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COMMENTARY

Cannabis Use Among Patients With Psychotic Disorders

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ABSTRACT

Amidst a rapidly changing legal landscape, cannabis use in the United States has become increasingly common in the past several years. There is strong evidence to suggest that chronic and early cannabis use increases the risk of developing a psychotic disorder, and there is at least moderate evidence that suggests ongoing cannabis use among individuals with a psychotic disorder worsens clinical outcomes (eg, decreased psychiatric medication adherence, more frequent psychiatric hospitalizations). In this Review Article, we provide a focused, clinically oriented overview of the epidemiology and characteristics of cannabis use among individuals with first-episode psychosis; evaluation of cannabis use; and treatment modalities, focusing on behavioral interventions suitable for outpatient primary care settings. We discuss the limited data supporting pharmacologic interventions for cannabis use disorder, specifically among individuals with first-episode psychosis, and the unique potential of cannabidiol to serve as a harm-reduction strategy for individuals who are not able or willing to achieve abstinence for cannabis.

Cannabis use is common among individuals with psychosis. In a meta-analysis of 35 studies, among 6321 patients with first-episode psychosis (FEP), 33.7% endorsed cannabis use.[1] Similarly, 30.7% (n = 124/404) of outpatients with FEP endorsed past-month cannabis use and 34.7% met criteria for lifetime cannabis abuse or dependence.[2] Here, we review the effects of cannabis use, motivations for use, and treatments. We use the term "psychosis" to refer to a range of disorders, such as schizophrenia, schizoaffective disorder, and unspecified psychotic disorders.

PATTERNS AND EFFECTS OF USE

Epidemiological studies suggest that early and heavy cannabis use increases the risk of developing psychosis[3-5] and that heavier use is correlated with higher risk of schizophrenia.[6] Evidence supporting this association, alternate explanatory models, and the potential neural mechanisms underlying the association are reviewed elsewhere.[6-8] After psychosis, initiation or continued cannabis use is associated with worse outcomes. For instance, a recent meta-analysis of 24 studies encompassing 16,565 patients compared clinical outcomes of patients who did and did not use cannabis over 0.5 to 13 years: patients who continued to use cannabis, compared with those who never used cannabis or discontinued use, had more psychosis relapses; continued cannabis users also had longer hospitalizations compared with nonusers.[9] Among young adults with recent-onset psychosis, those with concurrent substance use, including cannabis, were more likely to have recent legal involvement.[10] Interestingly, patients with psychosis who use cannabis, compared with nonusers, may have lower body mass index and total cholesterol levels.[11]

Given that cannabis use is associated with decreased antipsychotic medication adherence,[12] it is plausible that this reduced adherence contributes to the negative impacts. However, associations between continued use and outcomes persist or are only attenuated when controlling for antipsychotic administration[13] or adherence.[14] Likewise, this association remains significant after controlling for use of illicit substances other than cannabis.[15]

Furthermore, patients with psychosis who use cannabis daily and/or who use high-potency, hyper-concentrated forms of cannabis exhibit worse outcomes (eg, more relapses) compared with nonusers and less-frequent users,[16] and risk of relapse is highest in periods of active cannabis use.[17] Results from a recent multisite study among patients with FEP suggest that removing high-potency cannabis (tetrahydrocannabinol [THC] ≥ 10%) could prevent approximately 12% of patients with FEB and up to 50% at a single site.[18] Furthermore, among patients with FEP enrolled in coordinated specialty care, those with persistent cannabis use (compared with patients without cannabis use) demonstrated worse psychiatric symptoms and higher rates of suicidality, violent ideation, and legal trouble at baseline, and worse symptoms at the 1-year follow-up.[19] Continued monitoring of trends in psychosis is critical as the concentration of THC in cannabis rises[20] and state legalization increases.[21]

Understanding why individuals with psychosis use cannabis is a key component in developing effective, collaborative

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Abbreviations: CAST, Cannabis Abuse Screening Test; CBD, cannabidiol; CBT, cognitive behavioral therapy; CM, contingency management; CSC, coordinated specialty care; CUD, cannabis use disorder; CUDIT-R, Cannabis Use Disorders Identification Test-Revised; FEP, first-episode psychosis; IDDT, integrated, dual-diagnosis treatment; MET, motivational enhancement therapy; MI, motivational interviewing; RCT, randomized controlled trial; THC, tetrahydrocannabinol

treatment plans. Results from 2 systematic reviews[22,23] suggest that motivations for cannabis use include enhancement of positive affect, relief of negative affect, improvement in social well-being, and resolution of positive psychotic symptoms and medication side effects.

Simply recognizing negative consequences may not provide sufficient motivation to stop. For instance, a qualitative study[24] found that more than half of inpatient participants with schizophrenia believed that cannabis "makes your mental illness worse"; however, 40% to 70% simultaneously endorsed beneficial outcomes of cannabis use (eg, reducing tension, improving mood). These results suggest that interventions limited to psychoeducation may be ineffective.

ASSESSMENT

Brief scales can be used to assess problem severity and motivation to reduce use. These include the 5-item Severity of Dependence Scale,[25] the 8-item Cannabis Use Disorders Identification Test-Revised (CUDIT-R),[26] and the 6-item Cannabis Abuse Screening Test.[27] In each of these, sensitivity, specificity and predictive ability to identify cannabis use disorder (CUD) are generally acceptable.[28] These scales may be combined with clinical interviewing to assess cannabis use severity and to track treatment outcomes. Likewise, because distinguishing the effects of chronic cannabis use from non–substance-related psychosis is challenging, standardized instruments such as the CUDIT-R and Cannabis Abuse Screening Test can help isolate the symptoms of problematic use. In addition, structured recall measures of cannabis use, such as the Timeline Follow-Back, demonstrate high levels of agreement with biological assays (87% in a recent meta-analysis[29]).

Recently, Sami et al[30] have proposed a Cannabis Psychosis Score, which is composed of 5 domains: persistence (never used, ever used, or self-reported or urinalysis-confirmed use in past 30 days); abuse (no lifetime cannabis abuse, lifetime cannabis abuse, lifetime cannabis dependence); age at first use (never, ≥ 17 years, ≤ 16 years); money spent per week (7 categories in British pounds); and potency score (no or experimental use, low, high or "skunk"). Each domain score range is 0 to 2 and the total score ranges from 0 to 10, with higher scores suggesting greater use of cannabis in domains that are associated with risk of psychosis. The advantages of this approach include the multimodal assessment (eg, various forms of self-report and urine toxicology) and the consolidation of cannabis use behaviors that are pertinent to psychosis. A potential limitation in the application of this tool is that providers may not have ready access to the required information to score each domain. Regardless of the chosen cannabis use assessment tool, providers also should assess patient perceptions regarding how cannabis may be causing problems and what would motivate reduction in use.

BEHAVIORAL INTERVENTIONS

The National Institute on Drug Abuse recommends 3 behavioral treatment modalities for CUD: motivational interviewing (MI), also referred to as motivational enhancement therapy; cognitive behavioral therapy (CBT); and contingency management (CM).[31] Results of a Cochrane review of randomized controlled trials (RCTs) of psychosocial treatments for CUD suggested that CBT, motivational enhancement therapy, and their combined use, compared with inactive controls, led to significant, short-term (3- to 6-month) decreases in cannabis use and severity of dependence.[32] However, studies included in this meta-analysis were heterogeneous in participant selection, treatment setting, intervention intensity, and duration of follow-up. Few studies demonstrated efficacy past 9 months; overall abstinence rates were low, and multiple studies demonstrated no significant differences between intervention and control groups.[32]

Evidence specifically among individuals with psychosis and CUDs is inconsistent. The most comprehensive review of this topic to date reveals that the few RCTs of behavioral interventions in this population either demonstrate no or mild and time-limited (ie, < 6 months) effect of MI, CBT, CM, or any combination of modalities on cannabis use.[33] Furthermore, in an RCT comparing MI and CBT plus standard care versus standard care alone among patients with psychotic-spectrum disorders (N = 327) demonstrated no improvement in rates of hospitalization, relapses, psychotic symptoms, functioning, or self-harm in the intervention cohort; however, the intervention cohort was reported using less substance per day in the year after therapy.[34] In another pragmatic, multicenter RCT comparing CM with psychoeducation versus psychoeducation alone among patients with FEP and regular cannabis use (N = 551), the groups demonstrated no significant difference in time to acute psychiatric care, and the intervention was not cost effective.[35] Nonetheless, when behavioral approaches are used, adaptations for individuals with psychosis include simplifying open-ended questions, refining reflective listening skills, heightening emphasis on affirmations, and integrating psychiatric issues into personalized feedback.[33]

A structured approach is recommended, collaboratively developing a shared formulation to understand psychosis symptoms, normalizing psychotic experiences to reduce stigma, and focusing on distress reduction rather than altering symptoms.[36] Skills building focuses on coping with voices, exploring the evidence for unusual and distressing beliefs, and addressing negative symptoms. This can be effective in improving symptoms and functioning.[37]

Combined MI and CBT may be more effective than either intervention alone.[38] MI can be effective with patients experiencing substance problems yet expressing little desire or motivation to reduce use. Given the low risk for adverse effects associated with behavioral interventions, clinicians may employ these modalities on a case-by-case basis, guided by patient preferences and treatment response.

Beyond specific behavioral modalities, whenever possible, co-occurring psychosis and cannabis use should be treated simultaneously. In an RCT comparing integrated, dual-diagnosis treatment (IDDT) with treatment-as-usual among patients with schizophrenia and substance use disorders (60%-71% CUD), patients randomized to IDDT demonstrated significant decreases in alcohol and drug use, improvements in multiple psychiatric domains, and improved quality of life and psychosocial functioning.[39] Research similarly supports the implementation of a coordinated specialty care (CSC) model, a team-based, multimodal, multidisciplinary approach to addressing the needs of patients with first-onset psychosis; CSC includes pairing patients with a dedicated recovery coach who provides skills training, substance abuse treatment, and family psychoeducation.[40]

PHARMACOLOGIC INTERVENTIONS

The Food and Drug Administration has not approved any specific medication for CUD treatment. Preliminary evidence from RCTs suggests that there may be a therapeutic role for N-acetylcysteine, gabapentin, and naltrexone, as well as the cannabinoid receptor type 1 agonists nabilone and nabiximols (not legally available in the United States) in CUD treatment.[41] However, most RCTs of pharmacologic agents for CUD have focused on alleviation of withdrawal symptoms, are of relatively short duration, and do not provide information regarding long-term abstinence from cannabis. In addition, there are currently no data available to guide medication selection among patients with psychosis and CUD.

A recent systematic review of 22 studies of antipsychotic treatment of psychosis and comorbid cannabis misuse suggested no significant differences among haloperidol, clozapine, risperidone, olanzapine, ziprasidone, and quetiapine in reducing psychotic symptoms or decreasing cannabis use.[42] Preliminary evidence from small, short-term studies suggest clozapine may be superior to other antipsychotics for treatment of psychotic symptoms and cannabis use/craving among patients with psychosis[42]; however, these results await confirmation with larger and longer-term trials.

Cannabidiol (CBD), a cannabinoid that does not cause the euphoric "high" associated with THC, is a potential treatment for psychosis.[43-45] Preliminary data from RCTs suggest that CBD as monotherapy[46] or as an augmentation strategy to conventional antipsychotics[47] may decrease positive symptoms and improve cognition. However, other studies have not demonstrated any beneficial effect of adding CBD to an antipsychotic regimen.[48] Data from well-designed RCTs are needed before CBD can be recommended to treat psychosis. Of note, the high doses of CBD used in clinical trials are not typically achievable with nonpharmaceutical CBD formulations from community dispensaries.[49] Moreover, no published trials of CBD for psychosis have specifically been tested in patients with comorbid substance use disorders, despite the relatively high rates of cannabis and noncannabis substance use disorders in FEP.[2]

In considering treatment approaches, some authors[50] have suggested that patients with psychotic disorders who do and do not use cannabis may constitute at least 2 distinct groups based on evidence from neuroimaging and neurochemical studies of these populations. Refinement and application of these findings may improve the precision and efficacy of treatments, which may theoretically be tailored to the unique neurobiological profiles of patients based on their cannabis use patterns.

Regardless of the pharmacologic regimen chosen, clinicians should follow good-practice guidelines for pharmacologic treatment of comorbid psychotic and substance use disorders.[51] Specifically, treatment regimens should be simplified to promote adherence and reduce side-effect burden; use of long-acting injectable formulations of antipsychotics and medication organization tools (eg, app-based reminders, pill organizers) should be considered, and involvement of caregivers and case managers should be encouraged.

Even considering the inconsistent results of behavioral interventions for cannabis use among patients with psychosis and the lack of effective pharmacologic interventions, there is cause for hope. Work by Rebgetz et al[52] has documented natural recovery from cannabis use among patients with psychosis; study participants cited awareness of the negative impact of substance use and strong social support as factors that led to their sustained abstinence from cannabis. Likewise, among a cohort of patients with schizophrenia and comorbid substance use disorders (N = 130) followed over 10 years, 62.5% were actively attaining remissions from substance abuse.[53]

CONCLUSION

Cannabis use is common and problematic among individuals with psychosis. Especially among adolescents and young adults, it is a frequent complicating factor in the treatment of schizophrenia and early psychotic episodes. Psychiatrists should assess cannabis use by asking about the frequency of use and use of high-potency cannabis products, which can be especially risky. Brief scales are available to assist in assessment. No specific medications have consistently

demonstrated efficacy in reducing use. However, behavioral approaches, including MI and CBT, have a growing evidence base and can be effectively integrated into clinical management. Although there is no strongly supported intervention for individuals with cannabis use and psychosis, IDDT and CSC are associated with decreased substance use and psychiatric symptoms, as well as improved psychosocial functioning. ❖

Disclosure Statement

Dr Mathalon has consulted for Boerhinger Ingelheim, Cadent, and Syndesi. The other authors have no financial conflicts of interest to declare.

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Author Contributions

Matthew E Hirschtritt, MD, MPH, conceptualized the content of the manuscript; provided original content writing, drafting, and editing; and participated in the critical review and submission of the final manuscript. Kelly C Young-Wolff, PhD, MPH, Daniel H Mathalon, PhD, MD, and Derek D Satre, PhD, participated in the development of this manuscript by providing original content writing contributions, researching and reviewing relevant literature, and actively editing and drafting the final form of the manuscript for submission. All authors have given final approval for the manuscript.

Disclaimer

This manuscript was prepared by Dr Young-Wolff in her personal capacity. The opinions expressed in this article are the author's own and do not reflect the view of the National Institute on Drug Abuse, the National Institutes of Health, the Department of Health and Human Services, or the US government.

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