CNS Drugs
https://doi.org/10.1007/s40263-024-01148-2

CURRENT OPINION

The Complex Relationship Between Cannabis Use and Mental Health: Considering the Influence of Cannabis Use Patterns and Individual Factors

Kelly A. Sagar[1,2,3] · **Staci A. Gruber**[1,2,3]

Accepted: 27 November 2024

Abstract
The relationship between cannabis use and mental health is complex, as studies often report seemingly contradictory findings regarding whether cannabis use results in more positive or negative treatment outcomes. With an increasing number of individuals using cannabis for both recreational (i.e., non-medical) and medical purposes, it is critical to gain a deeper understanding of the ways in which cannabis may be helpful or harmful for those diagnosed with psychiatric disorders. Although cannabis is composed of hundreds of compounds, studies assessing the effects of "cannabis" most often report the impact of delta-9-tetrahydrocannabinol (d9-THC), the primary intoxicating constituent of the plant. While d9-THC has documented therapeutic properties, negative clinical outcomes commonly associated with cannabis are generally related to d9-THC exposure. In contrast, non-intoxicating cannabinoids such as cannabidiol (CBD) show promise as potential treatment options for psychiatric symptoms. In this article, findings from studies and reviews examining the relationship between mental health conditions (mood, anxiety, psychosis, and post-traumatic stress disorder [PTSD]) and cannabis use are summarized to highlight critical variables that are often overlooked, including those associated with cannabis use patterns (e.g., frequency of use, amount used, cannabinoid exposure, product choice, and route of administration). Further, this article explores individual factors (e.g., age, sex, genetics/family history) that likely impact cannabis-related outcomes. Research to date suggests that youth and those with a family history or genetic liability for psychiatric disorders are at higher risk for negative outcomes, while more research is needed to fully understand unique effects related to sex and older age.

1 Introduction

The relationship between cannabis use and mental health is a hot-button issue, sparking debate and generating polarizing opinions about its use in psychiatry. A growing number of research studies examining the etiology of psychiatric disorders have found imbalances in certain aspects of the endocannabinoid system (ECS) [1], and many individuals report using cannabis to successfully address psychiatric symptoms, such as reducing anxiety or improving mood. In fact, a recent survey study of 6413 past-year cannabis consumers found that individuals with psychiatric disorders reported higher self-perceived positive effects of cannabis use relative to negative effects; overall, positive effects were rated highest for mental health (67%), followed by quality of life (64%) [2]. In contrast, both national surveys and recent reviews have reported that cannabis use is associated with increased prevalence of psychiatric disorders and poorer outcomes (e.g., poorer treatment/medication adherence, relapse of symptoms) [3–5]. These seemingly contradictory findings leave both consumers and clinicians wondering how best to navigate the complicated cannabis landscape that in all likelihood includes a combination of risks and benefits.

When addressing this topic, it is critical to first recognize that the term "cannabis" is often used quite broadly to refer to anything that comes from the plant *Cannabis sativa L.* Importantly, however, the plant contains hundreds of compounds, including more than 100 phytocannabinoids [6],

✉ Kelly A. Sagar
ksagar@mclean.harvard.edu

[1] Cognitive and Clinical Neuroimaging Core, McLean Hospital, McLean Imaging Center, Belmont, MA, USA

[2] Marijuana Investigations for Neuroscientific Discovery (MIND) Program, McLean Hospital, Belmont, MA, USA

[3] Department of Psychiatry, Harvard Medical School, Boston, MA, USA

Published online: 04 January 2025

Key Points

While negative outcomes related to cannabis use often reflect recreational/non-medical use and more specifically delta-9-tetrahydrocannabinol (d9-THC) exposure, preclinical and clinical studies suggest that cannabidiol (CBD) holds promise for improving certain psychiatric symptoms.

Additional variables likely influence mental health outcomes, including cannabis use patterns (frequency of use, amount used, individual cannabinoid exposure, product choice, and route of administration), but higher exposure to d9-THC is generally more problematic.

Individual factors (age, sex, genetics, and family history) also impact outcomes; youth and those with a family history or genetic liability for psychiatric disorders are at higher risk for negative outcomes, while more research is needed to understand unique effects in older adults and in men versus women.

as well as additional compounds including terpenes and flavonoids, all of which exert unique biobehavioral effects [7, 8]. Historically, most cannabis-focused research studies, including those related to mental health, have examined the impact and effects associated with recreational cannabis (i.e., non-medical) use. As the goal of recreational use is to feel altered, intoxicated, or high, recreational consumers typically seek products with significant amounts of delta-9-tetrahydrocannabinol (d9-THC), the primary intoxicating constituent of the plant [9, 10]. Accordingly, studies reporting the effects of cannabis use largely report the impact of d9-THC rather than "cannabis." As a result, when headlines report that "cannabis" is detrimental for any number of things, the term is almost exclusively used as a proxy for d9-THC. In contrast, medical cannabis (MC) use generally refers to those using products to address specific symptoms or conditions. MC patients frequently select products with more varied cannabinoid profiles and often aim to avoid intoxication [11, 12]. As a result, clinical outcomes in MC patients are likely to differ from those observed in recreational users. It is also important to note that cannabis use disorder (CUD) reflects problematic cannabis use patterns regardless of the goal of use (recreational versus medical). Although CUD is likely more prevalent in those using recreationally, as they typically select higher THC products to feel high/intoxicated, problematic use can occur, regardless of whether for recreational or medical purposes. Unfortunately, the majority of observational studies assessing cannabis use do not consider cannabinoid content of the products used, a variable that can significantly influence whether effects are harmful, neutral, or beneficial [5].

Importantly, cannabis is available in a range of different product types (flower, oils, edibles, etc.) with unique constituent profiles, and can be used in a wide variety of ways (e.g., inhaled, ingested, sublingual, oromucosal, topical, transdermal administration) [13]. Specific product choice is generally dictated by an individual's goal of use; the cannabinoid profiles of products used for recreational use are often quite different from those used medically to provide relief from specific symptoms or conditions [9, 11, 12]. With the recent surge in MC use, other cannabinoids, particularly those that are non-intoxicating, have garnered increased interest. For example, cannabidiol (CBD) has shown promise as a potential treatment for several psychiatric disorders, particularly due to its observed anxiolytic [14] and antipsychotic properties [15–17]. Although dozens of "minor cannabinoids" exist and are becoming increasingly popular [18], this article will focus on assessing cannabis use in general, as well as the impact of d9-THC and CBD on mental health outcomes, particularly related to psychosis, anxiety, mood, and post-traumatic stress disorder (PTSD). Factors that likely mediate the relationship between cannabis use and mental health will also be discussed, serving as important examples of why this topic can be so polarizing and research findings so mixed.

2 Current Findings

2.1 Psychosis

Although the incidence of psychotic disorders, such as schizophrenia, is relatively low, with lifetime prevalence estimated to be $\leq 1\%$ of the population [19], they are considered chronic and debilitating. A relationship between cannabis use and psychosis is well documented, leading some to believe that this commonly observed association suggests that cannabis use causes psychosis [20, 21]. However, mounting research suggests that cannabis use alone is not sufficient to cause psychotic disorders [22–24], especially as only a small number of cannabis users develop psychosis [25], and increased cannabis use has not resulted in a simultaneous increase in rates of psychotic disorders. Instead, it is likely more appropriate to view cannabis use as a contributing factor to a condition with a multifactorial etiology (e.g., genetic predisposition, use of other drugs, familial and social factors) [24, 26], or the result of individuals having a shared vulnerability to psychosis and cannabis use [22, 27].

Regardless, for those with psychotic disorders who use cannabis, negative outcomes are often observed. In general, observational studies suggest that earlier onset of use, products with higher d9-THC content (potency), and increased frequency and amount of cannabis used are associated with higher rates of psychosis, relapse, longer hospitalization time, and poorer treatment outcomes [28]. In addition, a survey study ($N=25,747$) examining both positive and negative effects of cannabis use across psychiatric disorders found that individuals with psychosis ($n=400$) were more likely to report negative effects of cannabis across all categories assessed (friendships, physical health, mental health, family life, work, studies, and quality of life) compared with individuals with other mental health conditions and healthy controls [29].

While these studies provide evidence of a negative association between cannabis use and psychosis, additional work is now devoted to harnessing the potential therapeutic effects of cannabinoids, specifically CBD, as a potential option for addressing psychotic symptoms. While several preclinical studies report antipsychotic effects associated with CBD, a number of clinical trials have also yielded promising results, as highlighted by several recent reviews [15–17]. These reviews demonstrate that almost all studies assessing CBD in patients with psychotic disorders report that CBD administration appears to improve symptoms [1, 30]. Notably, in one double-blind, randomized clinical trial ($n=42$), CBD demonstrated comparable efficacy to amisulpride, a traditional antipsychotic medication [31]. Further, CBD treatment was considered well tolerated, did not significant impact hepatic or cardiac function, and was associated with significantly fewer side effects than amisulpride, including fewer symptoms on the Extrapyramidal Rating Scale, less weight gain, and lower serum prolactin increase (a predictor of galactorrhea and sexual dysfunction). Taken together, an interesting dichotomy emerges in which the literature suggests that overall, the negative effects of "cannabis" use noted in observational studies of individuals with psychosis are likely associated with d9-THC exposure, while CBD treatments are generally related to symptom improvements in those with psychosis.

2.2 Anxiety

Anxiety is the most common of all mental health conditions, with an estimated 4% of the global population currently experiencing an anxiety disorder [32]. In the USA, up to one-third of Americans experience an anxiety disorder at some point during their lives [33]. Cannabis use is prevalent among individuals with anxiety disorders, and more frequent use of cannabis predicts increased anxiety and depression [34]. However, the most commonly reported motives for cannabis use typically include relaxation and relief from anxiety [35]. Few studies have examined the causal nature of the association, and those that have often fail to control for important factors, resulting in mixed findings [36, 37]. Like the majority of psychiatric disorders, most believe the etiology of anxiety disorders is multifactorial and therefore not caused by a single factor such as cannabis use [38].

Both preclinical and clinical studies have revealed dose-dependent, biphasic effects of d9-THC on anxiety; higher doses are generally considered anxiogenic while lower doses may be anxiolytic, although the low-dose anxiolytic effects supported by preclinical research are more mixed across clinical investigations [39, 40]. Further, no consensus has been reached regarding specific d9-THC doses that yield anxiogenic versus anxiolytic effects, and much likely depends on individual factors (e.g., genetics, metabolism, tolerance). Importantly, both preclinical [41, 42] and clinical [43, 44] studies have demonstrated that CBD does not appear to worsen anxiety at any dose and may effectively relieve anxiety at mid-range doses. Not surprisingly, there is significant interest in pursuing the development of cannabinoid-based products for anxiety, particularly those rich in CBD. While additional work is needed, acute administration studies and clinical trials thus far have reported that CBD appears to be effective for reducing situational anxiety, such as public speaking tasks [45, 46], and for reducing anxiety in those with moderate-to-severe anxiety [47], social anxiety disorder [48, 49], and treatment-resistant anxiety [50]. In addition, a recent systematic review and meta-analysis [44] assessed eight clinical studies evaluating anxiety symptoms (i.e., anxiety disorders or anxiety induced by other medical conditions such as high paranoia and PTSD) in 316 participants (157 assigned to CBD treatment and 159 to a control group). Results demonstrated statistically significant reductions in anxiety symptoms across a variety of disorders: generalized anxiety disorder (GAD), social anxiety disorder (SAD), obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD).

2.3 Mood

Depression is characterized by persistently low mood or loss of pleasure or interest in activities that cause significant impairment in daily life. According to the World Health Organization, depression affects approximately 5% of adults worldwide [51]. While studies generally report an association between cannabis and mood disorders, nothing thus far has been established to suggest causality. The majority of observational studies conducted to date suggest that although many individuals report using cannabis for mood relief, those with depression who use cannabis may be at increased risk for more severe symptoms, have higher rates of suicidal ideation, lower utilization of psychiatric services, and a higher chance of developing problematic cannabis use

[52]. Similarly, research has shown that among patients with major depressive disorder with problematic cannabis use, depressive symptoms improved significantly after a 28-day period of abstinence (measured by decreasing levels of THC metabolites) [53].

Interestingly, however, Walsh and colleagues [35] reviewed the differential associations between medical versus non-medical use and depressive symptoms. The authors found that while most observational studies of non-medical cannabis use reported negative effects on mood, seven of nine cross-sectional studies assessing medical cannabis (MC) reported use was associated with better mood and a lower likelihood of experiencing a depressive event [35]. Given additional studies demonstrating that risk for negative outcomes is elevated with increased frequency and higher amounts of cannabis used [28], these seemingly contradictory study findings may be explained by differences in patterns of cannabis use (d9-THC versus CBD exposure, frequency and duration of use, etc.), but it is also possible that differences could reflect other variables such as age, sex, and genetic differences, among others.

Notably, previous studies largely reflect the use of cannabis for recreational/non-medical purposes. In the first longitudinal, observational study assessing MC use, pilot results from 13 patients revealed improved mood 3 months after initiating self-selected MC regimens. More recent analyses replicated findings in a larger sample of 54 patients and also revealed that improvements were sustained over 12 months of treatment relative to baseline (prior to initiation of MC) [54]. Further, findings revealed that clinical improvements were correlated with higher CBD, but not d9-THC exposure [54], underscoring the importance of assessing actual exposure to individual cannabinoids. Although no clinical trials thus far have directly assessed the use of CBD for depression [1], some assessing CBD or CBD-containing products for individuals with primary anxiety [47, 50] or other medical conditions [55] have also reported improvements in mood. Future work in this area is also supported by the documented ability of CBD to impact multiple neurotransmitter systems involved in depression (e.g., serotonergic, glutamatergic) as well as animal studies demonstrating rapid and sustained antidepressant effects of CBD [56].

Bipolar disorder (BD) affects approximately 4.4% of adults at some point during their lives. Cannabis use is extremely common among those with BD [57], and 20–50% of patients report some form of cannabis-related problems [58]. Further, patients with BD who engage in cannabis use often exhibit reduced treatment compliance, higher levels of illness severity, and increased likelihood to attempt suicide [58–63]. It remains unclear, however, whether cannabis use contributes to the pathogenesis of the disorder, or if patients are using cannabis to address symptomatology as a form of self-medication prior to a formal diagnosis [64–66]. Interestingly, some observational studies have shown that patients with BD frequently report subjective clinical improvements as a result of cannabis use [64, 67–70]. As previously noted, given that negative mental health outcomes related to "cannabis" are generally reflective of d9-THC exposure, a likely hypothesis is that exposure to specific cannabinoids represents a significant confounding variable that has yet to be fully explored in patients with BD.

CBD has great potential as a treatment for BD; as a compound with anxiolytic, antipsychotic, and anticonvulsant properties (anticonvulsants are often used off-label to treat BD), CBD-containing treatments could not only be effective, but may also help reduce the number of medications typically necessary to treat the various symptoms associated with BD [55]. One recently published clinical trial examined the use of adjunct CBD for acute bipolar depression; in this randomized, double-blind, placebo-controlled pilot study of 35 patients, depressive symptoms decreased significantly between baseline and the study endpoint, but no significant differences were noted between the CBD and placebo groups [71]. However, exploratory analyses suggested that higher doses of CBD were more effective than placebo, underscoring the need for additional research in this area.

2.4 Post-traumatic Stress Disorder (PTSD)

Global estimates from the World Health Organization suggest that about 70% of adults will experience a traumatic event at some point in their lives [72]. Although only a small percentage (roughly 4%) develop PTSD [72], many of those who do have difficulty finding effective treatments [73]. For example, a recent review of selective serotonin reuptake inhibitor (SSRI) treatments for PTSD reported symptom improvement in only 58% of SSRI participants compared with 35% of placebo [74], and although trauma-focused interventions can be effective, they are prone to high dropout rates [75]. Interestingly, studies demonstrate that the endocannabinoid system (ECS) is implicated in its biological processes of PTSD, including stress response regulation, fear extinction processes, and neuroplasticity for emotional regulation. Therefore, it is not surprising that rates of cannabis use are three to four times higher in individuals with PTSD compared with those without. Patients with PTSD often report using cannabis specifically to improve symptoms such as anxiety, sleep disturbance, hyperarousal, and avoidance of emotional triggers [76].

Although some research studies suggest that patients with PTSD may find relief with cannabinoid use, others caution that cannabis use may be actually be associated with more severe symptoms and may ultimately result in problematic patterns of use [77]; overall findings are decidedly mixed. In fact, a recent review conducted by Rodas and colleagues [78] examined ten studies assessing the effects of cannabis

and cannabinoids on symptoms of PTSD in patients without CUD; half of the studies reported clinical benefits while the other half reported either no effect or worsening of symptoms. Among three additional studies examining cannabinoid use in a sample of individuals with a dual diagnosis of PTSD and CUD, all three studies reported a heightened risk of symptom worsening. Accordingly, heterogenous findings may be related to factors such as whether an individual exhibits problematic cannabis use or CUD, which is highly correlated with product choice, and more specifically, higher THC exposure given its strong reinforcing biologic effects, which are related to higher addiction severity [79, 80]. In contrast, CBD is non-intoxicating and has a low potential for addiction as it lacks rewarding effects and is not associated with tolerance or withdrawal symptoms [81]. Importantly, Rodas and colleagues note that studies included in their review examined the effects of THC, CBD, and various concentrations of each, which were administered via several different routes (inhalation, tablets, oral spray), likely contributing in large part to these conflicting findings. In addition, some work also suggests mixed findings may be due to the fact that cannabis use may provide short-term relief, but long-term use may result in poorer outcomes [82]. Despite several reviews on the topic [73, 78, 83, 84], comprehensive data assessing the potential benefit and harms of cannabis use for PTSD are lacking, as most studies to date are limited by small sample sizes and poor control over other related variables. Given the high rates of cannabis use in those with PTSD and the need for alternative treatment options, additional empirically sound studies are warranted.

3 Factors Impacting the Relationship between Cannabis Use and Mental Health

The current state of the evidence regarding the impact of cannabis on mental health highlights a much more complex relationship than many believed in decades past. It is clear that the impact of cannabis on various mental health conditions depends on a range of factors, including those that are related to cannabis itself—for example, product choice, which dictates exposure to specific cannabinoids, and patterns of cannabis use (frequency, magnitude, etc.)—as well as a host of individual factors specific to the user, including age, sex, genetic profile, family history of psychiatric disorders, and others [2] (see Fig. 1). Below, several of these important, yet often overlooked, factors are discussed in greater detail.

3.1 Cannabis Product Choice and Use Patterns

Both d9-THC and CBD have established therapeutic properties, and given their different mechanisms of action, it is not surprising that each of these cannabinoids affect specific psychiatric symptoms differently. Importantly, individuals who use cannabis recreationally generally seek products high in d9-THC, a partial agonist at both CB1 and CB2 receptors [85, 86], and most studies assessing the effects of cannabis have focused on those using for recreational purposes. Accordingly, as previously stated, study findings assessing the impact of "cannabis" on mental health are primarily reporting the impact of exposure to d9-THC, which is often associated with negative effects, especially when used more frequently and in higher amounts. Fortunately, recently developed metrics [13] are likely to clarify findings by providing researchers the ability to assess overall exposure to individual cannabinoids by considering frequency and actual amount of specific product(s) used. These methods have provided initial evidence in observational studies that THC and CBD exposure have a differential impact on clinical outcomes, with higher exposure to CBD appearing to drive improvements in mood and anxiety [54].

Notably, until recently, relatively few studies focused on the impact of CBD, which is often touted for its wide-ranging therapeutic benefits. Mechanisms of action for CBD remain unclear; however, studies indicate that CBD has low affinity for both CB receptors and likely exerts its effects through indirect mechanisms and multiple receptor types [87, 88]. Currently, more than 65 molecular targets of CBD have been identified [89]; the most studied include $5HT_{1A}$, GPR55, and transient receptor potential (TRP) channels. Additionally, while some studies suggest that CBD may exert anxiolytic effects through allosteric modulation of $GABA_A$ receptors and antipsychotic effects via dopamine D2 receptors [89], it is more likely that multiple mechanisms contribute to its therapeutic effects [1]. Overall, CBD appears to be well tolerated, including in clinical trials where mid- to high-range doses are administered daily or more and shows promise across many studies assessing its use for psychotic, mood, anxiety, and post-traumatic stress disorders [1].

Further, while most work to date has focused on d9-THC and CBD, increasing numbers of cannabis products also contain a range of minor cannabinoids (e.g., cannabigerol [CBG], cannabinol [CBN], cannabichromene [CBC], tetrahydrocannabivarin [THCV]) given their purported health benefits. Dozens of other compounds, including terpenes and flavonoids (responsible for the scent, flavor, and color profile of cannabis chemovars), are also touted for their unique properties [7, 8, 18], including antiinflammatory and antioxidant effects, among others [90, 91], which may also play a role in mediating psychiatric symptoms given studies documenting a relationship between psychiatric disorders and both inflammation [92] and oxidative stress [93]. Products containing an array of cannabinoids, terpenes, flavonoids, and other naturally occurring compounds from

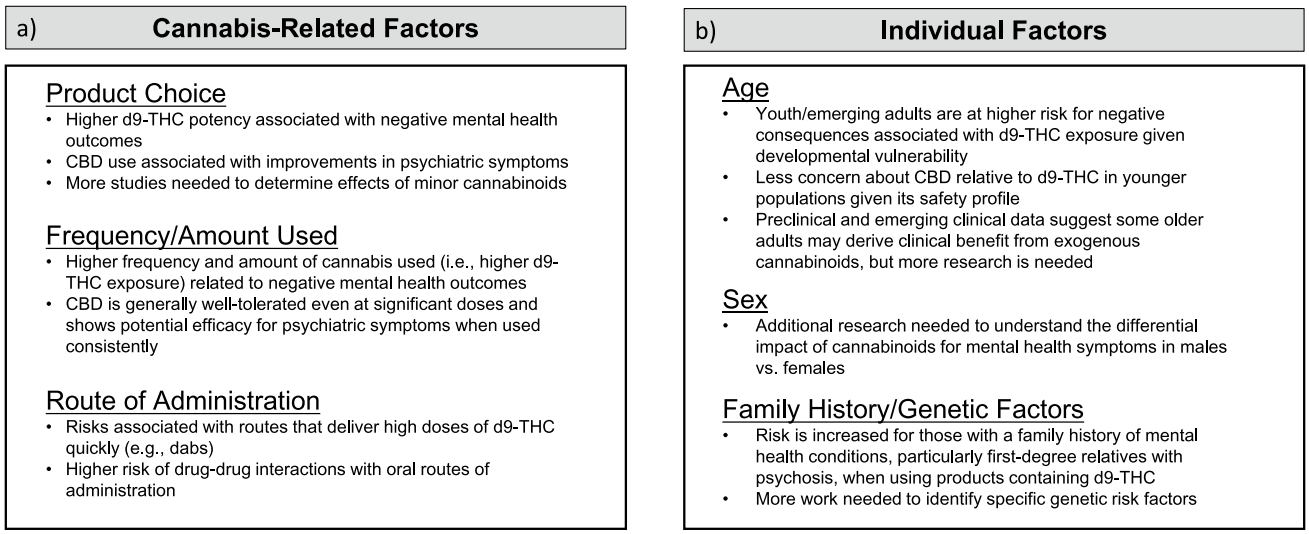

Fig. 1 Factors impacting mental health outcomes: a summary of cannabis-related factors (**a**) and individual factors (**b**). *d9-THC* delta-9-tetrahydrocannabinol, *CBD* cannabidiol

the plant are referred to as "full-spectrum" products, while those that contain this natural array but have no quantifiable d9-THC are termed "broad-spectrum." There is growing evidence that compounds in cannabis interact synergistically to enhance the therapeutic benefits of each compound in a phenomenon often referred to as the entourage effect, and some studies have shown that full- and broad-spectrum products that are high in CBD may be more efficacious or yield therapeutic effects at lower doses than isolated compounds [94–96], an important phenomenon to explore as cannabinoid-based drug development expands.

Further, cannabis products are available in many forms, including dried flower, concentrates (those with very high levels of d9-THC), oils and extracts, edibles/beverages, capsules and tablets, topical and transdermal preparations, and suppositories. Each of these product types can be used in different ways, commonly referred to as the route of administration (inhaled, ingested, applied under the tongue or on the skin, etc.). Although it is likely that different routes of administration will confer specific risks for mental health conditions given differences in bioavailability and pharmacokinetics, which influence time to get an effect, duration of effects, and potential drug–drug interactions, few studies have been conducted to date. However, choosing products high in d9-THC or those that utilize routes of administration that deliver high doses of d9-THC very quickly (e.g., dabs) are likely to pose a higher risk for negative outcomes. Unfortunately, individuals with psychiatric disorders tend to report more frequent cannabis use and use of more potent (i.e., higher d9-THC content) products [29]. Research has shown that using cannabis with higher d9-THC content is associated with stronger reinforcing effects [79, 97], greater addiction severity [80], and increased risk for psychosis [98]. Interestingly, one study found that daily use of lower potency cannabis was not associated with an increased risk of psychotic disorders [99]. Given that studies have generally assessed d9-THC potency via self-report of individuals' own products as high or low potency, additional studies that quantify the actual cannabinoid content of products used are warranted.

Some studies report fewer negative outcomes associated with cannabis use in those using products with low but detectable amounts of CBD [100]. As previously noted, numerous studies have noted positive clinical effects associated with CBD, including benefits for symptoms related to psychosis, anxiety, and mood [1, 30]. Further, studies of CBD have investigated its potential to prevent or treat CUD [101–103]. One initial study assessed 94 cannabis users while non-intoxicated, and again while acutely under the influence of their own chosen smoked cannabis products and found that those who used cannabis with higher amounts of CBD were less likely to demonstrate attentional bias to cannabis-related images [104], suggesting that CBD may protect against the development of CUD. Further, a small open-label clinical trial of vaporized CBD ($n=20$ at baseline, $n=9$ at follow-up) reported that 30% of patients reduced their daily cannabis consumption by at least 50% after 12 weeks, providing preliminary data regarding the efficacy of CBD for treating CUD [103]. Regardless of the observed clinical benefits of CBD and its potential for mitigating risks associated with cannabis use or treating symptoms of CUD, it is important to recognize the false belief that using any cannabis product containing CBD eliminates

the risk of adverse psychiatric effects related to d9-THC [105].

3.2 Age

In general, when it comes to the effects of cannabis, age matters. Due to critical neurodevelopmental changes that occur throughout childhood, adolescence, and emerging adulthood, younger individuals are more vulnerable to the adverse effects of any drug, including cannabis [106]. Importantly, preclinical work has demonstrated that CB1 receptor binding peaks during puberty, remains stable throughout early to mid-adulthood, and ultimately declines in older adulthood [107], while studies in humans similarly reveal higher CB1 receptor binding in younger versus older populations [108]. Given that CB1 receptor binding is at its highest in adolescence and since the ECS affects growth, differentiation, and connectivity of neurons [109–112], exposure to exogenous cannabinoids during adolescence and emerging adulthood, particularly CB1 receptor agonists such as d9-THC, is likely to disrupt the developmental trajectory. In fact, studies have shown that earlier onset (generally prior to age 15 or 16) of cannabis use is associated with poorer cognitive performance and alterations in brain structure and function in recreational consumers [113]. Studies have also shown that earlier initiation of recreational cannabis use is related to higher prevalence of psychosis, anxiety, and depression [114]. These findings are particularly important as cannabis use is common in younger cohorts; the most recent US National Survey on Drug Use and Health (NSDUH) survey found past-year cannabis use was most prevalent among emerging and young adults aged 18–25 (38.2%), and 11.5% of adolescents aged 12–17 also reported past-year use [115].

Given the therapeutic benefits of CBD combined with its lack of biologically reinforcing properties and low risk of addiction [81], its various mechanisms of action, and demonstrated therapeutic effects, there is considerably less concern about CBD relative to d9-THC exposure in younger populations. Although additional clinical trials are needed to determine efficacy, safety, and tolerability before recommending CBD as potential treatment strategy for pediatric populations experiencing specific psychiatric symptoms, one 12-week open-label trial of CBD in 31 individuals aged 12–25 with anxiety disorders reported decreased anxiety and depression scores and an adequate safety profile [50].

Given age-related changes that naturally occur in the ECS over time, including reduced signaling of CB1 receptors and decreased overall endocannabinoid tone [116, 117], as well as slowed metabolism [118], it is likely that cannabinoids impact older adults much differently than younger cohorts. For example, one preclinical study reported that low doses of d9-THC resulted in a reversal of age-related cognitive decline in mature and old mice, but the same exposure to d9-THC resulted in decrements among young mice [119]. The authors hypothesized that improvements in the older cohort may have been the result of upregulating the aging ECS via increased signaling secondary to low dose d9-THC exposure. Additional work has also revealed that repeated stimulation of CB1 receptors with higher doses of d9-THC leads to receptor desensitization and tolerance in young mice, but not older mice [120], further highlighting age-specific effects of d9-THC. In analyses of data from our own longitudinal, observational study of 54 individuals interested in initiating MC treatment [54], although older adults were not intentionally recruited, the average age of patients ($n = 54$) was nearly 50 years ($M = 49.17$). Findings revealed that after initiation of a MC treatment regimen, patients not only reported improved clinical state (significantly improved mood, anxiety, and sleep), but also exhibited improved cognitive performance on measures of executive function including the Stroop Color Word Test, Trails B, Wisconsin Card Sorting Test, and Letter Number Sequencing, as well as generally stable performance on the Rey Auditory Verbal Learning Test, a measure of verbal learning and memory. These findings stand in stark contrast to our previous studies of recreational users, which documented decrements on these same tasks, particularly in those who began using cannabis during their teenage years [121–123]. Additional data from this study of primarily adult/older adult MC patients (average age = 47.84 years, $n = 37$) also revealed significantly increased white matter coherence following 3 months of MC treatment; a matched comparison group of non-cannabis using adults/older adults did not demonstrate this change [124]. Importantly, previous work in younger, recreational consumers generally reports decreases in white matter coherence relative to non-cannabis users or their own pre-cannabis use assessments [125–128], further highlighting age-specific effects of cannabis on the brain.

Although studies assessing mental health outcomes in older adults are relatively scarce, two review articles recently summarized findings to date. Specifically, Wolfe et al. [129] observed greater frequencies of depression, anxiety, and substance use in those using cannabis, while Vacaflor and colleagues [130] similarly reported that the prevalence of lifetime mental health disorders was two times higher in older adults who had used cannabis in the past year compared with those who either had a more remote history of cannabis use or who had never used cannabis; however, the directionality of this relationship cannot be determined from these studies. Interestingly, Vacaflor and colleagues [130] also found that across seven clinical trials of cannabis or d9-THC/CBD products in older adults, short-term, low-dose MC use did not significantly increase the risk of serious mental health symptoms. Although rates of cannabis use remain lower in older adults compared with other age groups, as of 2019, NSDUH survey data suggest 6.4% of adults aged 50+ used

cannabis in the past month, a number that has grown significantly year after year, making older adults the fastest growing group of cannabis consumers in the nation [131, 132]. These statistics highlight the need for additional work examining the impact of cannabis and cannabinoids in older populations.

Finally, with regard to age-related effects of cannabis, it is possible that associations between cannabis and mental health are non-linear across the lifespan. For example, Leadbeater and colleagues [106] examined survey data from Canadian adolescents (the Victoria Healthy Youth Survey [V-HYS], $n=662$) and US adults (National Epidemiologic Survey on Alcohol And Related Conditions [NESARC-III], $n=36{,}309$) to examine the strength of associations with cannabis use from adolescence to older adulthood (ages 15–65). Overall, results highlighted unique patterns of associations between different mental health symptoms (e.g., depression, anxiety, and psychosis) at different ages. Specifically, relationships between cannabis use frequency and mental health symptoms revealed that more frequent use was associated with psychotic symptoms after age 22 and more depressive symptoms from ages 16–19 and after age 25; cannabis use frequency was not associated with anxiety symptoms in this sample. Similarly, McDonald et al. [133] used population-based survey data from 11,363 Ontario residents aged 12–24 who were followed over 6–9 years to examine potential associations between cannabis use and psychotic disorders. While this study examined a more limited age range, the authors reported a significant association between cannabis use and psychotic disorders during adolescence (ages 12–19), but not during young adulthood (ages 20–33). Notably, however, studies to date examining age-related effects have not examined product type or controlled for THC and/or CBD content.

3.3 Sex

Recent work has also begun to examine how sex assigned at birth and gender mediate the relationship between cannabis and mental health outcomes given underlying neurobiological differences in the ECS. For example, while men generally have more CB1 binding sites, women have more efficient CB1 receptors; differences between sexes have been also observed in the metabolic processing of d9-THC [134]. To date, studies suggest that women may be more susceptible to some of the negative mental health effects related to recreational cannabis use, including depression, anxiety, and suicidal ideation [135, 136]. In terms of specific cannabinoids, one study examining sex differences in the pharmacodynamics of oral and vaporized d9-THC found that women were more likely to endorse higher ratings of "anxious/nervous," "heart racing," and "restless" [137]. However, a scoping review examining sex and gender as potential moderators of the neuropsychiatric effects and pharmacokinetics of CBD reported mixed results [138], highlighting the need for more work in this area. Given an emerging trend of increased cannabis use among women [139–141], particularly for medical purposes (for anxiety, pain, menopause-related symptoms, etc. [141, 142]), additional research is needed to examine how cannabinoid exposure differentially impacts mental health symptoms in men versus women.

3.4 Family history and genetics

When considering the relationship between cannabis and mental health, it is also important to note that individuals with a family history of certain mental health conditions, particularly those with first-degree relatives with psychosis, appear to be at higher risk for adverse mental health outcomes associated with cannabis use [143]. This is likely due to a combination of psychosocial and genetic factors. Studies reviewing the role of genetics in the association between cannabis use and psychiatric disorders have found that while there is strong evidence for shared genetic influences in some disorders, other factors (environmental, personal, etc.) are likely key or potentially sole contributors [144, 145].

4 Conclusions

Overall, it is clear that the relationship between cannabis use and mental health is complex, with study findings often appearing mixed or inconsistent depending on the population under study. Relationships are also mediated by a variety of factors, including patterns of cannabis use and cannabinoid exposure, age, sex, family history, and genetics. While recreational cannabis use and higher exposure to d9-THC appear to be most commonly associated with negative mental health outcomes, evidence suggests significant potential for the use of CBD and CBD-containing products for the treatment of at least some psychiatric symptoms and conditions. Additional minor cannabinoids may also have therapeutic potential, and certainly warrant further investigation.

Nonetheless, it is important to recognize that a number of obstacles must be addressed in pursuit of cannabinoid-based, alternative treatment options for psychiatric disorders. Many individuals, particularly patients with psychiatric disorders, actively seek intoxication and therefore choose products with high THC content [29], which will likely have a negative impact on their mental health. However, it is possible that by offering an alternative treatment option that improves psychiatric symptoms (i.e., high-CBD products with low amounts or no THC) with fewer side effects than conventional medications, some individuals may reduce their use of high-THC product after achieving symptom remediation.

In addition, it must be acknowledged that cannabinoids, particularly CBD, have the potential to cause drug–drug interactions (DDIs), primarily due to their involvement with the hepatic cytochrome P450 (CYP450) system [146]. In particular, when CBD-based products are ingested, they require metabolism by the liver, raising significant concerns regarding potential DDIs [147]. Although few studies to date have assessed the significance of common DDIs with cannabinoids, evidence suggests moderate-to-strong interaction risks between CBD and drugs metabolized by CYP450 enzymes [148, 149]. Importantly, DDIs are most common for drugs with a narrow therapeutic index, raising concerns for certain psychotropic medications, such as antidepressants and anticonvulsants (often used off-label for certain mood disorders). Notably, however, it is possible to reduce the risk of DDIs by utilizing routes of administration that bypass first-pass metabolism in the liver. While inhalation avoids hepatic metabolism and has other pharmacokinetic benefits such as rapid onset of effects, there is often concern regarding potential respiratory consequences associated with smoking/vaping [150]. Alternative routes of administration including oromucosal (e.g., sublingual) or other drug delivery systems (e.g., dissolvable tablets, nasal spray) could be promising avenues to pursue. For example, sublingual administration of drugs bypasses first-pass metabolism and ensures rapid absorption, reportedly up to ten times greater than oral administration [151].

Overall, additional research is needed, including more work focused on sex differences and studies of older adults. Each of these factors are highly understudied, both on their own and in terms of their intersection with mental health, yet emerging evidence suggests these variables have a significant impact on clinical outcomes. Investigations assessing factors that may mediate mental health outcomes are also needed, such as those focused on assessing the impact of minor cannabinoids or whether certain genetic markers could identify those at increased risk for negative consequences or those who are likely to exhibit the greatest treatment response to cannabinoid-based therapeutics. Exploring each of these avenues is sure to provide a more nuanced and accurate view of the impact of specific cannabinoids on mental health for varied clinical populations. The field must move away from evaluating the effects of "cannabis" as if it were a single substance. Instead, research examining the influences of individual factors could eventually be used to design an algorithm to generate an evidence-based risk/benefit analysis tailored to each individual. While there is still much work to be done before a framework like this can be applied, this approach would ultimately make cannabis and cannabinoid use safer for all, and potentially provide symptom alleviation for many who continue to suffer from a range of psychiatric symptoms.

Declarations

Funding During manuscript preparation, S.G. and K.S. were supported by the National Institute on Drug Abuse (5R01DA048821, 5T32DA015036) and private donations to the Marijuana Investigations for Neuroscientific Discovery (MIND) Program.

Conflict of interest The authors declare the following competing interests: S.G. reported grants from Foria/Praxis Ventures and Charlotte's Web for projects outside the submitted work. Over the last 3 years, S.G. has reported receiving authorship fees from the Coalition for Cannabis Policy, Education, and Regulation (CPEAR) and presentation fees from Philip Morris International outside the submitted work. S.G. is also a scientific advisor for Ajna Biosciences. K.S. reported receiving fees from CPEAR outside the submitted work. No funding sources were involved in the preparation, review, or approval of the manuscript, or the decision to submit the manuscript for publication.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Data availability Not applicable.

Code availability Not applicable.

Author contributions The first draft of the manuscript was written by Dr. Kelly Sagar, with critical revisions provided by Dr. Staci Gruber. Both authors have read and approved the final submitted manuscript and agree to be responsible for this work.

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