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**The Potential Impact of Cannabis Legalization on the Development of Cannabis Use
Disorders**

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Abstract

Specific provisions of legal cannabis legislation and regulation could influence cannabis initiation, frequency and quantity of use, and progression to cannabis use disorder. This brief essay highlights scientifically based principles and risk factors that underlie substance use and addiction that can be leveraged to inform policies that might mitigate the development and consequences of cannabis use disorder. Specifically, pharmacologic, access/availability, and environmental factors are discussed in relation to their influence on substance use disorders to illustrate how regulatory provisions can differentially affect these factors and risk for addiction. Relevant knowledge from research and experience with alcohol and tobacco regulation are also considered. Research designed to inform regulatory policy and to evaluate the impact of cannabis legislation on cannabis use and problems is progressing. However, definitive findings will come slowly, and more concerted efforts and resources are needed to expedite this process. In the meantime, policymakers should take advantage of the large body of scientific literature on substance use to foster empirically-guided, common sense approaches to cannabis policy that focus on prevention of addiction.

Cannabis use has been linked to multiple short-term and long-term consequences including impairment in short-term memory, motor coordination, altered judgment, acute paranoia or psychosis and risk of chronic psychotic disorders, altered brain development, poor educational and vocational outcomes, and the development of cannabis addiction (Hall, 2009; Volkow et al., 2014). The majority of Americans currently support some form of cannabis legalization, and over half of U.S. states have enacted laws permitting the use of cannabis for medical and recreational purposes (Legal Cannabis Laws, LCLs) recognizing the potential for positive consequences of such policies (Geiger, 2016; ProCon.org, 2017). However, there is increasing societal concern that these laws may impact the prevalence and severity of the potential adverse effects of cannabis use. A critical issue, and the focus of this essay, is how LCLs may affect the prevalence of one of these consequences, the development of cannabis use disorder (CUD) or “addiction”.

CUD, like other substance use disorders, consists of a constellation of biopsychosocial impairments engendered by frequent and heavy cannabis use (Budney, 2006; Hasin et al., 2013). Concern about the proliferation of CUD warrants careful consideration because CUD has been associated with problems in multiple domains of psychosocial functioning (Colliver et al., 2006; Hasin et al., 2015), and rates of CUD increased in the U.S. over the past 10-15 years, particularly in LCL states (Hasin et al., 2015; Hasin et al., 2017; Wen et al., 2015).

Understanding how LCLs impact patterns of cannabis initiation and use among youth is particularly important to understand given this population’s neurobiological and psychosocial vulnerabilities. Earlier initiation of cannabis use exposes youth to greater risk for developing CUD as well as poor educational and vocational achievement, and increased mental health problems during adolescence and adulthood (C. Y. Chen et al., 2009; King and Chassin, 2007; Lopez-Quintero et al., 2011; Volkow et al., 2014).

LCLs comprise multiple specific provisions that detail regulatory processes for determining how cannabis products can be created, distributed, and accessed. Some of these provisions

have the potential to influence rates of cannabis initiation, frequency and quantity of use, and ultimately, progression to CUD. The current legislative process in the U.S. involves each state crafting its own unique model of cannabis legalization. This has resulted in highly diverse models each with potential for differential impact on the development of CUD. In order to understand how specific provisions within these models may impact development of CUD, one must first recognize and consider the factors known to influence substance use and development of problematic patterns of use. The etiology of CUD (as with all substance use disorders) is related to a collection of risk factors (McCrary and Epstein, 2013), and consideration of the impact of LCLs on addiction must keep in mind the interactions among such influences. This essay seeks to elucidate how LCLs may influence or interact with pharmacological, behavioral, biological, and sociocultural risk factors that determine the probability of developing a CUD by using data gleaned from behavioral and clinical pharmacology, neurobiology, behavior analysis, behavioral economics, and epidemiology. By identifying and clarifying these relationships, we hope this existing knowledge base will be used to guide policy, and to anticipate, mitigate, and prepare for the consequences of LCL enactment on the development of CUD. We will examine three “risk factor” areas: pharmacology of drug effects, access/availability of substances, and environmental influences.

Pharmacology

Substances, including cannabis, that are used recreationally and which pose a risk for the development of a clinical substance use disorder (“addiction”) are attractive to most humans because they function as reinforcers (Higgins et al., 2004). That is, the experience that immediately follows drug taking is desirable, and therefore the drug is likely to be used again. The strength of such a reward or reinforcement is determined by multiple factors, the most obvious of which is the direct effects of the substance on the central nervous system and the subsequent pleasurable or desirable experience.

Two elements that influence the direct effects of substance use are the dose or potency of the drug consumed and the method or route of administration by which it is used. The direct positive reinforcing effects of the primary psychoactive component of cannabis, delta-9-tetrahydrocannabinol (THC), are mediated by cannabinoid receptor (CB1) via activation of the mesolimbic dopamine system, the brain's reward system (Cooper and Haney, 2009). Higher potency (greater %THC) cannabis generally engenders more desirable or rewarding effects than lower potency cannabis. Users therefore, generally prefer and are more likely to repeatedly self-administer higher potency cannabis (Chait and Perry, 1994; Cooper and Haney, 2009). This putatively increases risk associated with higher THC potency. However, such risk might be counterbalanced partially by users' self-titrating the amount they consume. The effects of self-titration have not been well studied and the literature on its effects is equivocal (Ramesh et al., 2013; van der Pol et al., 2014; van der Pol et al., 2013).

In combination with dose/potency, how one uses cannabis (i.e., smoke, eat, vaporize) contributes to the magnitude of intoxication and subjective qualities of the experience. Smoking delivers THC to the central nervous system much more quickly than oral ingestion, leading to a more rapid onset of effects, and in some cases a more intense experience (Vandrey et al., 2017). Smoking cannabis, however, involves ingestion of noxious smoke, which produces potentially negative or undesirable sensations, and delivers known carcinogens into the body (Tashkin et al., 2002). Vaporizing or vaping cannabis, an increasingly popular method of cannabis use (Budney et al., 2015), reduces these potentially negative aspects of smoking, while providing a rapid onset of desirable effects comparable to the effects from smoking (Abrams et al., 2007). In summary, higher dose THC and the availability of desirable methods to deliver THC rapidly to the brain can be considered risk factors for repeated cannabis use and development of CUD.

So why are these pharmacological effects relevant to cannabis legislation's potential impact on problem development? As cannabis legislation has spread across the U.S., the potency of

cannabis products available for sale in medical and recreational dispensaries generally dwarfs that previously available through illegal markets (Carlini et al., 2017; ElSohly et al., 2016; Vandrey et al., 2015). New types of cannabis extracts have been documented to have THC concentrations of up to 75% (Raber et al., 2015). These high THC concentrated products are designed for use via vaping or smoking, or are sold as highly palatable edible products (e.g., chocolate bars, sodas, chewable candies, cookies, etc.). Moreover, vaping devices are many times sold alongside these products and are now available in an increasing number of vape shops that also sell flavored nicotine for use in electronic cigarette devices. Increases in product potency and diversity appear related to the presence of for-profit cannabis dispensaries (retail stores) that are motivated to increase sales (Borodovsky et al., 2016; Pacula et al., 2014b; Richter and Levy, 2014; Sevigny et al., 2014). Production and availability of high-potency cannabis may also be inadvertently exacerbated by taxation structures based on the weight of cannabis, which creates an incentive for manufacturers to develop low-weight, high-THC content products (Hall and Lynskey, 2016).

Such changes in the landscape of cannabis products and methods of use could impact cannabis initiation, repeated cannabis use, and the development of use disorders in multiple ways. First, higher potency products increase the probability of experiencing desirable effects in first-time users and require less ingestion of noxious smoke when using combustible methods. This putatively produces a more pleasurable first experience with cannabis and an increased likelihood of repeated use. Similarly, vaping or edible use of cannabis would avoid the need to ingest toxic smoke, and thereby increase the chances of trying cannabis for the first time and experiencing desirable effects. A more positive first experience combined with availability of highly palatable (edibles) and high potency products that do not require smoking might to facilitate an easier path to escalating and problematic cannabis use patterns (Agrawal et al., 2013; Fergusson et al., 2003). Youth that use vaping devices, report using extract preparations of cannabis with high THC content (Morean et al., 2015). Consequently vaping, particularly of

high potency cannabis, may increase the development of tolerance and the likelihood of withdrawal – two factors that contribute to the development of a use disorder (Loflin and Earleywine, 2014).

Clearly, specific provisions of cannabis policies and regulations can impact availability and use of high potency cannabis products or devices. For example, many current state cannabis laws stipulate possession amounts per individual (which vary substantially across states). These statutes have recently begun to address potency (THC content) of permitted cannabis products (Healthy Colorado Coalition, 2016). Recent California cannabis legislation (Proposition 64) has recognized these issues, listing cannabis potency as one of its state-funded research initiatives, asserting the state's authority to impose scientifically appropriate limits on potency levels (State of California, 2016). A few states have also limited use of cannabis to specific routes of administration (e.g. NY and MN do not allow smoking of cannabis).

The importance of imposing regulations on the content of psychoactive compounds in alcohol and tobacco products to effectively impact intoxication and development of addiction, has long been recognized, as has concern about product additives that may increase their addictive potential (Henningfield et al., 2004; Mosher and Johnsson, 2005). Indeed, the NIH and FDA have recently devoted substantial effort and funds to continue scientific inquiry about how best to regulate nicotine content and nicotine delivery devices to mitigate the development of addiction and limit other adverse effects of tobacco and nicotine use (Printz, 2014). Similar steps are clearly needed to guide regulatory efforts related to cannabis product potency and how such products are consumed.

Access/Availability

The ease or difficulty of accessing an intoxicating substance has an obvious, but often underestimated, influence on individual and population-level substance use initiation, frequency and amount of use, and consequently the risk of developing a substance use disorder. Behavioral economics provides a multi-dimensional conceptualization of access or availability of

a reinforcer (e.g., cannabis) that can help one appreciate its potential impact on use and addiction (Bickel et al., 2014; Hursh and Roma, 2013). The organizing construct of “unit price” describes how consumption is determined by the cost of the product divided by the magnitude of reward or reinforcement derived from the product, and the unit price of other products that are concurrently available. Most importantly, in this model, cost includes not only monetary price, but also the amount of effort and time required to obtain the product.

Accordingly, the mechanisms of access to cannabis dictated by LCLs can impact population-levels of use and the development of use disorders. For example, currently many states provide access to cannabis through licensed dispensaries (Pacula et al., 2014a). Some laws permit only a few dispensaries (Connecticut Department of Consumer Protection, 2016) while others permit hundreds (Colorado Department of Revenue, 2016). Greater numbers of places to purchase a product translates to lower cost (less travel time, lower transportation cost). Studies of alcohol and tobacco retail outlet density and residential proximity to outlets indicate a positive relationship with the initiation of use, heavier and more problematic use, and more difficulty quitting use (Cantrell et al., 2016; M. J. Chen et al., 2009; Kuntsche et al., 2008; Pacula et al., 2014b; Reitzel et al., 2011; Scribner et al., 2000). Similar relationships have emerged in the nascent cannabis literature. For example, states with medical cannabis laws that legally protect dispensaries have more adult and youth cannabis use treatment admissions than medical cannabis states that do not legally protect dispensaries (Pacula et al., 2015). More cannabis dispensaries per square mile also predicts more frequent cannabis use (Freisthler and Gruenewald, 2014), and higher CUD-related hospitalizations (Mair et al., 2015). Last, a greater number of dispensaries per capita predicts cannabis use and a younger age of initiation of vaping and edible products (Borodovsky et al., 2016; Borodovsky et al., 2017).

Another provision of many state LCLs related to access is whether or not individuals are permitted to grow cannabis, i.e., home cultivation (Pacula et al., 2014a). Home cultivation presents challenges for preventing the excessive growth of cannabis and its diversion. Home

cultivation may provide youth with easier access to cannabis, lower the age of first cannabis use, and increase the risk of developing a use disorder (Caulkins et al., 2012; Pacula et al., 2015). Between 1992 and 2011, over 85% of treatment admissions for CUD that occurred in states with medical cannabis laws, occurred in states that permitted home cultivation (Pacula et al., 2015). Home cultivation also predicts past month use and heavy use (≥ 20 day) (Pacula et al., 2015). It may also be associated with higher likelihood and younger age of onset of cannabis edible use (Borodovsky et al., 2017).

Last, state legislation can impact monetary price of cannabis. Economic projections of the price of cannabis associated with the proliferation of legalization clearly indicate substantial decreases compared to pre-legalization cost (Caulkins et al., 2012; Hall and Lynskey, 2016). Leveraging the clear and consistent negative relationship between monetary price and consumption of tobacco and alcohol products is a staple public health strategy for mitigating population-level use and harm associated with those substances (Chaloupka et al., 2002; Chaloupka et al., 2010; Farrell et al., 2003; Pacula et al., 2014b). Each state that legalizes the distribution and sale of cannabis will need to determine tax rates at the manufacturing, sales, and purchase levels. Keeping prices at a level that helps control excessive use through strategic and nuanced taxation policies would seem reasonable. However, enacting effective taxation policy is challenging, as much remains unknown about this nascent industry, and increased tax revenue must be balanced against the behavior of black markets in response to such policies (Caulkins et al., 2012). Of note, price may differentially impact frequency of use and the development of use disorders among various cannabis user subgroups (Pacula and Lundberg, 2014). How to use taxation to most effectively mitigate the prevalence and incidence of excessive use, adverse effects, and use disorders in the population will require careful thought and additional study.

Environmental Factors

Multiple aspects of the environment or context in which substances are available (e.g., neighborhood socioeconomic status, , cultural factors, societal norms and laws, marketing and advertising) exert an impact on the age of onset, probability, frequency, and amount of use, and problem development (Bickel and DeGrandpre, 1996). Here we briefly discuss just two such factors that are particularly susceptible to the influence of legislation and regulations—marketing and social norms regarding the perception of risk..

Exposure to commercial advertisement and promotion, portrayal of use (modeling) in entertainment media, point of sale advertising, and packaging have all been identified as “effective” marketing strategies that influence tobacco and alcohol initiation and rates of consumption (Anderson et al., 2009; Kollath-Cattano et al., 2016; Lovato et al., 2011). In response to these observations, government agencies and industry regulatory boards have either prohibited or made strong recommendations limiting the advertising and marketing of these substances. These licit substance industries have long known that heavy alcohol and tobacco users in the population generate the majority of profits (Chaloupka et al., 2002; Cook et al., 2002). The same may potentially be true for the emerging cannabis industry (Caulkins et al., 2015; Kilmer, 2014). This dynamic incentivizes companies to maximize profits by creating and sustaining heavy users of their products. This begins with marketing strategies that encourage initiation and continuation of use through shaping of product-related attitudes, beliefs, and expectations, and the normalizing of use (DiFranza et al., 2006; Landman et al., 2008; Pechmann and Knight, 2002). Adolescents are particularly susceptible and appealing targets for such strategies because earlier age of onset of use is associated with increased risk for later heavy tobacco, alcohol and cannabis use, and for alcohol and cannabis use disorders (Agrawal et al., 2006; Biener and Siegel, 2000; Chen et al., 2005; David J. DeWit et al., 2000; Evans et al., 1995; Perkonig et al., 2008; Swift et al., 2008). As might be predicted based on the alcohol and tobacco literature, data connecting cannabis advertising and age of onset are beginning to emerge (D'Amico et al., 2015; Roditis et al., 2016; Schuermeyer et al., 2014).

To date, state restrictions on cannabis marketing through advertising on TV, radio, billboards, or social media, or by sponsorship at cultural and sports events, have not aggressively addressed this risk factor (Barry and Glantz, 2016). If not constrained, there is little reason to expect that the rapidly expanding cannabis industry will self-regulate their marketing to decrease heavy cannabis use and CUD among vulnerable groups (Barry and Glantz, 2016; Caulkins et al., 2016; Kilmer, 2014; Pacula et al., 2014b; Richter and Levy, 2014). Policymakers at local, state, and federal levels can readily leverage knowledge of effective approaches to marketing and advertising gleaned from many years of research and practice in the tobacco and alcohol fields to preemptively mitigate their impact on the proliferation of cannabis use and problem development.

Cannabis legalization, whether medical or recreational, may affect social norms and perceptions of the risks from use cannabis use. Decades of epidemiological data from the U.S. demonstrate a negative relationship between prevalence of cannabis use and perceived risk of harmfulness (Johnston et al., 2015). Of concern, the perceived risk of cannabis has declined substantially over the past two decades (Keyes et al., 2016; Patek et al., 2015), and this has been accompanied by a parallel increase in the overall prevalence of cannabis use and the prevalence of CUD (Hasin et al., 2015). However, the literature on the relation between cannabis legalization and perceptions of risk to date has been equivocal. (Keyes et al., 2016; Miech et al., 2015; Schmidt et al., 2016; Schuermeyer et al., 2014; Wall et al., 2011). It is possible that a reciprocal relationship exists between cannabis risk perception and LCL enactment. For example, States with a pre-existing liberal cannabis culture may be more likely to enact LCLs, and those LCLs may subsequently reinforce the liberal cannabis culture. The mechanisms by which cannabis legalization can influence norms and perceptions are many.

Removing legal risks can impact population-level cannabis use by restructuring economic demand and changing patterns of use over time (Pacula and Lundberg, 2014). Enactment of medical cannabis laws has been tied to a significant portion of high school students indicating

that they would either try cannabis or use more cannabis if it became legal in their state (Palamar et al., 2014). However, other studies have not demonstrated robust relationships among cannabis legalization, risk perception, and use (Harper et al., 2012).

In 2014, states with medical cannabis laws averaged more than 13 medical conditions that could qualify individuals for use of cannabis, and the number of conditions continues to escalate. Such conditions include most any type of pain, diverse neurological disorders like Alzheimer's, epilepsy and ALS, simple nausea and disorders for which nausea or cachexia is part of the syndrome or treatment such as HIV/AIDS or cancer, disorders that involve muscle spasticity, and psychiatric disorders like PTSD (Bestrashniy and Winters, 2015). How this ubiquitous list of medical conditions for which states have deemed cannabis an effective treatment impacts public perception of the harmfulness, risk, and health-related beliefs associated with cannabis is not known, yet one can readily surmise with some confidence that it would reduce perceived concerns about the potential harms related to cannabis use. Moreover, when retail cannabis dispensaries outnumber Starbucks or McDonalds in a geographic area, as is the case in Colorado, the influence on social norms and access to cannabis could be substantial (Pacula et al., 2015; Rocky Mountain High Intensity Drug Trafficking Area, 2016).

Some legislative provisions could help curb normalization of cannabis use and the observed declines in cannabis use risk perception. Similar to bans on use of tobacco in public places (Komro et al., 2013), bans on use of cannabis in public may influence public attitudes and social acceptability of cannabis use. Fortunately, most states with active cannabis laws have banned use of cannabis in public. Other regulatory targets to consider include: clear and strict limits on advertising and marketing, a reduction in the number and visibility of dispensaries, restrictions on home cultivation, and restricting or eliminating state-approved use of cannabis for medical disorders (Barry and Glantz, 2016; Pacula et al., 2014b). This last target, the state-sanctioned medical use of cannabis, although the most controversial, warrants careful consideration especially if the goal is to seriously address trends toward normalization

and the reduction in perception of a potential for harm. Adequate evidence is sorely lacking for the clinical efficacy of cannabis or cannabinoids for the great majority of maladies currently approved (Belendiuk et al., 2015; D'Souza and Ranganathan, 2015; Whiting et al., 2015). Consequently, eliminating state approval for self-medicating this plethora of conditions with a substance that has substantial potential for misuse and addiction would seem rational. Taking action in this direction would more clearly align cannabis with the other common licit substances, alcohol, and tobacco, and perhaps facilitate more effective preventive educational programs. Which leads to a final legislative provision worthy of mention, the funding of mandatory prevention and intervention programs and research in the area of cannabis regulatory science funded with tax dollars from cannabis licensing and sales. A number of states already have included such provisions and research is underway (Skinner et al., 2016). The success of such funding mandates is not yet clear, but similar efforts have proven successful for alcohol and tobacco use prevention.

Concluding Comments

States across the U.S. are attempting to achieve a difficult legislative goal - the regulation of legal cannabis without increasing the prevalence of problematic cannabis use and CUD. Such efforts can benefit from a comprehensive working knowledge of the multiple factors that influence addiction. In this brief essay, we have identified a few well-established risk factors, based on research from multiple scientific disciplines, and attempted to illustrate how specific provisions of cannabis laws and regulations may impact these factors and thereby prevent or exacerbate the risk of addiction.

Direct study of the impact of legislation enacted to date is underway, however, the continuously changing legislative and regulatory environment across and within states makes this a most challenging endeavor (Pacula and Sevigny, 2014). Much is also yet to be learned about novel, high potency cannabis products and alternative methods for using cannabis that are readily available and commonly used. Research in this area progresses, but has been

slowed by statutes in the Federal Controlled Substances Act and Food and Drug Administration policies designed to protect public health. Federal guidance and funding that can enhance and expedite research efforts in these areas are sorely needed, and there exist some indications that this may be on the horizon. The National Institute on Drug Abuse, the National Center on Complementary Medicine and Integrative Health, and the National Institute of Neurological Disorders and Stroke of the NIH have taken substantial steps towards funding basic and clinic research in this area (National Institutes of Health, 2016).

Until new data emerge to guide policy, existing basic and clinical science on addiction in general, and cannabis use and problem development in particular, can be used to effectively inform policy decisions. Moreover, because cannabis can be considered highly similar to the other commonly used substances that have addictive potential, experience with alcohol and tobacco regulation can provide informed guidance on the impact of specific regulatory provisions on cannabis use and CUD (Budney, 2007; Budney and Lile, 2009; Vandrey and Budney, 2015). Enacting LCLs may have multiple negative and positive public health and cultural consequences. We hope that this brief essay calls attention to the large body of scientific evidence that can inform empirically guided, common sense approaches to cannabis policy that will focus on the prevention of addiction (Weiss et al., 2017).

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Highlights

- Legal cannabis law provisions may differentially impact risk of cannabis addiction
- Such laws may influence cannabis pharmacology, access, and culture
- Known factors that contribute to addiction should guide cannabis policy design
- Increased funding is needed to bolster cannabis regulatory science

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