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INVITED REVIEW

An update on cannabis use disorder with comment on the impact of policy related to therapeutic and recreational cannabis use

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Abstract
Confusion and controversy related to the potential for cannabis use to cause harm, or alternatively to provide benefit, continues globally. This issue has grown in intensity and importance with the increased recognition of the public health implications related to the escalation of the legalization of cannabis and cannabinoid products. This selective overview and commentary attempt to succinctly convey what is known about one potential consequence of cannabis use, the development of cannabis use disorder (CUD). Such knowledge may help guide a reasonable and objective public health perspective on the potential impact of cannabis use and CUD. Current scientific data and clinical observation strongly support the contention that cannabis use, like the use of other substances such as alcohol, opioids, stimulants, and tobacco, can develop into a use disorder (addiction) with important clinical consequences. Epidemiological data indicate that the majority of those who use cannabis do not have problems related to their use, but a substantial subset (10–30%) do report experiencing symptoms and consequences consistent with a CUD. Treatment seeking for CUD comprises a substantial proportion of all substance use treatment admissions, yet treatment response rates show much room for improvement. Changing cannabis policies related to its therapeutic and recreational use are likely to impact the development of CUD and its course; however, definitive data on such effects are not yet available. Clearly, the development of more effective prevention and treatment strategies is needed for those vulnerable to developing a CUD and for those with a CUD.

Keywords Cannabis · Cannabis use disorder · Marijuana · Policy · Prevalence · Treatment · Legalization

Introduction: does cannabis addiction exist and how do you define it?

Confusion, debate, and controversy related to the potential for cannabis use to cause harm, or alternatively to provide therapeutic benefit continues globally. Over the last decade, these issues have grown in intensity and importance with increased recognition of the substantial public health implications related to the escalation of (a) the decriminalization and legalization of cannabis and cannabinoid products, (b) the perception that cannabis has therapeutic potential for a numerous and diverse set of disorders, and (c) a burgeoning and lucrative cannabis industry. The seeming contradiction that a substance can cause harm and have therapeutic value is not unique to cannabis. Most substances (i.e., opioids, cocaine, stimulants, hallucinogens, tobacco, and even distilled alcohol) that have addictive potential, have also been deemed to have therapeutic potential and some have been used legitimately by medical providers. The current and pressing challenge with cannabis is to develop well-reasoned policies that consider factual information about risks and potential benefits of cannabis and cannabinoid compounds in service of mitigating potential harm and maximizing potential benefits.

This brief manuscript attempts to help address this challenge by conveying what is known about one potential harmful consequence of cannabis use, the development of cannabis use disorder (CUD), or what some refer to as cannabis addiction [1–3]. Although many people do not believe that cannabis has addictive potential, a large volume of scientific and clinical data demonstrate that a proportion of those who use cannabis do indeed develop an addiction that is much

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like that of other substance addictions [4]. Here, we provide a selective overview of the literature on CUD with associated commentary that highlights and discusses some key issues that contribute to misperceptions related to cannabis, and its potential consequences. To that end, we drew from (a) literature reviews and scientific articles on relevant topic areas identified in Pubmed using diverse search strategies, (b) articles cited in these reviews and articles, (c) the DSM-5 and its source materials, (d) databases and published reports from large epidemiological studies, and (e) select book chapters from recent texts on cannabis identified via google searches. Thus, this manuscript is not a systematic review of the scientific literature, rather, it is a selective overview and synthesis drawing from the large multidisciplinary literature relevant to the development and course of CUD. We end by providing some perspective on a pressing concern, that is, how might changes to the legal and regulatory status of cannabis impact the development of CUD and its consequences.

Because of the plethora of mixed messages about cannabis communicated to the public, policymakers, and healthcare workers, we believe it is important to clearly define some key terms prior to discussing the CUD literature. First, when we use the word "cannabis", we are referring to either the cannabis plant material or extracts from the cannabis plant that contain substantial amounts of tetrahydrocannabinol (THC). THC is the compound in the cannabis plant that produces the commonly desired euphoric-like effects (the "high") [2, 5]. THC interacts with the CB1 receptor in the brain to stimulate the typical "high" sought by most cannabis users. This high produces the desire for repeated use, which for some cannabis users develops into a CUD [6]. "Cannabis" in this article will not be referring to cannabidiol (CBD) products that contain no or very small amounts of THC. CBD is a compound in the cannabis plant that has recently generated a great deal of interest related to its potential therapeutic effects, and which does not produce euphoria when ingested [7]. Note that this working definition of "cannabis" as a substance that contains a substantive amount of THC is not the scientific definition of cannabis. It is used here because, when discussing the addictive potential of cannabis, it is crucial to distinguish between cannabis products with THC versus those with primarily CBD.

Second, it is important to clarify what is meant by CUD. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [3] and the International Statistical Classification of Diseases and Related Health Problems (ICD-10 or 11) have clear operational definitions of a syndrome that can develop from excessive use of cannabis (and any other substance) [1]. The DSM-5 criteria for a diagnosis of CUD, which are generic for all substance use disorders, specify 11 signs and symptoms that relate to impaired control over one's consumption, social impairment, risky use, and physical dependence, i.e., tolerance or withdrawal. Severity of CUD can range from mild (meeting 2–3 criteria), to moderate (4–6 criteria), to severe (7 or more criteria). The ICD operationalizes CUD somewhat differently from the DSM-5. ICD-10 has two separate CUD disorders: harmful use and a dependence syndrome (i.e., similar to the abuse and dependence diagnoses of the previous version of the DSM). The diagnosis of harmful use is defined as a pattern of psychoactive substance use that is causing damage to health, which may be physical or mental. The dependence syndrome is defined as a cluster of physiological, behavioral, and cognitive phenomena in which the use of a substance takes on a much higher priority for a given individual than other behaviors that once had greater value. A dependence syndrome is diagnosed if a person meets three of six specified criteria.

The specification and inclusion of CUD in both DSM and ICD, which both use generic criteria across all addictive substance use disorders, communicate a few important realities about cannabis and its potential for "addiction". First, health and medical experts and scientists consider CUD to be a valid and clinically important type of mental disorder that occurs in the general population, is not rare, and is experienced in much the same way as other SUDs [3, 8]. An overwhelming body of evidence for this assertion has accumulated and has been reviewed in detail elsewhere [9, 10]. The supporting data include research from nonhuman and human behavioral pharmacology, neuroscience and neuroimaging, genetics, clinical assessment and treatment, health service surveillance, and clinical epidemiology. Second, and particularly noteworthy, a valid cannabis withdrawal syndrome has been characterized such that a diagnosis of cannabis withdrawal disorder is included in the DSM-5 and experiencing withdrawal is one of the CUD diagnostic criteria.

In summary, CUD clearly develops and manifests in much the same way as other SUDs. The majority of those who have used cannabis do not develop a CUD, but among those that do, some develop a mild, some a moderate, and some a severe syndrome [11]. Below we review and discuss scientific information that we believe can assist readers to develop a reasonable public health perspective on CUD (see Table 1 for an overview of the primary issues probed in this review).

How prevalent is CUD and how severe are its associated consequences?

Cannabis is the most commonly used psychoactive and regulated drug in the world after alcohol and tobacco. In 2016, an estimated 192.2 million people had used cannabis within the past year for non-medical reasons [12]. Globally, from 1999 to 2015, cannabis use prevalence remained fairly constant at approximately 4% [13]. In 2016, estimates of use in the U.S. among those 18 and older indicate that past-year and

Table 1 Summary points on cannabis use disorder (CUD) and its consequences

Does cannabis addiction exist and how do you define it?
Cannabis (THC-laden products) has addictive potential
Cannabis use disorder (CUD) is diagnosed using either the ICD-10 or DSM-5 using the same criteria as for other substances
The manifestation of CUD is highly similar to that for other substance use disorders (SUDs)
How prevalent is CUD and how severe are its associated consequences?
The prevalence of CUD is comparable to other SUDs
CUD is more prevalent in high-income nations such as the U.S., Germany, and Australia
A substantial proportion, 11–30%, of those who use cannabis in the U.S. report having a CUD
CUD is associated with a myriad of psychosocial consequences and those who have CUD have increased odds of having other SUDs and psychiatric disorders
CUD, on average, may be less severe than other common SUDs
Do people seek treatment for CUD?
(1) Rates of treatment seeking globally and in the U.S. are comparable to the other SUDs
(2) Treatment admission rates appear to be lower in the U.S. compared to most European nations and Australia
(3) Those with CUD appear to seek treatment at lower rates than for other SUDs
How difficult is quitting or reducing cannabis use?
Short-term studies of those who use cannabis daily and are interested in quitting suggest that quit and reduction attempts are frequent and short lived, and achievement of sustained abstinence is rare
Behavioral interventions for CUD are efficacious (e.g., MET, CBT, CM, and integrated combinations); however, only the minority respond to treatment and relapse rates are high
The development and implementation of more effective strategies for prevention and treatment of CUD is much needed, particularly given this dynamically changing legislative climate
What impact will the changing legal environment have on the development of CUD?
Changing laws and regulations are highly likely to impact the development of CUD and its course, and perhaps treatment seeking
Definitive data on the effects of changes in the cannabis legal environment are not yet available; the constant fluctuations in the legislative and regulatory environment make this area of study difficult and the interpretation of current findings challenging

Each question and the corresponding answers above represent the five main sections of the current overview

past-month cannabis use prevalence was 14.1% and 9.1%, respectively. This reflects an increase from that observed in 2002, when past-year and past-month prevalence was 10.4% and 6.0%, respectively [14]. For adolescents (ages 12–17), past-year and past-month cannabis use prevalence in 2016 was 12.0% and 6.5%, respectively, which reflects a decrease from 15.8 and 8.2%, respectively, in 2002.

When evaluating prevalence data, it is important to recognize that any one index of prevalence, e.g., past-month cannabis use, cannot adequately characterize the heterogeneity of clinically relevant use patterns. For example, of those who used cannabis in the past 30 days, 38% used it on only 1–5 days, whereas 50% used on 11 or more days, and 21% used every day. The distribution of days of use within the past month can also vary as a function of age and time. Consider that among past-month cannabis users who were 18 years and older, the prevalence of daily or near-daily cannabis use increased from 33.1% in 2002 to 43.0% in 2016, but declined from 29.8% in 2002 to 22.8% among adolescents. Given the heterogeneity of cannabis use patterns and the likely differential consequences associated with each, use of more fine-grained measures (e.g., # of days of use, times used per day, level of intoxication, method of administration) in epidemiological assessments of cannabis use is needed to better describe and differentiate risky patterns of cannabis use [15].

Efforts to determine the potential global harm resulting from cannabis use can in part be determined from estimates of global prevalence of CUD [16]. In 2010, an estimated 0.2% of the population or 13.1 million people met CUD [16]. In the U.S., two recent general population studies reported much higher, but discrepant past-year prevalence rates for CUD. The National Epidemiologic Survey of Alcohol and Related Conditions (NESARC) provided a past-year prevalence estimate of 3% (2013) in comparison with 1.5% estimate from the 2015 National Survey of Drug Use and Health (NSDUH) [11, 14]. Comparable estimates of CUD have been reported in other high-income nations such as Germany (0.5% in 2012 [17]) and Australia (1% in 2007 [18]). Interpretation of these global estimates of CUD should consider that most of the data comes from studies data that disproportionately sample higher-income nations, and often studies differ substantially on the proxy criteria items used to measure CUD [16].

Global estimates of CUD reflect a statistically nonsignificant increase in prevalence from 2002 to 2010 [16].

In the U.S., two estimates of trends in CUD over the past decade again diverged [11, 14, 19]. The NESARC study estimated an almost twofold increase in the prevalence of past-year CUD from 2002 to 2013 (1.5–2.9%) [20], while the NSDUH estimated a slight decrease from 2002 to 2013 (1.6–1.5%) [14]. Although it is difficult to synthesize these global and US estimates, a recent WHO report concluded that the prevalence of CUD is high enough to consider it a public health problem (at least in higher-income nations), and its prevalence appears to have increased since 2000 [12].

Conditional prevalence

Estimates of conditional prevalence of CUD provide one indication of the "addictive potential" of cannabis. Conditional prevalence is operationalized as the percentage of individuals with CUD among those who have ever used cannabis or among those who currently use cannabis. Data from the NESARC study indicate that nearly three out of ten (30%) past-year cannabis users met criteria for CUD in 2013 [20]. By contrast, in 2016, the NSDUH estimated past-year CUD in a much lower proportion of past-year cannabis users (11.6%) [21]. Although these point estimates differ substantially, both survey studies indicate that the prevalence of CUD among past-year users declined—potentially reflecting a greater prevalence of less severe cannabis use. Trends among adolescents, available only from the NSDUH, also indicate that the prevalence of CUD among those who had used cannabis during the past year decreased from 27.0% in 2002 to 20.4% in 2014.

Comparing conditional prevalence for CUD to that of other substances provides additional information with which to gauge the addictive potential of cannabis. The NESARC study estimated the prevalence of alcohol use disorder among past-year alcohol users to be 17.5% [22], which is somewhat lower than for CUD (30%). For tobacco use disorder, conditional prevalence of a use disorder among past-year tobacco users was much higher (80%) [23].

In summary, the epidemiological literature suggests that CUD is not rare, and that its addictive potential appears comparable to other substances that pose risk for development of a use disorder, higher than some, lower than others. Although tentative, evidence also points to increasing prevalence of CUD in the U.S. and other high-income nations. Given the changing legal landscape of cannabis in the US and other countries and its potential impact on cannabis product access and availability, systematic and repeated studies of the prevalence of CUD are needed to better inform public health laws and policy related to cannabis use.

Severity and Consequences of CUD

As mentioned above, the diagnostic criteria for CUD appear to perform similarly to other SUDs [4, 24]. The general SUD diagnostic criteria fit for CUD. The criteria are stable, reliable, fall into a unidimensional construct, and all of the 11 DSM criteria are reported by cannabis users [24, 25]. In 2013, the addition of cannabis withdrawal, both to the DSM-5 criteria list for CUD and as an independent withdrawal disorder, further supports the conclusion that CUD is highly similar to other SUDs. Cannabis withdrawal can contribute to sustaining use and increase the likelihood of relapse, although unlike some other substance withdrawal syndromes, it does not precipitate serious medical or psychiatric risk [26]. Consistent with this, CUD generally manifests as a somewhat milder use disorder than other SUDs (i.e, fewer diagnostic criteria are met per CUD diagnosis) [24, 25, 27].

The most recent NESARC study reported that the estimated distribution of lifetime severity levels of CUD in the U.S. were: mild (2.85%), moderate (1.42%), and severe (2.0%) [11]. Severity level was positively related to cannabis use frequency. Level of severity also showed a robust positive relationship with other mental health and substance use problems, and a negative relationship to social, emotional, and cognitive functioning [11]. Hence, like other SUDs, the more severe the CUD diagnosis, the greater is the increase in the risk of physical and psychological symptoms that can negatively impact one's life.

CUD has also been associated with risk for other psychosocial problems. Those with CUD report greater disability [11, 28], report engaging in violent, suicidal and non-suicidal self-injurious behavior [29], and are more likely to report inpatient and emergency room visits than those without CUD [30]. Because those with CUD use cannabis more frequently than cannabis users without CUD [11], it warrants mention that increasing evidence has linked frequency of cannabis use, amount used, age of first use, and CUD severity with a wide array of cognitive impairments [31–34]. Further, some consequences that have been associated with CUD stem from the pharmacological effects of cannabis intoxication and chronic use (e.g., driving accidents, risky sexual behavior). Last, the degree to which cannabis use affects youth brain development and neurodevelopment processes is of increasing concern. Multiple basic and human laboratories have illustrated potential, harmful effects of cannabis use on neurodevelopment, and prospective studies are ongoing to try to determine the parameters of cannabis use (e.g., frequency per day/per month, age of initiation, THC concentration, quantity, etc.) that may independently or jointly underlie the development of CUD and related consequences [33, 35, 36].

Co-occurring disorders

Similar to other SUDs, those with CUD commonly have co-occurring psychiatric disorders and other types of SUDs [18, 37]. Data from the NESARC study indicate that compared to those without CUD, those with CUD during the past year are more likely to have additional SUDs (OR = 9.3) and psychiatric disorders such as anxiety disorders (OR = 2.8), personality disorders (OR = 4.8), mood disorders (OR = 3.8), and posttraumatic stress disorder (OR = 4.3) [11]. The most common SUDs that co-occur with CUD are alcohol (OR = 6.0) and nicotine (OR = 6.2). Co-use of tobacco among those with CUD has received increasing attention in the scientific literature, because it is associated with poorer clinical outcomes among those receiving treatment for CUD and because of the potential for additive health consequences from the inhalation of toxins from the smoke of combusted tobacco and cannabis products [38, 39].

Interestingly, among cannabis users, those with a psychiatric disorder are twice as likely to develop a CUD as those who do not have a disorder [40–43]. Moreover, the prevalence of psychiatric disorders among those who use cannabis appears to rise with increased frequency and severity of cannabis use suggesting that having a psychiatric disorder may increase the probability of transitioning from cannabis use to developing a CUD [44–47].

The high rates of co-occurrence of CUD and other psychiatric disorders raise multiple questions and concerns. Does this association reflect a tendency for those with other psychiatric disorders to use cannabis to alleviate symptoms associated with their other disorders, which eventually may develop into CUD? Are those who have psychiatric disorders particularly vulnerable to developing CUD once they initiate cannabis use? Or, does CUD, or the excessive cannabis use that drives it, make one vulnerable to the development of other psychiatric disorders? How does CUD impact the course of existing psychiatric disorders? Is there a relationship between how much cannabis or specified compounds of cannabis are used and the direction of effects on psychiatric disorders? Here, we can only raise these issues and touch on what is known, however, a more comprehensive discussion of these concerns is available elsewhere [48, 49]. Notably, having a co-occurring CUD and psychiatric disorders, regardless of whether the CUD or the psychiatric disorder is experienced first, is strongly implicated in worse cannabis cessation outcomes and worse outcomes related to the psychiatric conditions (see [48] for a review). In contrast, there appears to be little data suggesting a positive relationship between cannabis use or CUD and the course of treatment outcome for persons with other psychiatric disorders.

Perhaps, the most clear implications from the research on CUD and co-occurring disorders are similar to that for other SUDs. First, providers need to be aware that many CUD patients will be experiencing other psychiatric symptoms or disorders, and optimal interventions may need to address these problems concurrently or sequentially. Second, those seeking treatment for many common psychiatric disorders should be screened for cannabis use and CUD, so that it can be evaluated, monitored, and strategically addressed in the context of treatment for those disorders. Last, the escalation of legal cannabis laws and implementation of the provisions of those laws, which increasingly include the "approval" of cannabis for therapeutic use for a number of psychiatric disorders, raises increasing concern about the impact of cannabis use and CUD on the course and treatment of psychiatric disorders and the converse. We discuss this concern in more detail below.

Do people seek treatment for CUD?

Emerging data from 22 European nations suggest first-time treatment admissions for cannabis as the primary substance of concern are highly prevalent and increased from 2003 to 2014 [50]. The United Nations Office on Drugs and Crime estimated that from 2003 to 2016 the proportion of all SUD treatment admissions that were for cannabis increased from roughly 8–15% in eastern and southeastern Europe, 19–30% in western and central Europe, 29–48% in Oceania, 9–16% in Asia, 28–33% in North America, and decreased from roughly 64–51% in Africa [13].

Total SUD treatment admissions in the U.S. from 2002 to 2015 declined to 18.6% (see the Treatment Episode Data Set (TEDS) [51]). Primary cannabis treatment admissions decreased at a noticeably greater rate from 2002 to 2015 (26%) [51]. As a proportion of all SUD treatment admissions, primary cannabis treatment admissions demonstrated a modest decrease from 15.3% (288,418) of total admissions in 2002 to 13.9% (213,001) in 2015. The observation that there was a greater reduction in cannabis admissions than that of total SUD admissions may be linked to how CUD patients are referred to treatment. The TEDS survey indicated that 50.7% of admissions in 2015 were mandated by a court or juvenile justice referral, which is about 20% greater than that for admissions for alcohol (33.2%) and cocaine (28.3%). Whether or not the changing legal status of cannabis across the U.S. has impacted rates of treatment seeking is difficult to determine, but these data suggest a potential contribution. Of note, the proportions of referrals from other sources for cannabis admissions were: self or family (18.7%), alternative community referral (16.5%), substance abuse care provider (4.7%), alternative health care provider (4.7%), school (3.4%), or employer (0.6%).

The number of adolescent (i.e., ages 12–17) treatment admissions for all SUDs decreased by 58.1% from 2002 to 2015, and the number of primary cannabis-related

admissions decreased by 50.1% [52, 53]. However, unlike the admission data for all age groups, the proportion of adolescent SUD treatment admissions that were for CUD rose from 63% in 2002 to 76% in 2015. Interestingly, data from the 2017 Monitoring the Future annual U.S. survey showed that the risk perception of harm from regular cannabis use among 8th, 10th, and 12th grade students in 2017 was the lowest since 1990 [54].

Although these data indicate substantial treatment seeking for CUD, it is estimated that in the U.S., only 7–8% of individuals with CUD have utilized treatment that is specific to cannabis in the past year [11, 55]. Although this may seem surprisingly low, only 13.5% of individuals with any past-year SUD received treatment in the U.S [56, 57]. This U.S. percentage of treatment engagement is considerably lower than other high-income nations. For example, in Australia, 36% of those with CUD seek treatment [18]. Potential factors that may contribute to the lack of treatment utilization include desire for self-reliance, perceptions that treatment is not necessary, a lack of awareness of the problem, and stigma [58, 59]. Adults seeking treatment for CUD attribute multiple problems to their cannabis use (e.g., procrastination/low productivity, memory issues, low energy, financial or employment difficulties, guilt about use, cannabis withdrawal, low self-confidence/self-esteem, insomnia, and distressed personal relationships) [60, 61], as do adolescents (e.g., neglected responsibilities, not able to do homework or study, missed school or work, went to school high, missed out on things because they spent too much money on cannabis, had arguments with family, and continued using despite promising oneself not to, and noticed unpleasant changes in personality) [62]. Interestingly, despite attributing such problems to cannabis, only 34% of these youth deemed their cannabis use a problem [62].

To better identify who may be in need of and benefit from treatment, a number of validated brief screening instruments have been developed to identify persons at risk for cannabis-related problems, e.g., Cannabis Use Identification Test (CUDIT-R), the Cannabis Abuse Screening Test (CAST), Cannabis Use Problems Identification Test (CUPIT), Alcohol, Smoking and Substance Involvement Screening Test (ASSIST), the Marijuana Problem Index (MPI), and the Cannabis Problems Questionnaire for Adolescents (CPQ-A) [63–69]. These instruments can be self-administered, and thus easily incorporated in most healthcare settings or used for self-evaluation. A growing literature has demonstrated that pairing such assessments with brief motivational interventions can be effective for reaching those with CUD outside of specialty SUD clinics [70], as we discuss in the following section.

How difficult is it to quit or reduce cannabis use?

As documented above, similar to those who use other substances, a proportion of those who use cannabis who are experiencing problems related to their use enter treatment indicating a desire or need to stop or reduce their use, while others try to quit without professional assistance. This raises an important question relevant to understanding the implications of developing a CUD: how difficult is it to quit or substantially reduce cannabis use?

Multiple sources of data provide some insight on this change process and subsequent outcomes. First, a few prospective, non-treatment studies that followed individuals who were contemplating reducing or quitting their cannabis use suggest that change is not easy. The most intensive, but short-term study was conducted in the U.S. and obtained daily data from primarily adults who used cannabis daily (most also met criteria for a CUD), who intended to stop or reduce use in the next 3 months [71]. Findings replicated a smaller previous study [72] illustrating that participants tended to make multiple brief quit or reduction attempts, many transitioned between periods of reduced use, abstinence, and usual use patterns, and very few achieved sustained abstinence or sought treatment [71, 73].

General population studies from three different countries have assessed remission rates over time for those with CUD and other SUDs [74]. Annual remission rates for CUD, defined as no longer meeting criteria for active CUD, were estimated at 17%. This rate was marginally higher than opioid use disorder (10–20%) and cocaine use disorder (5–13%), and about the same as stimulant use disorder (16%). Another study conducted in Germany focused solely on cannabis use among young adults and reported similar results [75]. Approximately, 15% of those with CUD and 25–39% of regular heavy users who did not meet CUD criteria were no longer using cannabis 3–4 years later. Although these conclusions must be considered tentative given the limitations of the individual studies, they are consistent with other natural history study observations that illustrate both the recalcitrant nature of cannabis use among those with CUD or who use daily, and the natural progression towards reduced use or cessation during the lifespan.

The clinical trials' research on CUD provides a similar perspective on how difficult it is to stop or substantially reduce cannabis use. In the past 8 years, numerous reviews of this literature have provided similar synopses and converge on similar conclusions [4, 12, 48, 76–83]. More than 30 published controlled trials have most commonly evaluated three psychosocial treatment approaches:

motivational enhancement (MET), cognitive–behavioral (CBT) and contingency management (CM) interventions. As with treatment research on other SUDs, methodological variability across studies, such as the lack of uniform outcome measures, few comparisons to non-treatment controls, heterogeneous samples, and variable lengths of treatment and post-treatment follow-up, make it difficult to systematically combine findings across studies and evaluate the relative efficacy of treatment approaches. That said, "positive" outcomes at the individual level (i.e., abstinence or substantial reduction in use) with these interventions have ranged from approximately 20–53% when assessed at the end of treatment to 15–45% at 6- or 12-month follow-ups, with results from most studies being at the lower half of these success ranges [4, 12, 48, 76–83]. The majority of the reviews suggest that adding CM, i.e., monetary incentives provided contingent on documented abstinence, to MET, CBT or their combination, has demonstrated the most robust treatment effects across clinical trials. This literature also suggests that more intense psychosocial treatments over longer intervals (i.e., four or more sessions) appear more robust than the briefer motivational approaches.

Brief interventions for CUD (i.e., typically 1–2 sessions), which primarily utilize interviewing strategies drawn from the motivational interviewing literature, have demonstrated small to moderate effects, and have been investigated in specialty and non-specialty treatment settings (see reviews: [83, 84]). The availability of these more accessible and less burdensome approaches is particularly important for reaching a larger proportion of those with CUD who might benefit from treatment.

Similarly, the recent exploration of technology-delivered ("digital') health interventions (DHIs) to prevent escalation of cannabis use and to treat CUD offers great potential for extending the reach and enhancing outcomes of evidence-based treatments (see reviews: [83, 85, 86]. Such DHIs have been tested as in-clinic and remote alternatives to therapist-delivered behavioral counseling. Some have been designed to use as an adjunct to in-person counseling or pharmacotherapy, and others as web-accessed, stand-alone interventions for the general public. And, others have been used as alternatives to in-person brief interventions in university health centers and pediatric and primary care health settings [83, 85]. To date, more robust outcomes with DHIs have been reported when patients receive at least minimal contact with a therapist. Nonetheless, the small effects observed with brief DHIs in medical settings and stand-alone internet accessed TDIs [87] have substantial public health implications because of their potential to reach those who would not otherwise access treatment.

The scientific literature on treatment approaches for youth with CUD has produced findings similar to that with adults. Multiple reviews published in the last decade indicate that a number of well-specified individual, group, and family-based interventions are efficacious, and benefit a significant proportion of youth [88–95]. However, like with adults, the majority of youth who enter these treatment studies typically do not show evidence of a clinically meaningful response, and relapse rates are substantial. A few individual trials report on interventions with greater response rates (e.g., MDFT: [96]), but as with the adult literature, the substantial variability in study sample characteristics and outcome measures, make it difficult to compare results across trials. A recent review suggests that combining/integrating evidence-based approaches to broaden the scope of the intervention appears to enhance outcomes for youth who enroll in treatment for SUD [88, 95]. As in the adult literature, brief interventions and innovative DHIs are being developed and tested in attempts to extend the reach and enhance the efficacy of interventions for youth with SUDs including CUD [97].

Last, a growing literature that includes human laboratory studies and clinical trials has evaluated the potential of various medications as stand-alone or adjunct treatments for those with CUD. Targets of these medications include (a) reduction in withdrawal or cessation of use with agonist-like medication that target the CB1 receptor (substitution therapies), (b) specific withdrawal symptoms or relapse triggers such as mood, sleep, or craving, (c) reduction in the reinforcing effects of cannabis with antagonist or inverse agonist medications that "block" the CB1 receptor or opioid receptors that interact with the cannabinoid system, and (f) comorbid psychiatric conditions that may partially contribute to ongoing use of cannabis to relieve psychiatric symptoms. Multiple reviews of this pharmacotherapy literature illustrate that we have yet to identify medications that are effective for engendering cannabis abstinence or significant reductions in use [6, 82, 98–101]. Some positive signals of potential efficacy have been observed for a few medications, but replication studies have either failed to confirm the results or have not been reported.

Overall, the findings from CUD intervention studies with adults and youth clearly indicate that successful outcomes are not easily achieved. Rates of response appear comparable to outcomes achieved with other SUDs, although drawing firm conclusions about their relative efficacy is tenuous because of the lack of rigorous comparative studies [4, 79, 82, 102]. The observations from natural history and controlled treatment studies, by and large, strongly suggest the need for continued exploration and development of intervention approaches that can positively impact a greater number of those who develop CUD.

How will the changing cannabis legal and regulatory environment impact the development of CUD?

Concerns about potential adverse consequences of relaxing legal and regulatory restrictions on the sale and use of cannabis products, particularly on youth, have been raised and debated in governmental bodies, the scientific literature, and the press. Of most relevance to the present discussion is the impact of this changing legal landscape on CUD development and its course. Some assert and we agree that empirical data on this issue that come primarily from the U.S. are equivocal and premature [103]. However, a careful reading of literature combined with knowledge of well-established risk factors for the development of SUDs, including CUD, strongly suggest that without thoughtful regulatory and preventative actions to counter the potential negative impact of lax cannabis policies and regulations, one can expect increases in cannabis use and CUD over time, particularly among those most vulnerable [9, 48, 103–105].

We have previously discussed three "risk factors" for the development of CUD that can be moderated by regulatory policy and provisions: pharmacology of drug effects, access/availability of substances, and environmental influences [9]. Related to pharmacological effects, changes in cannabis laws have been accompanied by changes in the availability of much more potent (high %THC) products and alternative drug delivery methods (vaporizers, dab rigs, edibles). The products now available on the street and in cannabis dispensaries include cannabis plant material products that contain up to 25–35% THC, and cannabis "concentrate" products that contain up to 85% THC. Such products and delivery methods may (a) provide more efficient delivery of the psychoactive effects, (b) produce more reinforcing effects and (c) perhaps expedite the development of tolerance and withdrawal [106–109]. These potential effects can contribute to the development of CUD or any SUD by increasing the likelihood of repeated use and the desire to use a greater amount of the active compound, which for cannabis is THC [110].

Specific provisions and regulatory frameworks within legal cannabis laws can impact the degree of access to cannabis products or devices. Such access effects are often underestimated but they should not be given what has been observed in the alcohol and tobacco fields [111, 112]. Access is determined by multiple factors including cost and proximity which determine how much effort is required to obtain a substance, in addition to the simple availability of the products for purchase [113]. These facets of availability interact with the pharmacological effects of the substance to influence use initiation, and amount, frequency, and continuation of use.

A few examples unique to the current cannabis landscape warrant mention. First, the increased availability of vaping devices and edible cannabis products have provided ways for individuals to use cannabis that are perceived as "safer" [114, 115]. These methods allow cannabis to be administered without inhaling toxic smoke that contains carcinogenic material. Of concern, however, is that vaping and edible use may entice a subset of youth or adults to initiate or reinitiate cannabis use, who otherwise may have avoided use because of concerns related to smoking [107]. Moreover, not having to ingest smoke may also increase use among those who had previously used or currently use cannabis. Other access-related regulatory provisions such as those allowing home cultivation of cannabis can also make cannabis more readily available and reduce cost of various cannabis products including those with high potency [116].

Most experts predicted that cannabis legalization and commercialization would result in a substantial decreases in cost compared to pre-legalization costs [103, 117], and indeed, emerging evidence of changing cannabis prices corroborates those predictions. These data are concerning because of fundamental economic principle: lower cost results in increased purchases. This relationship has been clearly demonstrated in the alcohol and tobacco fields, and will assuredly apply to cannabis products [118–121]. Manipulating the cost of products primarily through taxation has been a successful public health strategy for alcohol and tobacco, and many States in the U.S. are now experimenting with how best to tax cannabis manufacturing and sales.

Two "environmental" factors, marketing and social norms, related to the changes in cannabis policies are particularly important to address in relation to how they may influence the development of CUD. First, as with cost effects, the impact of advertising and marketing on the tobacco and alcohol industries has been well-researched. A primary marketing strategy used in those industries is to normalize use by shaping beliefs and expectations with the goal of prompting initiation and sustaining regular and heavy use, because most sales and profits come from heavier users and those with use disorders [122–124]. Youth are appealing targets for this strategy, because earlier age of onset of substance use robustly predicts risk for the development of later tobacco, alcohol and cannabis use disorders [125–131]. As would be predicted given the emergence of a multi-billion dollar cannabis industry, data connecting cannabis marketing and age of initiation are beginning to emerge [132–135]. Marketing and advertising are rampant in many states, as the cannabis industry already has a strong presence on the internet. As such, one can expect the burgeoning cannabis industry will capitalize on lax restrictions and effectively engage in practices designed to prompt use, particularly among those vulnerable for developing CUDs [118, 135–138].

The escalation of the sanctioning of cannabis use for therapeutics and recreation combined with the marketing and advertising of the cannabis industry most likely impacts beliefs about the effects of cannabis, social norms, and perceptions of risk related to cannabis use. This raises multiple concerns for persons with or at risk for developing psychiatric conditions, because they are also at greater risk for developing a co-occurring CUD. We have reviewed such concerns extensively elsewhere [48], hence here we briefly broach two issues. First, and perhaps most troubling is the government approval of cannabis for psychiatric and other medical conditions combined with the cannabis industry's marketing of cannabis products for such conditions. Such marketing is occurring without clinical evidence of therapeutic efficacy and with extant data showing potential adverse effects on most psychiatric conditions. Encouraging cannabis use in these vulnerable populations, particularly given the availability of alternative effective therapies, can undermine recovery or management of their psychiatric conditions, and perhaps increase the probability of developing a psychiatric disorder [48].

Second, a reduction in perceived risk of cannabis combined with the increased belief that cannabis can be a therapeutic agent for multiple medical conditions may have significant influence on treatment seeking among those with CUD. The number of states with legal cannabis laws has increased nearly threefold from 2009 to 2015, while the percentage of cannabis-related adult treatment admissions relative to other SUD admissions has decreased by approximately 30–40%. As per above, approximately half of referrals to treatment for cannabis problems in the U.S. have come from legal or judicial sources. With legal consequences likely to decrease in the current cannabis regulatory environment, self-recognition or family/friend recognition of a cannabis problem will become more necessary to prompt persons with CUD to get help. If perceptions of cannabis-related harm continue to decrease, the probability of recognizing and attributing problems to cannabis use will also be reduced. Such an effect would be particularly undesirable, because self or family/friend referrals for cannabis-related treatment admissions are already low compared to those for other SUDs [53].

In summary, legalization of cannabis for therapeutic or recreational use has the potential to substantially impact cannabis use initiation, use patterns, and the development and course of CUD. Such effects can manifest via multiple mechanisms, many of which are well-known risk factors for substance use and addiction in general. Studies of the effects of cannabis legalization are ongoing. However, at present, definitive data concerning the impact of cannabis legalization are not yet available in large part, because such legislative changes are both nascent and diverse. Nonetheless, existing clinical and social science on the nature of addiction, together with knowledge about cannabis use and CUD, can be used to effectively inform regulatory provisions and preventative measures that can help mitigate potential harms that may accompany legalization.

Conclusions

Current scientific knowledge and clinical observation strongly support the contention that cannabis use—like the use of other substances such as alcohol, opioids, stimulants, and tobacco—can develop into a use disorder, a.k.a., an addiction, that has substantial clinical consequences. The clinical epidemiology studies reviewed here indicate that at least one in ten of those who currently use cannabis self-report having problems that meet the criteria for a use disorder as indicated in the DSM and ICD. These data also indicate that the majority of those who use cannabis do not have problems related to their use, but an important subset may develop a CUD. Among those that develop a CUD, the severity of the disorder ranges from mild to severe, and the severity level appears to be positively related to deficits in cognitive and psychological functioning. A small but substantial proportion of those with CUD seek treatment, and these patients make up a substantial proportion of all admissions for SUDs; indeed for youth, they make up the great majority of all admissions. Additional research is needed, however, to better estimate the prevalence of CUD and how it relates to rates of treatment seeking. The clinical trials research on CUD with both adults and adolescents clearly demonstrates that a number of behavioral treatments are efficacious. Unfortunately, these studies also show that the majority of patients who receive these interventions do not show evidence of clinically meaningful positive change in their cannabis use, illustrating that quitting cannabis for those with CUD is difficult. Most noteworthy is that each of the statements above can be applied to all other licit and illicit substances that humans use recreationally and that are known to have addictive potential.

It is of clear public health importance that we: (a) continue to educate the public, our policymakers, and our healthcare providers on the potential harms which can occur from the use of cannabis products that contain significant amounts of THC; (b) develop and implement cannabis regulatory policies that seek to mitigate the potential for known negative consequences of cannabis use, particularly in populations that are vulnerable to the development of CUD; and (c) foster clinical research on prevention and treatment that can more effectively assist those at risk for and those who are currently experiencing the consequences of CUD.

Compliance with ethical standards

Conflict of interest Neither author has any conflicts of interest other than research and training support from the NIH-NIDA.

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