kaprio, J.; Boks, M. P. M.; Bell, J. T.; Spector, T. D.; Gelernter, J.; Boomsma, D. I.; Martin, N. G.; MacGregor, S.; Perry, J. R. B.; Palmer, A. A.; Posthuma, D.; Munafò, M. R.; Gillespie, N. A.; Derks, E. M.; Vink, J. M. GWAS of Lifetime Cannabis Use Reveals New Risk Loci, Genetic Overlap with Psychiatric Traits, and a Causal Influence of Schizophrenia. *Nat. Neurosci.* **2018**, *21* (9), 1161–1170. https://doi.org/10.1038/s41593-018-0206-1.
27. Caton, C. L. M.; Hasin, D. S.; Shrout, P. E.; Drake, R. E.; Domínguez, B.; First, M. B.; Samet, S.; Schanzer, B. Stability of Early-Phase Primary Psychotic Disorders with Concurrent Substance Use and Substance-Induced Psychosis. *Br. J. Psychiatry* **2007**, *190* (2), 105–111. https://doi.org/10.1192/bjp.bp.105.015784.
28. Kreis, I.; Lagerberg, T. V.; Wold, K. F.; Åsbø, G.; Simonsen, C.; Flaaten, C. B.; Engen, M. J.; Lyngstad, S. H.; Widing, L. H.; Ueland, T.; Melle, I. Behind the Heterogeneity in the Long-Term Course of First-Episode Psychosis: Different Psychotic Symptom Trajectories Are Associated with Different Patterns of Cannabis and Stimulant Use. *Schizophr. Res*. **2024**, *271*, 91–99. https://doi.org/10.1016/j.schres.2024.07.006.
29. Krebs, M.-O.; Kebir, O.; Jay, T. M. Exposure to Cannabinoids Can Lead to Persistent Cognitive and Psychiatric Disorders. *Eur. J. Pain* **2019**, *23* (7), 1225–1233. https://doi.org/10.1002/ejp.1377.

30. Kirli, U.; Binbay, T.; Alptekin, K.; Kayahan, B.; Elbi, H. The Relationship between Alcohol-Cannabis Use and Stressful Events with the Development of Incident Clinical Psychosis in a Community-Based Prospective Cohort. *Turk. J. Psychiatry* **2021**. https://doi.org/10.5080/u26410.
31. Cookey, J.; McGavin, J.; Crocker, C. E.; Matheson, K.; Stewart, S. H.; Tibbo, P. G. A Retrospective Study of the Clinical Characteristics Associated with Alcohol and Cannabis Use in Early Phase Psychosis. *Can. J. Psychiatry Rev. Can. Psychiatr.* **2020**, *65* (6), 426–435. https://doi.org/10.1177/0706743720905201.
32. Bramness, J. G.; Hjorthøj, C.; Niemelä, S.; Taipale, H.; Rognli, E. B. Discussing the Concept of Substance-Induced Psychosis (SIP). *Psychol. Med.* **2024**, *54* (11), 2852–2856. https://doi.org/10.1017/S0033291724001442.
33. Alderson, H. L.; Semple, D. M.; Blayney, C.; Queirazza, F.; Chekuri, V.; Lawrie, S. M. Risk of Transition to Schizophrenia Following First Admission with Substance-Induced Psychotic Disorder: A Population-Based Longitudinal Cohort Study. *Psychol. Med.* **2017**, *47* (14), 2548–2555. https://doi.org/10.1017/S0033291717001118.
34. Niemi-Pynttäri, J. A.; Sund, R.; Putkonen, H.; Vorma, H.; Wahlbeck, K.; Pirkola, S. P. Substance-Induced Psychoses Converting into Schizophrenia: A Register-Based Study of 18,478 Finnish Inpatient Cases. *J. Clin. Psychiatry* **2013**, *74* (1), e94-99. https://doi.org/10.4088/JCP.12m07822.
35. Di Paolo, M.; Calabrese, A.; Nosari, G.; Ciappolino, V.; Cirella, L.; Caldiroli, A.; Capuzzi, E.; Clerici, M.; Buoli, M. Clinical Variables and Peripheral Biomarkers Associated with Substance-Induced Psychotic Disorder: Differences Related to Alcohol, Cannabis, and Psychostimulant Abuse. *J. Pers. Med*. **2024**, *14* (3), 325. https://doi.org/10.3390/jpm14030325.
36. Ghafouri, M.; Correa da Costa, S.; Zare Dehnavi, A.; Gold, M. S.; Rummans, T. A. Treatments for Cannabis Use Disorder across the Lifespan: A Systematic Review. *Brain Sci.* **2024**, *14* (3), 227. https://doi.org/10.3390/brainsci14030227.
37. Mehr, N. K.; Lavasani, F. F.; Noroozi, A.; Farahani, H.; Gharraee, B. Effectiveness of the Adolescent-Community Reinforcement Approach for Treating Cannabis Use Disorder in Iranian Adolescents: A Randomized Controlled Trial. *Acta Psychol. (Amst.)* **2024**, *251*, 104604. https://doi.org/10.1016/j.actpsy.2024.104604.
38. Myran, D. T.; Pugliese, M.; Tanuseputro, P.; Cantor, N.; Rhodes, E.; Taljaard, M. The Association between Recreational Cannabis Legalization, Commercialization and Cannabis-Attributable Emergency Department Visits in Ontario, Canada: An Interrupted Time–Series Analysis. *Addiction* **2022**, *117* (7), 1952–1960. https://doi.org/10.1111/add.15834.
39. Bader, P.; Boisclair, D.; Ferrence, R. Effects of Tobacco Taxation and Pricing on Smoking Behavior in High Risk Populations: A Knowledge Synthesis. *Int. J. Environ. Res. Public. Health* **2011**, *8* (11), 4118–4139. https://doi.org/10.3390/ijerph8114118.
40. Goud, S. S.; Radhika, M. S.; Indla, V.; Kolli, N. Cannabis Use and Effect of Cannabis Abstinence on Cognitive Functioning in Young People — an Observational Case-Control Follow-up Study from Rehabilitation Centre in Andhra Pradesh. *Middle East Curr. Psychiatry* **2022**, *29* (1), 61. https://doi.org/10.1186/s43045-022-00228-7.
41. Hoch, E.; Murawski, M.; Ferri, M.; Feingold, D. Cannabis Use Disorder: An Overview of Treatment Approaches in Europe. *Eur. Arch. Psychiatry Clin. Neurosci.* **2025**, *275* (2), 315–326. https://doi.org/10.1007/s00406-025-01964-7.
42. Sherman, B. J.; McRae-Clark, A. L. Treatment of Cannabis Use Disorder: Current Science and Future Outlook. *Pharmacother. J. Hum. Pharmacol. Drug Ther.* **2016**, *36* (5), 511–535. https://doi.org/10.1002/phar.1747.
43. Ghafouri, M.; Correa da Costa, S.; Zare Dehnavi, A.; Gold, M. S.; Rummans, T. A. Treatments for Cannabis Use Disorder across the Lifespan: A Systematic Review. *Brain Sci*. **2024**, *14* (3), 227. https://doi.org/10.3390/brainsci14030227.

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