

Risk for Cannabis Use Disorder in People Who Use Cannabis to Cope with Internalizing Disorders: Implications for Policy and Practice

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Abstract

The prevalence of Cannabis Use Disorder (CUD) is increasing in the United States, likely related to increasing cultural and legal acceptance of cannabis. While most cannabis users will not develop a CUD, certain behaviors may increase risk. For example, smoking to cope with anxiety or depressive disorders is associated with higher rates of cannabis use. Users who smoke to cope with these internalizing disorders (anxiety, depression) increase the addictive potential of cannabis. Systems that potentially maintain problematic use in people with internalizing disorders include the reward processing and the stress responsivity systems. Both exhibit neurobiological changes after chronic heavy cannabis use and are affected across internalizing disorders. The shared importance of these systems may warrant several recommendations for policy and practice. Some reexamine cannabis-related policy, invest in local communities, and improve cannabis education.

Keywords

cannabis, cannabis use disorder, internalizing disorders, anxiety, depression, stress, reward

Social Media Post

Overlapping reward processing and stress responsivity systems may partially explain increased risk for Cannabis Use Disorder in people using cannabis to cope with internalizing disorders. This area of literature suggests evidence-based recommendations for policy and practice.

- Clinicians can refresh their knowledge on evidence-based medicinal cannabis guidelines and engage in open, honest, and nonjudgmental conversations with their clients about cannabis use to empower their clients to make the best decisions for themselves.

Key Points

- Cannabis Use Disorder (CUD) is a condition associated with serious functional impairment and is increasing in prevalence in the United States.
- The reward processing and stress responsivity systems are implicated in CUD and internalizing disorders (such as anxiety or depression) and may explain some of the increased risk for CUD development in people with internalizing disorders.
- Policymakers should consider the most current scientific evidence when writing new cannabis-related policy. Policymakers should also consider revisions to current cannabis policies (especially medicinal policies) to better align with the scientific evidence.
- Communities play an important part in providing opportunities for non-drug-related activities and infrastructure that may help reduce problems related to substance use. Policymakers should invest in community infrastructure and mental healthcare.

Introduction

Growing cultural and legal acceptance of cannabis use is taking place in the United States (U.S.). As of June 2023, while cannabis remains illegal and classified as a Schedule I drug at the federal level, 23 states and the District of Columbia have legalized recreational use, and 38 states have legalized medicinal use (National Conference of State Legislatures, 2023). Legalization of both recreational and medicinal cannabis has demonstrated some clear positive impacts, such as less money, time, and hardship spent on prosecuting cannabis possession criminal cases; decreased criminal prosecution of cannabis possession in groups of people who have historically experienced disparities; decreased opioid-related overdoses; and increased tax

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revenue to fund various public policy priorities such as mental health and substance use treatment and education (Firth et al., 2019; Todd, 2018).

Cannabis and cannabis products are widely thought to hold therapeutic benefit for a multitude of disorders, though only three cannabis products are approved by the U.S. Food and Drug Administration (FDA) for medicinal use, all of which are synthetic tetrahydrocannabinol (THC), which is the primary psychoactive cannabinoid found in cannabis plants, or cannabidiol (CBD), which is a non-psychoactive cannabinoid found in cannabis plants. These approved products include dronabinol and nabilone for chemotherapy-related nausea, nabilone for HIV-related low appetite, and CBD for two rare seizures disorders. Additionally, 1:1 ratio of CBD and THC has been approved by some regulatory agencies outside the U.S. for multiple sclerosis-related spasticity and neuropathic pain (Potenza et al., 2023). While research evaluating the medicinal properties of cannabis products are underway, there is very mixed evidence about efficacy of cannabis products for treatment of various conditions, and the FDA has not approved any cannabis products for therapeutic use for many of the conditions it is promoted to treat (Khalsa et al., 2022). Despite the lack of evidence for the therapeutic use of cannabis for many conditions, many states have legalized its use for treatment of various medical conditions, some of which include psychiatric conditions such as posttraumatic stress disorder (PTSD), anxiety disorders, depression, or “other debilitating illnesses where medicinal use has been deemed appropriate and has been recommended by a physician” (Britannica ProCon.org, 2023). This seems to be an open door for physician recommendation or authorization of cannabis product use for any disorder. Furthermore, many healthcare trainees have expressed a lack of knowledge about and competence in medicinal cannabis practices (Zolotov et al., 2021), highlighting a gap in training on an increasingly relevant issue.

While the legalization of cannabis in various ways has undoubtedly had positive impacts, consider also the risks legalization poses in order to mitigate potential negative outcomes for individuals who use cannabis. Cannabis Use Disorder (CUD) is one such outcome, which refers to a pattern of continued cannabis use despite significant impairment. These impairments span across three domains of criteria, including loss of control of cannabis use, interpersonal or role dysfunction, and negative physical or psychological effects (American Psychiatric Association, 2022; Hasin et al., 2016). CUD prevalence is rising and is expected to continue rising with growing cultural and legal acceptance of cannabis use (Hasin & Walsh, 2021). In 2021, an estimated 16.267 million noninstitutionalized residents of the United States aged 12 or older met criteria for CUD in the prior year (Substance Abuse and Mental Health Services Administration, 2022). Although most cannabis users will not develop CUD (Cogle et al., 2016), some factors may contribute to greater risk of developing a CUD. One such

factor is using cannabis to cope with internalizing disorders (INTDs), such as anxiety and depression, which is associated with other risk factors such as more frequent use (Bresin & Mekawi, 2019; Sofis et al., 2020).

Associations Between Internalizing Disorders and CUD

The self-medication hypothesis posits that substances are used to temporarily relieve distressing depressive and anxiety symptoms, which can ultimately lead to the development of an independent substance use disorder (SUD; Khantzian, 1997). Specific to cannabis, INTDs are associated with CUD (Grant et al., 2004; Onaemo et al., 2021) and cannabis is often used as a coping strategy to reduce negative affect. Indeed, acute anxiolytic (i.e., anxiety-reducing) effects are commonly reported after cannabis intoxication, which may serve to negatively reinforce cannabis use (Glodosky & Cuttler, 2020; Hathaway, 2003). Further, coping with negative affect and mood enhancement are common motives for continued marijuana use (Bresin & Mekawi, 2019). Relatedly, greater marijuana use frequency is positively related to using marijuana to self-medicate symptoms of anxiety and depression, as well as physical symptoms, such as pain (Moore et al., 2021; Temple et al., 2014). Despite reports that cannabis is used as an anxiolytic, hallmark symptoms of CUD include 1) distress associated with prolonged use despite attempts to quit or cut down and 2) adverse psychological effects resulting from acute intoxication or withdrawal (American Psychiatric Association, 2022). The anxiolytic or anxiogenic (i.e., anxiety-generating) effects during cannabis intoxication may depend, in part, on pharmacological factors, such as delta-9-THC or CBD percentages (Sharpe et al., 2020). In addition, CUD severity and INTD symptoms may reinforce one another. This would be consistent with allostatic models of addiction (Koob & Volkow, 2010): As disordered substance use becomes more severe, neurobiological changes in reward processing and stress sensitivity produce a predominant negative affective state, ultimately maintaining disordered use (Koob et al., 1999; Lowe et al., 2019).

According to the self-medication hypothesis, INTD symptoms should longitudinally predict future substance use (Khantzian, 1997); however, the reverse relationship is also possible (Turner et al., 2018). Although comorbidity between disordered cannabis use and INTD symptoms is prevalent, the nature of the relationship is unclear. For example, several studies have found that cannabis use longitudinally predicts depression and anxiety status (Patton et al., 2002), incidence of anxiety disorders (Kedzior & Laeber, 2014), and greater symptoms of unipolar depression and bipolar disorder (Bovasso, 2001; Jefsen et al., 2023), even after covarying for common confounding variables (e.g., neuroticism, familial psychiatric history, and childhood

adversity). Further, a recent meta-analysis of 14 longitudinal studies found a moderate, positive association between heavy (i.e., at least weekly) cannabis use and depression incidence (Lev-Ran et al., 2014). On the other hand, null effects have also been reported (Danielsson et al., 2016; Feingold et al., 2015). A 3-year longitudinal study of over 34,000 U.S. adults in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) database (Feingold et al., 2016) failed to find a prospective association between CUD measured at baseline and anxiety disorders diagnosed at a 3-year follow-up, or a reverse relationship of anxiety disorders predicting cannabis use frequency or CUD status. Another study using the same sample of U.S. adults from the NESARC database failed to find CUD status at baseline predicted a diagnosis of major depressive disorder (MDD) 3 years later (Feingold et al., 2015). However, they did find that MDD at baseline had a significant, positive relationship with future cannabis use but not CUD status.

Finally, the influence of confounding variables on the prospective relationship between cannabis use and INTD symptoms shows mixed results. For instance, a small meta-analysis of five longitudinal studies tested baseline cannabis use's association with future incidence of anxiety disorders after adjustment for common confounding variables (Kedzior & Laeber, 2014). There was an overall positive association between cannabis use and anxiety symptoms, despite two of the five studies reporting null effects (Fergusson et al., 1996; van Laar et al., 2007). However, confounding factors such as other substance use (i.e., tobacco, alcohol) appear to heavily influence the relationship between cannabis and mental health problems (Degenhardt et al., 2001). Further, Danielsson et al. (2016) found cannabis use predicted greater symptoms of depression and anxiety, as well as a significant effect in the reverse direction, at a 3-year follow-up. However, all associations became null after covarying for common confounding influences, such as other substance use, education status, and environmental factors (e.g., location of childhood upbringing; Danielsson et al., 2016).

Taken together, there is strong evidence of INTD symptoms and problematic cannabis use comorbidity, yet evidence of a prospective relationship is mixed, possibly due to the influence of third variables (i.e., childhood adversity, poly-substance use history). Mixed evidence for a longitudinal relationship precludes generalizations about causal links between CUD and INTD symptoms. To further understand this relationship, researchers may benefit from examining common overlapping neurobiological systems affected by CUD and INTDs. Considering neurobiological systems demonstrate good predictive validity regarding addiction (Koob, 2013) and INTDs (Martin et al., 2009; Nestler et al., 2002), these systems may contribute to the maintenance of comorbid CUD and INTDs.

Reward and Stress Systems in Cannabis Use and Internalizing Disorders

Broadly, long-term substance use leads to a cascade of neurobiological changes that contribute to greater substance use severity and INTD symptoms. Initially influenced by McEwen's conceptualization of allostatic load (McEwen, 1998), Koob and Le Moal (2001)'s allostatic model of addiction posits that repeated substance use alters neurobiological reward and stress homeostatic thresholds. Similarly, the relationship between INTD symptoms and altered reward/stress systems can be examined within an allostatic framework, whereby chronic psychopathologically-mediated stress from anxiety and depressive symptoms alters neurobiological systems responsible for reward processing and stress reactivity. In each case, the body continuously exerts energy to regain homeostasis, but such "wear and tear" from chronic substance use or INTD symptoms leads to repeated allostatic states, eventually developing into an allostatic load indicative of greater psychopathology.

First, chronic cannabis use appears to be associated with alterations in several reward-related indices spanning self-report, behavioral, and neuroimaging studies. Two recent meta-analyses examining cannabis use and facets of reward processing (e.g., anhedonia, reward anticipation) (Pacheco-Colon et al., 2018; Skumlien et al., 2021), as well as one meta-analysis examining drug addiction more broadly and reward processing (Luijten et al., 2017) provide partial support for this relationship. For instance, cross-sectional data appear mixed between the association of cannabis and self-reported anhedonia and motivation. Similarly, cross-sectional neuroimaging studies spanning PET and fMRI demonstrate mixed results of cannabis use and reward anticipation. Across different substances, such as cannabis, alcohol, and cocaine, a meta-analysis by Luijten and colleagues (2017) found differential striatal activity between reward anticipation (blunted activity) and reward outcome (enhanced response), suggesting alterations in reward processing may not be unique to cannabis, but may generalize to other substance use. Despite a majority of evidence examining cannabis use and alterations in reward valuation being cross-sectional, longitudinal evidence suggests that chronic cannabis use is associated with blunted neural activity in brain regions responsible for reward anticipation (Martz et al., 2016; Van Hell et al., 2010), deficits in reward- and punishment related trial and error learning (Castellanos-Ryan et al., 2017), and reduced self-reported initiative and persistence (e.g., motivational capacity; Lac & Luk, 2018). Notably, inconsistent findings between cannabis and reward processing may be related to operationalization variability (i.e., operationalizing "light" vs. "heavy" cannabis users) and variability between studies in accounting for confounding variables, such as other substance use or INTD symptoms.

Reward dysregulation is also observed in studies examining depression and anxiety. For instance, people with depression, relative to those without clinical psychopathology, exhibit decreased sensitivity to reward (Huys et al., 2013), decreased effort-related motivation to attain rewards (Treadway et al., 2012), and blunted cortical reactivity to rewarding stimuli (Nelson et al., 2018). In those with anxiety, individual differences in trait anxiety appear related to dysregulated activity in brain regions responsible for reward-related decisions, such as the ventromedial prefrontal cortex (vmPFC; Hu, 2018), which may contribute to observed blunted neural responses to anticipated negative outcomes among individuals with greater anxiety (Gu et al., 2010). Relative to healthy controls, those with Generalized Anxiety Disorder were also less effective at decreasing and increasing their emotional response (i.e., cognitive regulation) to food-related images during a task requiring evaluation of how much they wanted pleasant stimuli (i.e., food images; De la Peña-Arteaga et al., 2022), lending further support to an association between anxiety symptoms and altered reward processing and regulation. In addition to altered reward processing, depressive and anxiety symptoms are often associated with dysregulated stress responsivity.

Similar to reward processing, a large literature base examines alterations in subjective, hormonal, and neural stress response in cannabis users and those with internalizing psychopathology. In support of the allostatic model, cannabis users, relative to non-using control groups, have demonstrated blunted HPA-axis reactivity, as measured by cortisol and ACTH, relative to non-using or abstinent individuals (Somaini et al., 2012). Further, cannabis users tend to display blunted amygdala reactivity to threatening images relative to a non-using control group (Cornelius et al., 2010). Within the context of acute stress, cannabis users also demonstrate a blunted subjective and hormonal (i.e., cortisol measured) response to a laboratory-administered acute stress task, relative to a non-using control group (Cutler et al., 2017). Most recently, cannabis users, relative to non-users, demonstrated blunted cortisol (HPA) reactivity to a social stress task (Simon et al., 2023).

Consistent with an allostatic model, INTDs are also associated with altered stress-related functionality, spanning immune, cardiovascular, nervous, and hormonal systems (McEwen, 2004; Vinkers et al., 2021). One of the primary biological systems related to stress reactivity is the hypothalamic-pituitary-adrenal (HPA) axis, which regulates the release of cortisol in response to stress-related hormones, such as norepinephrine. In those with anxiety and depressive disorders, chronically elevated cortisol and norepinephrine levels contribute to stress sensitivity and the maintenance of psychopathology (McEwen, 2003; Wolkowitz et al., 2001). A quadratic relationship of HPA reactivity to depression and anxiety exists, such that low and high INTD symptoms are related to HPA hypo-reactivity, while median level of symptoms is related to HPA hyper-reactivity (Wardenaar

et al., 2011). Further, excessive or insufficient stress-related neurotransmitters may also be related to the pathogenesis of both anxiety and depressive disorders (Boyer, 2000).

Taken together, reward and stress system alterations in CUD and INTDs overlap substantially. Overall, evidence is mixed regarding the relationship between chronic cannabis use and reward system alterations; however, a small base of longitudinal studies find that greater cannabis use is related to decreased reward anticipation and motivational capacity. INTDs are also associated with altered reward processing, such as decreased sensitivity to reward in depression and less neural reactivity to anticipated negative consequences. Finally, chronic cannabis use is related to dysregulation of the HPA-axis, such that cortisol levels after an acute stressor are blunted relative to a non-using control group. In contrast with this, HPA-axis dysregulation in anxiety and depression is related to stress sensitivity, though evidence also suggests higher levels of anxiety and depression are related to HPA-axis hypo-activity. Reward and stress dysregulation may contribute to a greater allostatic load, ultimately maintaining harmful cannabis use and clinically significant INTDs.

Recommendations for Policy and Practice

Cannabis-related policy is a heavily debated issue in current U.S. politics, as current policy decisions will have a lasting impact on public health. Given this widespread impact, a multilevel approach to cannabis-related policy is warranted. Evidence-based policy recommendations related to the use of cannabis for treating INTDs are provided at public health, community, and individual levels.

Public Health Policy

Current medicinal cannabis state laws are not based on scientific evidence. Few conditions listed in the eligible conditions for physician authorization for use of medicinal cannabis are supported as indications for cannabis products. State medicinal cannabis laws should be revised to align with the science, which currently only supports therapeutic use of cannabis for a handful of conditions, many of which only indicate CBD rather than THC (Potenza et al., 2023). Most pertinent to the scope of this review, internalizing psychiatric conditions, such as anxiety and depressive disorders, should be removed from the lists of eligible conditions unless strong evidence supporting those indications emerges. This is imperative due to the increased risk for CUD in individuals with these conditions, likely related to the overlapping reward and stress circuitry between the disorders.

The most heavily debated cannabis-related policy is legalization of recreational use. While some people receive authorization for medicinal cannabis use to treat an INTD, many more are likely to obtain their cannabis from recreational or illegal sources while reporting coping as a motive for use.

Cannabis use is highest among individuals with high compared to some or no anxiety in states where recreational use has been legalized (Weinberger et al., 2020), suggesting that recreational legalization may be linked to increased use among people with high anxiety. Many other factors outside the scope of this review should be considered when making decisions related to recreational legalization. If legalization was deemed appropriate, harm reduction approaches could be implemented to help prevent negative outcomes of cannabis use in people with INTDs. For example, regulation of available products to control THC potency could reduce the anxiogenic effects of cannabis products and risk of CUD. Furthermore, additional education could be provided to the public about heightened risk of CUD or other cannabis-related problems among people with INTDs. While cannabis use does not come with risk of fatal overdose like other drugs do, the public should be made aware of potential adverse effects that may occur, such as the cannabis withdrawal syndrome or exacerbation of other mental health symptoms.

The current body of research on cannabis, especially that of medicinal properties of cannabis, is lacking overall. Despite a huge increase in U.S. cannabis research funding from approximately \$30.2 million in 2000 to approximately \$143 million in 2018 (O'Grady, 2020), there are clear gaps in our knowledge about cannabis-related effects, particularly pertaining to therapeutic uses for cannabis. Funding for cannabis research should be increased, and equity should be given to research related to therapeutic uses. Additionally, current federal laws governing cannabis research complicate access to cannabis products for administration research. Emphasis should be placed on making higher potency cannabis strains available for research since they are commonly used among cannabis users and currently available cannabis products for research have not kept up with increasing potency levels of products used recreationally. This may involve rescheduling or descheduling cannabis on the U.S. Drug Enforcement Agency's (DEA) drug schedule.

Theoretically, using cannabis to cope with INTDs would not be necessary if there were accessible and effective mental health care options available to everyone. A national survey in the U.S. found that only 47.2% of adults with a current psychiatric disorder had received treatment in the past year (Substance Abuse and Mental Health Services Administration, 2022). Current first-line treatments for INTDs include psychological and pharmacological interventions (Health Quality Ontario, 2019). Unfortunately, many barriers exist to accessing these treatments. Some of these barriers include stigma of seeking treatment, transportation problems, long waitlists, lack of qualified clinicians, and unwanted medication side effects (Alvidrez & Azocar, 1999; Mohr et al., 2006; Young et al., 2001). There is a very clear need for improved access to mental healthcare in this country. Policy recommendations have been outlined extensively elsewhere, including initiatives to increase

incentives and reduce barriers for mental healthcare workers to serve people in more rural areas and greatly increase the overall number of mental healthcare workers (Diehl et al., 2017). Further consideration should also be given to brief, cost-effective interventions for anxiety or depressive disorders, which have shown effectiveness in primary care settings (Cape et al., 2010) and in single-session formats (Schleider & Weisz, 2017). Early intervention may reduce the risk of CUD development by reducing the need for cannabis as a coping tool.

Community-Level Initiatives

With dysregulation of reward and stress systems playing such a strong role in both INTDs and CUD, the availability of alternative (non-drug) reinforcers within a community is vital to helping people develop healthy coping strategies. Community investments in infrastructure that promotes park and trail access, physical activity, youth programs, or other recreational activities have been highlighted as important to reducing problems related to substance use (Acuff et al., 2023; Leventhal et al., 2015). Additionally, historical socioeconomic and racial disparities in access to alternative reinforcers that are linked to higher vulnerability to substance-related harms (Collins, 2016; Leventhal et al., 2015) underscore the need for heavier investments in these communities.

Another relevant community-level initiative is the expansion of medicinal cannabis education provided to healthcare trainees and healthcare professionals. Training programs and licensing bodies, especially those involved in mental healthcare or primary care, should implement requirements for their members to receive training in evidence-based medicinal cannabis practices, including the potential benefits and adverse effects of medicinal use or use to cope with an INTD. This sentiment is shared by 80% of family physicians who completed a survey about medicinal cannabis-use education (Kondrad & Reid, 2013).

Individual-Level Initiatives

At the individual level, clinicians working with individuals with INTDs or those who use cannabis should be seeking out up-to-date research on medicinal cannabis products to maintain an awareness of current evidence-based recommendations. They should also be engaging in open, honest, and nonjudgmental conversations with their clients about cannabis use, the risks of using cannabis to cope with INTDs, whether they be medicinal or recreational products, and empirically supported indications for cannabis products to empower their clients to make the best decision for themselves. If clients decide to use cannabis to cope, clinicians can recommend harm reduction approaches to minimize cannabis harms. Individuals using or considering using cannabis to cope with any disorder should also seek out current

information about cannabis effects from a reliable source or a trusted clinician to help them make a fully informed decision.

Conclusion

Coinciding with the everchanging cultural and legal landscape of cannabis in the U.S., the prevalence of CUD is increasing. Due to the potential for functional impairment in people with CUD, it is crucial to understand risk factors that increase the likelihood of developing disordered cannabis use. Because chronic heavy cannabis use and INTDs (such as anxiety and depressive disorders) are associated with neurobiological changes in the reward processing and stress responsivity systems, a great deal of caution should be taken before recommending or using cannabis to cope with INTDs. Furthermore, there is little to no evidence that cannabis use improves INTD symptoms over time, in contrast to the marketing of cannabis as a therapeutic for anxiety and depressive disorders and the perception of many recreational users who use cannabis to cope with INTDs. In fact, the longitudinal studies examining cannabis use and INTD symptoms have generally reported either no association or that heavier cannabis use predicts *increased* INTD symptoms. Recommendations for policy and practice spanning public health, community, and individual levels were made. These recommendations range from revising laws regulating cannabis product availability to increasing access to alternative reinforcers in local communities to improving education about the lesser-known effects of cannabis that may increase the likelihood of developing disordered use.

Policymakers are charged with the responsibility of writing and passing laws and policies that will affect our population health for decades to come, so we strongly emphasize the importance of constructing laws and policies from an empirically supported foundation. While the science regarding the substantial dysregulation in reward and stress systems across CUD and INTDs is clear, much less is known about how these dysregulated systems interact across disorder types. Due to the possibility of increased risk of CUD in people who use to cope with INTDs and the lack of evidence supporting cannabis as a therapeutic for INTDs, policymakers should limit access to cannabis products for the sole purpose of coping until the evidence points strongly in favor of cannabis as a therapeutic agent for INTDs. Furthermore, harm reduction policies can be implemented to minimize harms from cannabis. The demand for cannabis as a therapy for INTDs highlights the immense need for improved mental health resources in the U.S. Investments in community infrastructure and mental health resources could help allay some of the demand of cannabis as a coping mechanism.

Clinicians are our frontline workers, often bridging the gap between science and the public. The public entrusts clinicians with their health, as they are the experts in their

respective fields. While acknowledging the intense time and cognitive demands of being a clinician, it is imperative that any clinician working with clients potentially using cannabis to cope with INTDs be aware of the increased risk of cannabis-related problems accompanying such behavior. These clinicians should be able to provide their clients with current, scientifically-based recommendations for cannabis use (or non-use) and the potential risks of its use. Improved knowledge in this area will allow clinicians to more confidently have nonjudgmental conversations with their clients about their substance use. To better serve these efforts, clinician training programs should offer educational material on cannabis, and clinicians who have not received this in their training should seek this training through a continuing education mechanism or the current body of scientific literature. A small investment of time by clinicians could lead to improved mental health outcomes and prevention of CUD development in many of their clients.

The risks of using cannabis to manage symptoms of an INTD are clear. The evidence commands clinicians and policymakers to take action during this critical period in the cannabis cultural landscape to minimize harm and improve the lives of their clients and constituents.

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