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Assessing evidence supporting cannabis harm reduction practices for adolescents at clinical high-risk for psychosis: a review and clinical implementation tool

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Review Article

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Abstract

Cannabis use is consistently associated with both increased incidence of frank psychotic disorders and acute exacerbations of psychotic symptoms in healthy individuals and people with psychosis spectrum disorders. Although there is uncertainty around causality, cannabis use may be one of a few modifiable risk factors for conversion to psychotic disorders in individuals with Clinical High Risk for Psychosis (CHR-P) syndromes, characterized by functionally impairing and distressing subthreshold psychotic symptoms. To date, few recommendations beyond abstinence to reduce adverse psychiatric events associated with cannabis use have been made. This narrative review synthesizes existing scientific literature on cannabis' acute psychotomimetic effects and epidemiological associations with psychotic disorders in both CHR-P and healthy individuals to bridge the gap between scientific knowledge and practical mental health intervention. There is compelling evidence for cannabis acutely exacerbating psychotic symptoms in CHR-P, but its impact on conversion to psychotic disorder is unclear. Current evidence supports a harm reduction approach in reducing frequency of acute psychotic-like experiences, though whether such interventions decrease CHR-P individuals' risk of conversion to psychotic disorder remains unknown. Specific recommendations include reducing frequency of use, lowering delta-9-tetrahydrocannabinol content in favor of cannabidiol-only products, avoiding products with inconsistent potency like edibles, enhancing patient-provider communication about cannabis use and psychotic-like experiences, and utilizing a collaborative and individualized therapeutic approach. Despite uncertainty surrounding cannabis' causal association with psychotic disorders, cautious attempts to reduce acute psychosis risk may benefit CHR-P individuals uninterested in abstinence. Further research is needed to clarify practices associated with minimization of cannabis-related psychosis risk.

Introduction

The prospect of delaying or circumventing the onset of psychosis has emerged as a target for preventative treatment and research, with the definition of Clinical High Risk for Psychosis (CHR-P). Typically experienced in adolescence or young adulthood, this risk status includes diverse constellations of attenuated symptoms of psychosis, including subthreshold hallucinations, delusions, and cognitive disorganization that are associated with distress or impairment (Salazar de Pablo et al., 2021a; Yung et al., 1996). Most CHR-P individuals carry additional psychiatric comorbidities, especially anxiety and depressive disorders (Addington et al., 2017; Lim et al., 2015; Salazar de Pablo et al., 2021a). Specialized CHR-P treatment involves wraparound care including individual, group and family psychoeducation and treatment to enhance patients' insight, resilience and social support in aims to delay or prevent conversion to psychosis (Thompson et al., 2015). A recent meta-analysis finds that 35% of CHR-P individuals develop clinically significant psychosis within a decade of study baseline (Salazar de Pablo et al., 2021b). Among those who do not convert to psychosis, at least one-third continue experiencing clinically significant attenuated psychotic symptoms (Beck et al., 2019). Ongoing translational CHR-P research includes both attempts at refining diagnostic prediction algorithms (using multimodal biomarkers to elucidate specific risk factors) and developing interventions to delay or reduce psychosis via psychotherapeutic and pharmacological clinical trials (Amminger et al., 2022; Miklowitz et al., 2022; National Institute of Mental Health, 2022).

Cannabis is the most commonly used psychoactive substance in the United States after alcohol and tobacco (Substance Use & Mental Health Services Administration, 2023). With recreational cannabis use legalized in 22/50 US states as of April 2023, access has increased and a cultural shift toward greater tolerance of cannabis use is apparent (National Conference of State Legislatures, 2023). Cannabis use is associated with acute cognitive and motor impairment, as well as chronic respiratory and cardiovascular complications; earlier initiation of use predicts problematic consumption later in life (National Academies of Sciences, Engineering, and Medicine, 2017). While animal research clearly indicates that adolescent exposure to exogenous cannabinoids worsens cognitive and psychiatric phenotypes via neurodevelopmental perturbations, human studies' methodological limitations constrain inference into whether humans experience similar brain changes, resulting in inconsistent findings (Levine, Clemenza, Rynn, & Lieberman, 2017). For example, a recent meta-analysis including seven studies indicates that among individuals with first-episode psychosis, neurocognitive functioning does not significantly differ between those who use cannabis and those who do not (Sánchez-Gutiérrez et al., 2020).

CHR-P individuals are significantly more likely than their age-matched healthy peers to report both lifetime and past-month cannabis use (Buchy et al., 2015). Mood and social enhancement are primary motives for cannabis use among both CHR-P youth and typically developing youth; however, CHR-P individuals also frequently report using cannabis to cope with negative affect (Gill et al., 2015). Seeking short term relief via self-medicating behavior may be risky, since CHR-P individuals who use cannabis may experience transiently increased anxiety and low mood, as well as chronic worsening of depression, interpersonal problems, and difficulty controlling thoughts (Dragt et al., 2012; Peters et al., 2009; Radhakrishnan et al., 2022). Cannabis use can also acutely exacerbate positive symptoms of psychosis (i.e., delusions, hallucinations, and cognitive disorganization) (Bhattacharyya et al., 2015, 2009; D'Souza et al., 2005, 2004; Kleinloog et al., 2012; Liem-Moolenaar et al., 2010; Morgan et al., 2018). A growing body of epidemiological evidence supports linkage between adolescent cannabis use and increased incidence of subsequent chronic psychotic disorder (Andréasson, Engström, Allebeck, & Rydberg, 1987; Arseneault, 2002; Di Forti et al., 2019; Hjorthøj et al., 2023; van Os, 2002). However, proof of causality (and a mechanistic rationale to accompany it) remains elusive. If cannabis use indeed causally increases psychosis risk, it may represent an important modifiable risk factor for conversion to psychosis. This explanatory gap complicates public health messaging to at-risk populations who would likely benefit from recommendations based on the evidence presently available.

This article critically examines the existing scientific literature regarding the relationship between cannabis use and psychosis risk and offers practical clinical suggestions for CHR-P populations using a harm reduction-inspired approach. Harm reduction emphasizes positive change and aims to minimize risks associated with ongoing use (Hawk et al., 2017). Rather than demanding ambivalent or unwilling individuals adhere to abstinence, harm reductionists embrace individual autonomy and strive to maximize quality of life (National Harm Reduction Coalition, 2020). A psychoeducational brochure summarizing the content of this article in plain language for independent or provider-assisted use, as well as a harm reduction-inspired worksheet for addressing cannabis use with CHR-P individuals, are offered for community use (See online Supplemental materials).

Materials and methods

A narrative review approach was utilized to synthesize findings across distinct fields in order to offer clinical recommendations based on the current evidence, in line with prior published clinical guidelines (Brooke, Lin, Ntoumanis, & Gucciardi, 2019; DeLuca et al., 2022; Harrop, Ellett, Brand, & Lobban, 2015). Primary search terms included *CHR-P, Clinical High Risk, Ultra High Risk, UHR, psychosis, psychotic, psychotomimetic, cannabis, cannabinoid,* and *endocannabinoid*, with additional search conducted from resulting publication key words. Further references were obtained by snowballing, utilizing sources cited by relevant articles. An emphasis was placed on meta-analyses and randomized controlled trials (RCTs). All included studies were peer-reviewed and published in scholarly journals or government public health databases. Case reports, abstracts, preclinical research (unless otherwise noted), non-English articles, articles not specific to individuals with CHR-P or development of psychosis spectrum disorders, articles reporting on identical samples, and articles reviewing substance usage globally were excluded ($n = 25$). Systematic literature review was conducted between January and July 2022. Additional representative publications through May 2023 were included.

Section 1: Cannabis and its effects on the brain

Cannabis and its constituents

The *Cannabis* genus of plants contains over 100 unique compounds called phytocannabinoids, or cannabinoids. One of the principal psychoactive cannabinoids, Δ-9-tetrahydrocannabinol (referred to herein as THC unless otherwise noted), confers acute psychological effects including intoxication, positive subjective drug effects, sedation, introspection, impaired working memory, appetite stimulation, anxiety, and psychotic-like experiences. Another highly prevalent cannabinoid is cannabidiol (CBD). CBD is non-intoxicating, though investigations of potential anxiolytic, antipsychotic, and anticonvulsant applications are promising (Amminger et al., 2022; Bhattacharyya et al., 2010; McGuire et al., 2018; White, 2019). Also present in cannabis are hundreds of other compounds, such as terpenes, and minor cannabinoids, concentrations of which vary between chemovars (Ferber et al., 2020). This variability makes it challenging to disentangle each compound's contributions to outcomes in higher-order mental states.

As cannabis' commercial marketplace has expanded in recent decades and as producers refine agricultural and extraction techniques, availability and use of high-potency THC cannabis and cannabis-based products is increasing (Cash, Cunnane, Fan, & Romero-Sandoval, 2020). The US Drug Enforcement Agency data on seizures of unregulated cannabis indicate that samples increased from approximately 4% to 15% THC on average from 1995 to 2021, while CBD levels remained negligible (See Fig. 1; National Institute on Drug Abuse, 2022).

Mechanism of psychoactive effects relevant to CHR-P

THC produces psychoactive effects via the endocannabinoid (eCB) system – a family of signaling molecules and receptors associated with learning and memory, reward, motivation, pain processing, and emotion regulation. Endocannabinoids modulate the release of other neurotransmitters (Covey, Mateo, Sulzer, Cheer, & Lovinger, 2017). Thus, as a partial agonist of the

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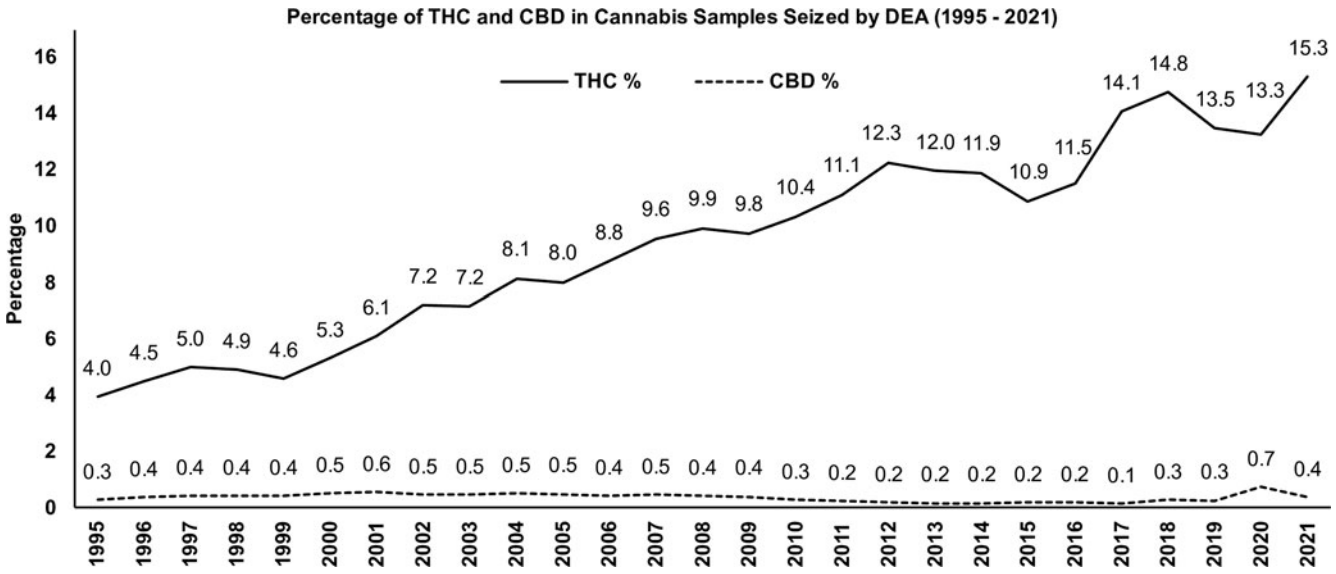

Figure 1. Percentage of THC and CBD in cannabis samples seized by DEA (1995–2001). Adapted from *National Institute on Drug Abuse*, 2022. Retrieved 02/05/2023 from https://nida.nih.gov/research-topics/marijuana/cannabis-marijuana-potency

cannabinoid 1 (CB1) receptor, THC disrupts neural circuits supporting diverse functions. eCB system dysregulation has often been observed in patients with idiopathic psychotic disorders (Garani, Watts, & Mizrahi, 2021). Many have speculated how cannabinoid-induced neurobiological alterations could potentially contribute to development of chronic psychotic disorders, but no consensus currently exists (Bossong & Niesink, 2010; Malone, Hill, & Rubino, 2010). Within the heterogeneous CHR-P population we lack knowledge of the molecular and cellular factors influencing divergent clinical trajectories and how they may interface with cannabis exposure. As the eCB system plays a central role in brain maturation, adolescents may be particularly vulnerable to its effects (Ellgren et al., 2008). In animal models chronic exposure to exogenous cannabinoids during adolescence especially disrupts eCB-mediated cortical development (Dow-Edwards & Silva, 2017; Miller et al., 2019). Yet it remains unclear whether such changes occur in humans, or whether they drive psychosis. Investigating the potential contribution of cannabis use upon vulnerable brain development may improve our understanding of overall psychosis risk (Collins et al., 2023; Howes & Onwordi, 2023).

The mechanisms linking THC's pharmacology to its phenomenological effects remain unclear. The mesolimbic D2 dopamine receptor hyperactivity hypothesis (i.e., that excessive signaling through D2 receptors in subcortical and limbic regions drives positive psychotic symptoms, most strongly supported by the efficacy of antidopaminergic antipsychotic medications) has long been invoked to explain both THC's rewarding properties and the positive symptoms of idiopathic psychosis (Bloomfield, Ashok, Volkow, & Howes, 2016; Brisch et al., 2014). Recent work supports a more nuanced model, in which mesolimbic dopamine changes occur via modulation of presynaptic GABA/glutamatergic neurons – on whose axon terminals CB1 receptors reside (Covey et al., 2017; Radhakrishnan et al., 2015). The resultant excitation-inhibition imbalance feeding onto mesolimbic dopamine neurons is hypothesized to generate the observed decreases in cortical synchrony (Cortes-Briones et al., 2015), as well as impaired information processing and associative functions, mimicking idiopathic psychosis (Sherif, Radhakrishnan, D'Souza, & Ranganathan, 2016).

Differential effects of CBD relevant to CHR-P

CBD is hypothesized to utilize dozens of distinct mechanisms of action. Its psychoactive effects are unlike THC's, characterized primarily by slight drowsiness and reduced anxiety under some conditions (Freeman et al., 2019). There is currently mixed evidence for CBD attenuating THC-induced psychotic-like symptoms in healthy individuals. Two RCTs in healthy adults found that high-dose CBD pre-administration attenuated intravenous THC's acute psychotomimetic effect (Bhattacharyya et al., 2010; Englund et al., 2013). Similarly, a large cross-sectional, web-based study reported a subtle but significant inverse relationship between CBD concentration and self-reported positive symptoms (Schubart et al., 2011). Conversely, two RCTs revealed no attenuating effect of CBD at concentrations present in recreational cannabis (Englund et al., 2022; Lawn et al., 2023), and another noted attenuation of THC-induced psychotic symptoms only for low-frequency cannabis users (Morgan et al., 2018). Thus, CBD's acute psychosis attenuation may depend on THC dose and cannabis use frequency. Small-scale clinical trials have demonstrated safety and efficacy of oral CBD use as a potential antipsychotic, though larger trials would be needed to support formal recommendations (Leweke et al., 2012; McGuire et al., 2018; Zuardi et al., 2009, 2006). A large-scale RCT in CHR-P participants assessing CBD's efficacy in reducing positive symptoms of psychosis is also currently underway (Amminger et al., 2022).

Section 2: The relationship of cannabis use and psychosis-risk: Causation or correlation?

Medical and scientific literature has long recognized the existence of an *acute* cannabis-induced psychotic state, in which symptoms remit following cessation of drug use. Scholarly attention has also been given to cannabis' impact on the incidence of *chronic* psychotic disorders. Experimental and observational research on acute

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THC-induced psychotic-like symptoms seek to bridge the current explanatory gap, providing a framework for understanding how THC use may affect long-term psychosis outcomes.

THC and acute exacerbation of psychotic-like experiences

There is substantial overlap between some of THC's acute adverse effects and psychosis spectrum symptoms, including paranoia, distorted audiovisual and time perception, disorganized cognition, and anxiety. Initial clinical studies demonstrated that intravenously administered THC transiently induces positive and negative symptoms of psychosis in healthy individuals and those with schizophrenia, in a dose-dependent manner (D'Souza et al., 2005, 2004). Many subsequent clinical experiments in healthy adults have replicated these findings with inhaled and oral-use THC (Bhattacharyya et al., 2015, 2009; Kleinloog et al., 2012; Liem-Moolenaar et al., 2010; Morgan et al., 2018).

To our knowledge, as of April 2023 only one double-blinded, placebo-controlled study of cannabis in CHR-P participants has been published. In this exploratory study, CHR-P participants smoked cannabis and temporarily experienced significant exacerbations of paranoia, visual illusions, time distortions, feelings of strangeness, cognitive impairment, and anxiety – effects not observed in people not at risk for psychosis (Vadhan, Corcoran, Bedi, Keilp, & Haney, 2017). Observational CHR-P studies similarly report transient exacerbations of anxiety, depression, and positive symptoms shortly following cannabis use (Corcoran et al., 2008; Peters et al., 2009). Notably, an observational study found that CHR-P individuals who experience acute psychotic-like symptoms during cannabis use were 4.9 times more likely to eventually develop psychosis than CHR-P individuals who are cannabis users who do not experience these symptoms during cannabis use (see Fig. 2; McHugh et al., 2017). CHR-P individuals who experience psychotic-like symptoms in the context of cannabis use may represent a subpopulation with a distinct clinical trajectory, warranting dedicated early intervention and greater research attention. The existence of subpopulations with divergent responses to cannabis may account for variable results of prior analyses of cannabis use among the inherently heterogeneous overall CHR-P population.

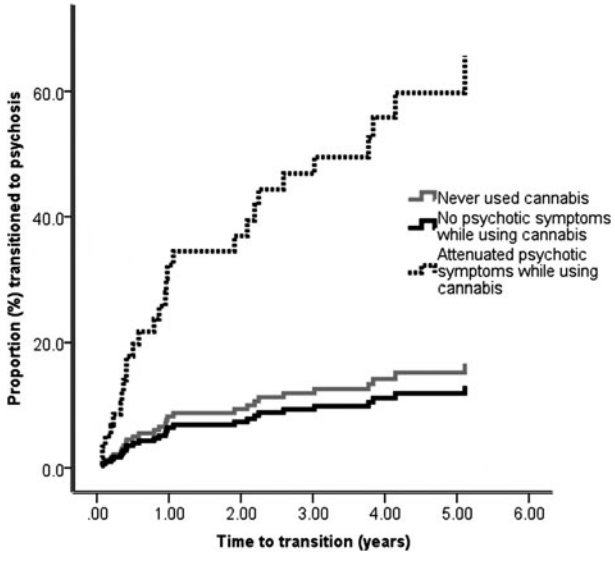

Figure 2. Survival functions modeling time to transition to psychotic disorder based on presence of psychotic-like symptoms during cannabis use ($n = 190$) (McHugh et al., 2017). Adapted from Fig. 1 of 'Cannabis-induced attenuated psychotic symptoms: implications for prognosis in young people at ultra-high risk for psychosis', by McHugh et al., 2017, *Psychological Medicine*, 47, p. 616–626. Copyright 2017 by Cambridge University Press.

Similarly, observational studies of healthy individuals who use cannabis reveal that individuals scoring highly on schizotypal personality measures reported higher levels of psychotic-like symptoms during and shortly after using cannabis (Mason et al., 2009; Stirling et al., 2008). Frequency of use is positively related to schizotypy among these individuals, which authors speculated may arise from a gradient of heightened dopamine system sensitivity along the psychosis spectrum (Stirling et al., 2008).

Epidemiological evidence for a relationship between cannabis use and psychosis risk

Several large-scale epidemiological studies revealed an association between cannabis use and risk for psychotic disorder. Among the first reports was a longitudinal study of 45 000+ male Swedish military conscripts, providing compelling evidence for a relationship between cannabis and schizophrenia. Over 15 years, those who had used cannabis on 50+ occasions throughout their lives were 6 times more likely than never-users to develop schizophrenia (Andréasson et al., 1987). Subsequent large, general population prospective cohort studies supported this trend. A later study in New Zealand followed 1037 healthy individuals from age 11–26 and contributed two novel findings: (1) A significant increase in incidence of schizophreniform disorder among those who initiated cannabis use before age 15, but not before age 18, and (2) Initiation before either ages 15 or 18 was associated with more severe psychotic symptoms at age 26 (Arseneault, 2002). Similarly, in the Netherlands 4045 healthy individuals and 59 with previously diagnosed psychotic disorder (ages 18–64, mean 41.4) were assessed annually over three years. Lifetime (pre-baseline) cannabis use predicted psychosis at follow-up better than new initiation of cannabis use between baseline and follow-up, with a greater effect among those with a prior history of psychosis (van Os, 2002). Earlier initiation also predicted greater incidence of subthreshold symptoms in a large 10-year cohort study of healthy individuals (Kuepper et al., 2011), as well as greater severity of subthreshold psychotic symptoms in two large cross-sectional surveys of Dutch and Greek adolescents (Schubart et al., 2011; Stefanis et al., 2004). Concerns regarding adolescents' particular susceptibility to neurodevelopmental perturbations have been raised when considering a cannabis-mediated pathway to psychotic disorder. In a cross-sectional study, adolescents who use cannabis daily to weekly reported more severe psychotic-like symptoms than both adults who use cannabis at the same frequency and adolescents with minimal cannabis exposure (Lawn et al., 2022). Further work is needed to explore differential susceptibility of the adolescent brain to cannabis' neuropsychiatric effects.

Moreover, meta-analyses have affirmed a dose-dependent relationship between frequency of cannabis use and later incidence of a psychotic disorder (Kiburi, Molebatsi, Ntlantsana, & Lynskey, 2021; Marconi, Di Forti, Lewis, Murray, & Vassos, 2016; Moore et al., 2007). An international case–control study including first-episode patients found daily cannabis use to be associated with 3.2-fold increased risk of developing a psychotic disorder; people who used high-potency cannabis had 4.8-fold increased risk (Di Forti et al., 2019). A survey of 100 000+ US adults found frequent cannabis use to be associated with self-reported psychotic disorder; past-year cannabis users also self-reported psychotic

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disorder significantly more often than non-past-year cannabis users (Livne, Shmulewitz, Sarvet, Wall, & Hasin, 2022). Recent evidence also suggests that young males may be particularly vulnerable to these effects (Hjorthøj et al., 2023).

Notably, meta-analyses indicate that among individuals with first episode psychosis, those with a history of cannabis use experienced their first episode 2.7 years younger than those who never tried cannabis (Godin & Shehata, 2022; Large, Sharma, Compton, Slade, & Nielssen, 2011). This earlier-onset trend is exacerbated by THC concentration (Di Forti et al., 2014), though there is mixed evidence for frequency of use moderating earlier onset (Godin & Shehata, 2022; Wainberg, Jacobs, di Forti, & Tripathy, 2021). Earlier psychosis onset confers worrisome prognostic factors: greater disability, more frequent relapse, increased antipsychotic nonadherence, decreased treatment efficacy, and longer hospitalizations (Compton et al., 2009). In the general population, age of initiation, frequency of use, comorbid substance use, childhood trauma, and genetic risk have been reported to moderate the relationship between adolescent cannabis use and conversion to psychosis (Kiburi et al., 2021).

In contrast, the direct impact of cannabis use on conversion to psychosis in CHR-P is less clear. Earlier initiation of cannabis use is associated with younger onset of subthreshold psychotic symptoms (Dragt et al., 2010, 2012). Two meta-analyses failed to find lifetime endorsement of cannabis use predictive of conversion in CHR-P (Carney, Cotter, Firth, Bradshaw, & Yung, 2017; Kraan et al., 2016), though a separate comparison found increased conversion among CHR-P individuals with cannabis use disorder (CUD), suggesting a potential dose-dependent effect (Kraan et al., 2016). Shorter latency to conversion among CHR-P individuals with CUD has been observed, though adjusting for alcohol use negated a predictive relationship between CUD and long-term conversion risk (Auther et al., 2015). Specific aspects of cannabis use have been reported to predict conversion in CHR-P: earlier initiation of use, increased frequency of use, continued use following CHR-P diagnosis, and experiencing psychotic-like symptoms during cannabis use (Dragt et al., 2010; McHugh et al., 2017; Valmaggia et al., 2014). However, other studies found no evidence for a gradient in conversion risk with increasing frequency of subclinical cannabis use in CHR-P (Auther et al., 2012; Phillips et al., 2002; Yung, Phillips, Yuen, & McGorry, 2004). To explain the absence of a clear association, some researchers have speculated that cannabis use may predict the emergence of CHR-P symptoms without contributing to psychosis conversion (Addington et al., 2014). Although plausible, prior CHR-P cannabis use research lacks the nuance to support the specificity of the hypothesis. For example, comparisons of lifetime cannabis use are often binary, binning single-time through daily users together as compared to never-users. Prior studies have also been limited by the exclusion of CHR-P individuals with CUD (to avoid confounding), small sample size of participants who use cannabis, ascertainment bias toward help-seeking individuals, aggregation of all non-medicinal psychoactive substances into 'substance use', and minimal longitudinal data (Addington et al., 2014; Auther et al., 2015; Yung et al., 2004). Moreover, as the CHR-P population is inherently heterogeneous, consideration of subgroups predisposed to distinct cannabis use patterns may shed light on prior discordant findings.

Causation or spurious correlation?

It remains unclear whether the relationship between adolescent cannabis use and increased incidence of psychotic disorder is causative or correlative. Two main hypotheses have been proposed: one suggesting a *causal* role (adolescent THC use directly contributes to elevated risk of developing a psychotic disorder), while the other emphasizes *shared vulnerability*, whereby other factor(s) predispose the individuals to both use THC and to develop a psychotic disorder – independently of each other (Gillespie & Kendler, 2021).

The *causal* hypothesis has garnered more attention within the existing literature. However, consideration of the *shared vulnerability* hypothesis is warranted, as mechanisms remain unclear. Coincidental correlation (or bidirectional causation) suggests the existence of shared risk genes for both cannabis use and psychotic spectrum experiences found in Genome-Wide Association Studies (Gillespie & Kendler, 2021; Karcher et al., 2019; Pasman et al., 2018; Power et al., 2014; Vaissiere, Thorp, Ong, Ortega-Alonzo, & Derks, 2020). This hypothesis is based, in part, by variation in the CADM2 gene, which correlates with both schizophrenia and lifetime cannabis use (Pasman et al., 2018). Mendelian Randomization, a method which uses genotypes as variables to reduce confounding and aid causal inference, provided assumptions are met, has been used to define the relationship between cannabis use and genes underlying increased risk for schizophrenia. Two Mendelian Randomization analyses found a causal influence of schizophrenia risk genes on lifetime cannabis use (Gage et al., 2017; Pasman et al., 2018), while another reported the opposite (Vaucher et al., 2018). However, authors conceded that binary binning of all cannabis users under 'lifetime use' as previously described may too have introduced confounding (Gage et al., 2017). Studies of co-twins and other relatives have demonstrated modest causal impact of CUD on psychotic-like experiences and disorders, with notable contributions of personal, shared genetic, and environmental factors (Giordano, Ohlsson, Sundquist, Sundquist, & Kendler, 2015; Karcher et al., 2019; Nesvåg et al., 2016). Lifetime cannabis use, but not CUD, has been shown to moderate the effect of schizophrenia polygenic risk score on frequency of psychotic-like experiences (Schaefer et al., 2021; Wainberg et al., 2021). A longitudinal study of Danish national registry data (3 000 000+ individuals) found that while cannabis abuse increased risk of later schizophrenia by 5.4-fold, risk was also significantly increased–albeit more modestly–by alcohol, hallucinogen, sedative, and other substance use (Nielsen, Toftdahl, Nordentoft, & Hjorthøj, 2017). If individuals are predisposed to both use cannabis and develop psychosis, the possibility of an illusory relationship cannot be fully discounted.

Skeptics of a *causal* hypothesis point out the dissociation between recent decades' significant increases in cannabis use and relatively stable global rates of schizophrenia diagnoses (Degenhardt, Hall, & Lynskey, 2003). However, recent work indicates elevated rates of first-episode psychosis in regions with predominantly high-potency cannabis (Di Forti et al., 2015, 2019). Moreover, limitations have been identified within existing prediction models, including gaps and lags in incidence data (Hickman, Vickerman, Macleod, Kirkbride, & Jones, 2007).

A *reverse causality* (i.e., self-medication of psychotic symptoms) relationship is poorly supported by the scientific literature. Longitudinal and experience sampling studies found a temporal sequence of cannabis use preceding psychotic-like experiences, but psychotic symptoms did not predict subsequent cannabis use (Kuepper et al., 2011; Verdoux, Gindre, Sorbara, Tournier, & Swendsen, 2003). CHR-P individuals do not significantly endorse using cannabis to relieve positive symptoms as a motive

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for their use (Gill et al., 2015). Further, the most common reason for cessation of cannabis use in a longitudinal study of 182 CHR-P individuals was exacerbation of positive symptoms (Valmaggia et al., 2014). Additional research to clarify factors driving continued cannabis use in CHR-P is warranted.

Section 3: Harm reduction recommendations

Experts already recommend that individuals with a history of psychosis avoid using cannabis (D'Souza et al., 2022; Fischer et al., 2017), though in practice barriers may impede abstinence. Recognizing this, providers should consider a harm reduction approach, which focuses on minimizing the negative consequences of risky behaviors without necessitating willingness to extinguish them entirely (Coronado-Montoya, Tra, & Jutras-Aswad, 2022; Hawk et al., 2017). As described, converging experimental and epidemiological evidence suggest that cannabis may be driving increased risk of psychotic symptom experience, both acutely and chronically. Thus, a cautious clinical recommendation is to urge against cannabis use among CHR-P individuals as well (D'Souza et al., 2022).

Reducing or eliminating cannabis use could delay first episode onset–which is associated with a better prognosis (Compton et al., 2009)–or entirely prevent conversion to psychosis in some individuals. Regardless of whether a causal relationship exists, decreasing THC exposure may still benefit some CHR-P individuals by lessening acute exacerbations of subthreshold psychotic symptoms, anxiety, and low mood (Childs, Lutz, & de Wit, 2017). Since CHR-P individuals often use cannabis to self-medicate negative affect (Gill et al., 2015), replacing cannabis use with healthier coping strategies remains of clinical interest. The benefits of open, collaborative dialogue encouraging replacement coping strategies to cannabis use among CHR-P individuals are many, and the risks are minimal.

In light of converging evidence, we now offer the following specific clinical guidelines and recommendations for harm reduction in CHR-P individuals who use cannabis. See online Supplemental Materials for a plain-language psychoeducational brochure and worksheet distilling key harm reduction recommendations for patients to use independently or with a provider.

Minimize THC and substitute CBD in cannabis use

Given the mounting evidence that THC can cause transient psychotic-like symptoms and may contribute to chronic psychotic disorders – both in a dose-dependent manner – CHR-P individuals are recommended to minimize their THC intake. Meanwhile, high doses of CBD (much greater than found in retail cannabis or cannabis-derived products) have been shown to attenuate THC's psychotomimetic effects (Bhattacharyya et al., 2010; Englund et al., 2013; Schubart et al., 2011), though low doses of CBD may be ineffective (Englund et al., 2022; Lawn et al., 2023). CHR-P individuals who do not want to entirely stop using cannabis should consider switching to cannabis products with minimal THC and high CBD concentrations. Although thresholds of psychoactive effect have yet to be rigorously determined, the US Department of Agriculture currently restricts content of THC in hemp (a non-controlled substance) to 0.3% (*Hemp and the 2018 Farm Bill*, 2019). This could serve as a conservative benchmark for harm reduction purposes. See online Supplemental Materials for further consideration of potential advantages and disadvantages to this approach.

Avoid high potency THC concentrate products

Experimental evidence supports a dose-dependent effect of THC on acute psychotic-like experiences (D'Souza et al., 2004). High doses of THC can also transiently worsen anxiety in healthy individuals despite reducing it at low doses (Childs et al., 2017), and anxiety reduction is a top motive for cannabis use in the CHR-P population (Gill et al., 2015). Cannabis concentrates are steadily growing in popularity, containing approximately 52% THC on average and up to 95% (Bidwell, Martin-Willett, & Karoly, 2021). Their high potency makes regulating dosage difficult if one sought to avoid inducing psychotic-like symptoms and anxiety (or exacerbating chronic psychosis risk). Use of cannabis concentrates can be viewed as akin to rapidly drinking liquor and should be targeted for intervention.

Use caution with infused oral products like edibles

Consumption of cannabis-infused foods ('edibles') carries unique risks. Unlike inhaled cannabis, edibles can take hours before effects are realized, with latency and potency varying between consumers of the same batch based on biological factors like metabolism, weight, and sex (Reboussin et al., 2019). Edibles, relative to inhaled cannabis, produce a longer lasting psychotropic effect due to liver metabolism of Δ-9-THC to 11-hydroxy-Δ-9-THC, a psychoactive metabolite of THC that is also a CB1 receptor agonist (Wiley, Barrus, Farquhar, Lefever, & Gamage, 2021). Homemade edibles are prone to variation in concentration within and between batches. Though edibles are increasingly perceived as a healthier alternative to smoking, they may pose a greater risk for both over-intoxication and induction of psychotic-like experiences than inhaled cannabis (Reboussin et al., 2019). Thus, providers should educate CHR-P cannabis users about oral cannabis use and its unique psychotomimetic risks.

Reduce frequency of cannabis use

Reducing frequency of cannabis use may also lower risk of developing chronic psychotic disorder. In the general population, more frequent use is associated with increased incidence of both psychotic disorders and transient symptoms (Kiburi et al., 2021; Marconi et al., 2016; Moore et al., 2007; Wainberg et al., 2021). There is mixed evidence available for CHR-P regarding lower conversion risk with decreasing frequency of use (Auther et al., 2012; Kraan et al., 2016; Phillips et al., 2002; Valmaggia et al., 2014; Yung et al., 2004). It is unclear whether decreasing usage will change long-term clinical outcomes. Regardless, reducing frequency of use would lessen the likelihood of acute symptom exacerbation and decrease the brain's cumulative THC exposure.

Conclusion

THC can acutely induce psychotic-like symptoms in healthy individuals and CHR-P individuals alike, per experimental and observational studies. Adolescent cannabis exposure has been linked to increased rates of subsequent psychotic disorder and psychotic-like experiences in the general population, though studies in CHR-P have been mixed, partly due to methodological limitations. Bridging the explanatory gap between THC's acute psychotomimetic effects, its impacts on neurodevelopment, and naturalistic studies finding increased rates of psychotic disorder among people who use cannabis remains challenging. Beyond strengthening predictive multimodal biomarkers in CHR-P and

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elucidating cannabis' psychopharmacology, more nuanced investigations of cannabis use behavior in CHR-P youth and corresponding clinical trajectories are warranted.

Clinicians are cautioned against overstating the present evidence suggesting that associations between cannabis use and increased risks for chronic psychosis indicate causality; this may ultimately weaken intervention efforts. Here we draw interim conclusions, acknowledging remaining uncertainty regarding causality, and provide actionable guidelines to reduce risks associated with cannabis use based on the available evidence. Harm reduction practices include reducing frequency of use, THC concentration and use of products with inconsistent potency such as edibles that are not accurately labeled and do not adhere to local testing and manufacturing regulations. These strategies complement psychoeducation and regular communication with patients regarding cannabis use and psychotic-like experiences, facilitated by a collaborative and individualized therapeutic approach (see online Supplemental Materials for additional clinical considerations).

When implementing harm reduction strategies to reduce cannabis use with CHR-P youth, it is important to emphasize identification, trial, and mastery of alternative effective coping strategies before attempting to extinguish maladaptive yet purposeful coping behaviors such as cannabis use. Use of coping strategies such as engaging in enjoyable activities or seeking social support are associated with a lower likelihood of relapse in voluntary cannabis-quit attempts (Buckner, Zvolensky, & Ecker, 2013; Marlatt & Donovan, 2005). Tools such as symptom diaries or experience sampling may be useful for assessing coping strategies in real-time and tailoring interventions to individuals' specific needs. Cannabis use is associated with increased risk of developing psychotic disorders, especially in vulnerable populations; to mitigate these risks we may now offer CHR-P patients and their health providers meaningful recommendations for harm reduction from the robust range of presently available knowledge.

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