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Cannabis regulatory science: risk-benefit considerations for mental disorders

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Abstract

The evolving legal cannabis landscape in the U.S. continues to present novel regulatory challenges that necessitate the development of a Cannabis Regulatory Science. Two specific issues of concern within Cannabis Regulatory Science are (1) the impact that cannabis use has on the incidence, prevalence, and severity of mental disorders, and (2) how cannabis laws and regulations modify this impact. In this paper, we first provide several conceptual points that are useful for evaluating the relationship between cannabis use and mental disorders. Second, we selectively review and comment on data relevant to the relationship between cannabis use and depression, several forms of anxiety, posttraumatic stress disorder, schizophrenia, and bipolar disorder. Next, we discuss regulatory and public health parallels between the nascent cannabis industry and the pharmaceutical, tobacco, and alcohol industries. We focus on specific types of industry practices that may harm those with or at risk for mental disorders. We then offer recommendations for legal cannabis regulations that could mitigate this harm. Last, we discuss future research goals for building the field of Cannabis Regulatory Science and addressing the potential negative impact of cannabis on those with mental disorders.

Keywords

cannabis; marijuana; legalization; mental disorders; psychiatric; regulatory science

Introduction

Cannabis legalization has gained unprecedented momentum around the world and continues to evolve rapidly. In the U.S., states not only differ in whether they have legalized medical or commercial (i.e., recreational) cannabis, or both, but importantly, each state has taken a unique approach to designing its legal cannabis laws (LCL). States vary dramatically in the

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number and types of qualifying medical conditions, requirements for becoming a medical cannabis patient, the types and potency of products that can be used, the amount of personal cannabis one can possess, and the regulation of production, distribution, marketing, and sale of cannabis (Barry & Glantz, 2016; Bestrashniy & Winters, 2015; Chapman, Spetz, Lin, Chan, & Schmidt, 2016; Pacula, Hunt, & Boustead, 2014; Pacula, Powell, Heaton, & Sevigny, 2015; Williams, Olfson, Kim, Martins, & Kleber, 2016). These specific components of laws warrant careful consideration and study as each has the potential to mitigate or increase the negative or positive public health consequences related to cannabis use. Unfortunately, few states have effectively utilized scientific evidence concerning cannabis or the public health effects of various regulatory mechanisms, to construct their laws and regulations (Barry & Glantz, 2016; Weiss, Howlett, & Baler, 2017).

This article concentrates on the potential impact of components (i.e., provisions) of legal cannabis laws on one vulnerable subgroup - those with and those predisposed to developing mental disorders. Historically in the United States, individuals with mental disorders have experienced stigma, marginalization (Perese, 2016), and a disproportionate amount of burden engendered by legal and illegal addictive substances (Centers for Disease & Prevention, 2013; Jane-Llopis & Matytsina, 2006; Kessler, 2004). Those with mental disorders account for a substantial portion of the total amount of tobacco and alcohol consumed in the U.S. (Grant, Hasin, Chou, Stinson, & Dawson, 2004; Lasser et al., 2000; Meier, Purshouse, & Brennan, 2010). Cannabis consumption patterns are no different. It is estimated that those with past-year mental disorders consume approximately 80% of all cannabis consumed in the U.S. (Lev-Ran, Le Foll, McKenzie, George, & Rehm, 2013). Thus, this population will clearly be affected by legal cannabis – perhaps more so than other subgroups. The design of legal cannabis laws and corresponding regulations should reflect an acute awareness of this disproportionate vulnerability.

Developing regulations that mitigate the impact of cannabis on those with mental disorders is complicated by the interacting dynamics of commercial and medical cannabis legalization. From a commercialization perspective, a multibillion-dollar for-profit cannabis industry (ArcView Market Research, 2016) is emerging and behaving in ways reminiscent of the tobacco and alcohol industries (Barry & Glantz, 2016; Carlini, Garrett, & Harwick, 2017; Pacula, Kilmer, Wagenaar, Chaloupka, & Caulkins, 2014; Richter & Levy, 2014; Subritzky, Lenton, & Pettigrew, 2016; Subritzky, Pettigrew, & Lenton, 2015). Our history with the tobacco and alcohol industries has clearly demonstrated that loose regulation of these industries and their products is detrimental to public health (Bero, 2003; Jahiel & Babor, 2007) – particularly for vulnerable populations such as those with mental disorders (Apollonio & Malone, 2005; Hirshbein, 2012; Prochaska, Hall, & Bero, 2008).

In addition to concerns about commercial cannabis, the medical cannabis laws that are now effective in 29 U.S. states and Washington D.C. permit therapeutic cannabis use for diverse and often diagnostically ambiguous medical conditions. These medical cannabis laws convey to the public that cannabis is an effective therapeutic agent for the multitude of conditions listed within and across state laws. The combination of commercialization and medicalization of cannabis appears to be contributing to individuals supplementing or replacing their use of FDA-approved psychiatric medications with cannabis to treat

depression, anxiety, and symptoms of psychosis (Boehnke, Litinas, & Clauw, 2016; Bradford & Bradford, 2016; Corroon, Mischley, & Sexton, 2017; Nunberg, Kilmer, Pacula, & Burgdorf, 2011; Piper et al., 2017; Reiman, 2016; Reinarman, Nunberg, Lanthier, & Heddleston, 2011). Similar trends are emerging in Canada (Lucas & Walsh, 2017; Lucas et al., 2016; Walsh et al., 2013). This is occurring despite little to no controlled clinical evidence supporting the therapeutic efficacy of cannabis for mental disorders (Belendiuk, Baldini, & Bonn-Miller, 2015), and despite data indicating that medical cannabis patients with a history of psychiatric problems have more problematic cannabis use than medical cannabis patients without a history of psychiatric problems (Ware, Martel, Jovey, Lynch, & Singer, 2018).

This chaotic regulatory landscape necessitates the expeditious development of a Cannabis Regulatory Science to generate the data necessary for creating evidence-based cannabis regulations that maximize public health benefits and minimize public health harms. The goal of the present commentary is to contribute to this effort by focusing on the relationships among cannabis use, cannabis legalization, and mental disorders. Specifically, this paper will (1) present conceptual points regarding the relationship between cannabis and mental disorders that may be useful for readers; (2) review the relevant relationships between cannabis and mental disorders at multiple levels of analysis (e.g., epidemiological, clinical, behavioral pharmacological); (3) draw several parallels from the pharmaceutical, tobacco, and alcohol industries to identify how legal cannabis laws and a for-profit cannabis industry will likely influence cannabis use among those with mental disorders; (4) present recommendations for regulations based on the current literature and historical precedents with other substances; and (5) present considerations for future research that will help create a robust Cannabis Regulatory Science body of research related to cannabis and mental health.

Of note, we will not address how cannabis use and legalization may affect non-cannabis substance use disorders (SUD) (e.g., alcohol, cocaine, opioid, or tobacco use disorder) even though such SUDs are a subgroup of “mental disorders” and disproportionately co-occur with mood, anxiety, and psychotic disorders (Grant et al., 2016). A meaningful discussion of this topic requires an analysis of several additional concepts (e.g., gateway hypothesis, substitution effects, pharmacological synergy, etc.) that are beyond the scope of this commentary. Second, we discuss cannabis use disorder (CUD) but do so within the context of its significant co-occurrence with other mental disorders. We refer those interested in a discussion of the specific relationships among cannabis legalization, cannabis use, and CUD (excluding other types of mental disorders) to our previous commentary (Budney & Borodovsky, 2017).

The relationship between cannabis and mental disorders

Conceptual Points

Before addressing the known relationships between cannabis use and specific mental disorders, several broad concepts warrant discussion. The concepts outlined below will help guide critical evaluation of the relevant scientific literature.

First, the cannabis plant contains over 100 distinct cannabinoid compounds, and the amount of each compound varies substantially across plants (ElSohly & Gul, 2014). The compounds most relevant to this discussion (but certainly not the only relevant compounds) are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is the primary psychoactive constituent of cannabis and exhibits reinforcing and rewarding properties (Cooper & Haney, 2009). Synthetic pharmaceutical-grade THC is FDA approved to treat weight loss in AIDS patients and chemotherapy-induced nausea (AbbVie Inc., 2018). A closely related compound – nabilone – is also FDA approved for treating the latter condition (Throckmorton, 2016). In contrast, to date, studies on CBD have not shown any clear signs of abuse liability (Babalonis et al., 2017), and individuals who have consumed as much as 600 mg of CBD reportedly did not demonstrate signs of intoxication in a laboratory study (Martin-Santos et al., 2012). Additionally, emerging data suggest that CBD-based medications may be promising therapeutic agents for several neurological disorders (Fasinu, Phillips, ElSohly, & Walker, 2016).

The effects and therapeutic value of consuming a pharmaceutical-grade formulation of a single cannabinoid (e.g., THC or CBD) can be dramatically different from the effects of ingesting the entire cannabis plant. Furthermore, ingesting the entire plant (or a formulation) that has differing amounts of each compound, (e.g., a plant containing 20% THC and 0.3% CBD vs. a plant containing 0.5% THC and 4.0% CBD), would have obvious differential pharmacological effects. Thus, not only is it essential to identify the specific compounds being administered when evaluating the effects of “cannabis” on behavior and specific health conditions, but the dose of each compound and the commensurate interactions must be considered as well. Evaluation of dose is further complicated by other potential pharmacodynamic characteristics of cannabinoid compounds. For example, biphasic effect profiles have been posited for cannabinoids; that is, a low dose may produce one effect (e.g., reduction in anxiety) and a high dose may cause the opposite effect (e.g., increased anxiety) (Mechoulam & Parker, 2013).

Second, the chronicity of use of a particular cannabinoid or combination of cannabinoids (such as those present in the cannabis plant) could impact the medical risk-benefit profile. For example, a cannabinoid could have a clinically meaningful impact on a mental disorder when administered acutely, but adversely affect the development or course of a mental disorder when repeatedly administered over time. Paradoxical characteristics like these are not uncommon among medications. Consider benzodiazepines for example. This class of medications is effective as a short-term aid for reducing debilitating symptoms of anxiety disorders (Dell’osso & Lader, 2013). And yet, long-term benzodiazepine use carries several risks such as development of a substance use disorder, cognitive decline, and exacerbation of anxiety (Dell’osso & Lader, 2013). The point is that evaluating the risk-benefit profile of a psychoactive compound used for medical purposes requires consideration of both short- and long-term consequences.

Third, a drug’s reinforcing effect should not be mistaken as a therapeutic one. Psychoactive substances like THC (or alcohol, stimulants, opioids) produce euphoric effects via interactions with reward-related neurocircuitry. More relevantly, these substances can also temporarily reduce pre-drug negative mood states without resolving the underlying cause of

the mood disturbance. This combination of effects likely renders the substance more reinforcing for persons with mental disorders. That is, in addition to the typical positive reinforcing effects experienced by users, individuals with mental disorders may also experience *negative reinforcement* when ingesting the substance (i.e., relief from negative emotional states such as depressed mood). One might interpret this latter effect as therapeutic, but it in fact likely contributes to the increased vulnerability to substance use and development of substance use disorders (SUD) among those with mental disorders. Whether or not this constitutes "self-medication" (Khantzian, 1997) in the traditional sense of the term is of little importance. The relevant point is that using a substance to achieve temporary symptomatic relief may not be therapeutic, particularly if continued use of the substance exacerbates or helps maintain (rather than resolving) a mental disorder.

Last, when interpreting the results of research studies or case illustrations, it is essential to consider the history of cannabis use of the individuals under study. Whether individuals have ever used cannabis, how recently they have used, and how frequently they have been using all can contribute to tolerance to cannabis effects, and to the probability and severity of cannabis withdrawal when cannabis is discontinued. This, in turn, may have a dramatic impact on the observed effects in any one study (Kirk & De Wit, 1999; Schlienz, Budney, Lee, & Vandrey, 2017).

In sum, any meaningful discussion and evaluation of the effects of cannabis on mental disorders must explicitly specify what cannabinoid compounds are being evaluated, how much of and for how long the compounds were administered and evaluated, the potential conflation of reinforcing properties and therapeutic utility, and the cannabis use history of the persons included in the evaluation.

The prevalence and co-occurrence of cannabis use and mental disorders

The cross-sectional relationship between cannabis use and mental disorders can be understood in two ways – the prevalence of cannabis use among those with mental disorders (Lev-Ran, Le Foll, et al., 2013) or the prevalence of mental disorders among cannabis users (Stinson, Ruan, Pickering, & Grant, 2006). In both cases, the scientific literature is clear that the co-occurrence of cannabis use or CUD and major depressive, psychotic, anxiety, posttraumatic stress, and bipolar disorders is disproportionally large when compared to either those who do not use cannabis or to those without mental disorders (Agosti, Nunes, & Levin, 2002; Green, Young, & Kavanagh, 2005; Hasin et al., 2016; Lev-Ran, Imtiaz, Rehm, & Le Foll, 2013; Lev-Ran, Le Foll, et al., 2013; Teesson et al., 2012). Furthermore, the prevalence of mental disorders among cannabis users appears to rise in parallel with the frequency and severity of self-reported cannabis use (Cheung et al., 2010; Degenhardt, Hall, & Lynskey, 2001; Stinson et al., 2006; Zvolensky, Cougle, Johnson, Bonn-Miller, & Bernstein, 2010). Of note, the elevated prevalence of CUD among those with mental disorders does not appear to be simply a function of an elevated prevalence of lifetime cannabis use. Several cross-sectional and longitudinal studies have demonstrated that cannabis users with mental disorders are approximately twice as likely as cannabis users without mental disorders to have or develop CUD (Florez-Salamanca et al., 2013; Lev-Ran, Le Foll, et al., 2013; Lopez-Quintero et al., 2011; Martins & Gorelick, 2011).

Specific mental disorders and their relationships with cannabis use

In this section, we present summaries of the known and potential therapeutic and adverse effects of cannabis and cannabinoids on depression, anxiety, posttraumatic stress disorder, schizophrenia, and bipolar disorder. Given space limitations, this summary is broad in scope, but lacking in detail. More in-depth discussions of this literature can be ascertained from cited original articles and reviews.

Depression—Cannabis users commonly report that they use cannabis to help with their depression (Aggarwal et al., 2013; Bonn-Miller, Boden, Bucossi, & Babson, 2014; Reinarman et al., 2011; Walsh et al., 2013). However, there are no randomized controlled clinical trial data demonstrating the use of medical cannabis (plant) or pharmaceutical-grade cannabinoids for the treatment of major depressive disorder (Whiting et al., 2015). Several studies of various patient populations with serious physical medical conditions (e.g., HIV, Multiple sclerosis) have measured depressive symptoms as a secondary outcome, and have noted improvements in mood (Walsh et al., 2017). However depressive symptoms were not the primary endpoints in these studies, and this effect was not on Major Depressive Disorder. Relief from the symptoms associated with serious chronic medical conditions like HIV or Multiple sclerosis would be expected to improve negative moods commonly associated with enduring chronic illness. Interestingly, the medication rimonabant, a CB1 receptor antagonist (i.e., blocks the effects of cannabinoids like THC), was removed from the U.S. and European markets after determining that a small portion of those who used it experienced side effects of depression and suicidality. This observation reflects an important relationship between the endocannabinoid system and mood regulation, and hence, raises the possibility of developing cannabinoid-based medications to treat mood disorders (Hill & Gorzalka, 2009; Le Foll, Gorelick, & Goldberg, 2009; Micale, Di Marzo, Sulcova, Wotjak, & Drago, 2013). Moreover, preclinical data indicate that CB1 receptor agonism may increase serotonergic-related neural activity suggesting that cannabinoid compounds may be useful for improving negative mood (Bambico, Katz, Debonnel, & Gobbi, 2007; Gobbi et al., 2005).

The extant data that address whether or not cannabis use can contribute to depression are equivocal, but when a relationship has been observed, cannabis use is most often associated with an increased, rather than decreased risk of depression. A systematic review of longitudinal studies that controlled for baseline depression indicated that cannabis use (particularly heavy cannabis use) was associated with increased risk for subsequently developing depression (Lev-Ran et al., 2014). However, some nationally representative longitudinal data suggest that this relationship is mediated by associations with other SUDs (Blanco et al., 2016), or suggest an opposite causal direction (i.e., that having major depressive disorder at baseline increases the risk of subsequent cannabis initiation) (Feingold, Weiser, Rehm, & Lev-Ran, 2015). Studies that have not accounted for the frequency of cannabis use or the age of cannabis use onset have found no relationship (Danielsson, Lundin, Agardh, Allebeck, & Forsell, 2016). Clinically, individuals with depression who continue to use cannabis throughout treatment make less improvement on their mental health symptoms than individuals with depression who do not use cannabis during treatment (Bahorik et al., 2017). Last, individuals from twin pairs who use cannabis

frequently (≥100 times) are more likely to report major depression than their less frequent or non-using monozygotic twin (Agrawal et al., 2017).

In sum, the endocannabinoid system is involved in mood regulation, and thus there may be potential for development of cannabinoid-based medications for depression. However, use of cannabis plant material ingested by the general population likely facilitates the onset or worsening of symptoms of depression. Interpretation of positive findings from cannabis studies that observe decreased depression secondary to relief from chronic medical conditions (e.g., Multiple sclerosis), must consider and test alternative explanations such as that the improved mood is caused by the reduction in the chronic condition. Last, self-reported temporary relief from depression (negative reinforcement) likely contributes to the high prevalence of CUD among those with depressive disorders. Caution is warranted in labeling such acute symptomatic relief as therapeutic.

Anxiety—The relationship between cannabis and anxiety that can be gleaned from the extant literature is complex. Some CB1 receptor agonist compounds, e.g., THC, have demonstrated potential anxiogenesis, while other compounds such as CBD have shown anxiolytic properties (Crippa et al., 2009). The potential relations between cannabis and anxiety are further complicated by evidence suggesting that a single cannabinoid - such as THC - can mitigate stress responses when consumed at low doses (7.5 mg), but exacerbate stress at higher doses (12.5 mg) (Childs, Lutz, & de Wit, 2017). Moreover, anxiety is a common symptom reported during cannabis withdrawal (Budney, Moore, Vandrey, & Hughes, 2003), and thus some reports of anxiolytic effects of cannabis may merely reflect mitigation of anxiety-related cannabis withdrawal symptoms.

That said, cannabis users commonly report that cannabis helps with their anxiety (Bonn-Miller, Boden, et al., 2014; Reinarman et al., 2011; Walsh et al., 2013) and daily cannabis users provided with 3% THC cannabis cigarettes report feeling more relaxed after use (Hart et al., 2002). However, there are few controlled studies that clarify the effect of cannabinoid compounds on clinical anxiety. Some data suggest that CBD reduces public speaking anxiety (Bergamaschi et al., 2011) and self-reported anxiety symptoms among patients with social anxiety disorder (Crippa et al., 2011). Studies of patients with chronic pain treated with pharmaceutical-grade cannabinoids (e.g., dronabinol, nabilone, and nabiximols) demonstrate improvements in symptoms of anxiety compared to placebo (Whiting et al., 2015). However, similar to the depression data reported, these types of studies focused on treatment of non-psychiatric medical conditions and impact on anxiety or anxiety disorders were secondary outcomes. Thus these reductions could readily be explained by indirect effects that stem from a reduction in chronic pain.

Cannabis use can elicit acute episodes of intense anxiety as well as exacerbate symptoms of anxiety among those with an anxiety disorder (Crippa et al., 2009). Several controlled laboratory studies on the acute effects of cannabis or cannabinoids in humans support this notion. For example, individuals with varied lifetime histories of cannabis use who were given up to 5 mg of intravenous THC reported significant increases in anxiety (D'Souza et al., 2004). Similar results were observed among subjects with varying patterns of cannabis use administered oral THC (15 mg) or a combination of 16.2 mg THC/15.0 mg CBD

delivered via an oromucosal spray (Karschner et al., 2011). In a study of cannabis edible products, 18 participants with no past 90-day cannabis use, consumed a cannabis brownie containing either 10, 25, or 50 mg of THC. One participant provided with a 25 mg brownie, experienced severe anxiety and had to temporarily discontinue study participation (Vandrey et al., 2017). In another study, individuals who had used cannabis less than 15 times in their life, had not used cannabis in the past month, and had never experienced negative psychological effects from cannabis were given either 10 mg of oral THC, 600 mg of oral CBD, or placebo over three sessions (Martin-Santos et al., 2012). The dose of THC significantly increased anxiety compared to placebo and CBD, but no differences were observed between CBD and placebo. Finally, relatively infrequent cannabis users (<10 cannabis joints per month) have reported greater anxiety after using increasingly more potent (29–69 mg THC) cannabis joints (Hunault et al., 2014).

Some have suggested that the impact of cannabis on anxiety may also vary by sub-type of anxiety disorder (Walsh et al., 2017). For example, two independent analyses of longitudinal data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study indicate that baseline cannabis use is associated with elevated incidence of social anxiety (Blanco et al., 2016; Feingold, Weiser, Rehm, & Lev-Ran, 2016) but not other types of anxiety. Frequency of use may also impact the relationship between cannabis and anxiety. Longitudinal analyses of youth indicate that daily cannabis use is associated with having an anxiety disorder later in life (Degenhardt et al., 2013). Studies that have not accounted for the frequency of cannabis use or age of cannabis use onset have found no relationship in either direction, that is, early cannabis use did not relate to later anxiety nor did early anxiety predict later cannabis use (Danielsson et al., 2016).

In sum, the relationship between cannabis and anxiety is complex, similar to observed relationships between depression and cannabis use. Factors such as cannabis use history, cannabis potency, predisposition to an anxiety disorder, and consumers' ability to titrate dose, may all affect the extent to which individuals experience the acute effects of cannabis as being anxiogenic or anxiolytic. This last factor concerning titration warrants special attention. Cannabis products and methods of administration that allow a person to closely titrate his or her level of intoxication (e.g., vaping low-THC plant material) reduce the risk of over-intoxication and thus the risk of an acute episode of anxiety. Currently available high-THC cannabis products (e.g., concentrates) consumed via rapid methods of administration such as "dabbing" (M. Loflin & Earleywine, 2014), offer little ability to titrate and thus place individuals at a higher risk of ingesting anxiogenic doses of THC. Finally, as with depressed mood, cannabis (with THC or THC and CBD) can provide temporary relief from some anxiety symptoms in some individuals who are feeling stressed or anxious, but there are no controlled data to suggest it helps *resolve* anxiety disorders. Available data suggest that CBD-based (non-THC) compounds may warrant controlled testing for certain anxiety disorders, but to date, their clinical utility as an anxiolytic has not been demonstrated.

Posttraumatic stress disorder (PTSD)—Most recently, cannabis has garnered a great deal of media, legislative, and scientific attention as a potential treatment for PTSD. Such attention can likely be tied to two sources. Military veteran groups have been publicly

lobbying for legal access to cannabis for their PTSD (Ugwu, 2017). Second, human studies have reported that both THC and CBD may help facilitate extinction of conditioned fear memories (albeit under different administration procedures) (Das et al., 2013; Rabinak et al., 2013). Moreover, two studies report that pure pharmaceutical-grade THC has significantly reduced nightmares in those with PTSD (Jetly, Heber, Fraser, & Boisvert, 2015; Roitman, Mechoulam, Cooper-Kazaz, & Shalev, 2014) and veterans with PTSD often endorse using cannabis as a sleep-aid (Bonn-Miller, Babson, & Vandrey, 2014). However, other research suggests potential adverse impact of cannabis and cannabinoids on PTSD symptoms and its course. One study has demonstrated that compared to adults who do not use cannabis, chronic cannabis users showed worse ability to extinguish previously conditioned fear responses (Papini et al., 2017). Cannabis use and CUD have been associated with worse PTSD treatment outcomes, and stopping cannabis use has been associated with better PTSD treatment outcomes (Bonn-Miller, Boden, Vujanovic, & Drescher, 2013; Wilkinson, Stefanovics, & Rosenheck, 2015). Moreover, veterans with PTSD and a history of heavy cannabis use who discontinue cannabis use at the start of their PTSD treatment are less responsive to treatment than those with no history of cannabis use or lighter cannabis use (Bonn-Miller et al., 2013).

As with depression and other anxiety disorders, the data on the relationship between PTSD and cannabis are highly complex and equivocal (Haney & Evins, 2016; M. J. Loflin, Babson, & Bonn-Miller, 2017). Generally, the clinical data suggest a negative impact of cannabis use on PTSD outcomes. Nonetheless, additional research is warranted that addresses the aforementioned issues: testing of specific cannabinoids and doses, acute vs. chronic administration, cannabis tolerant vs. non-tolerant patients, and symptomatic relief versus impact on resolution of the disorder. Clinical trials addressing some of these issues are underway (O'Neil et al., 2017).

Schizophrenia—An extensive literature has accumulated over the past 20 years on the effects of cannabis on the development and course of schizophrenia and related psychotic disorders, and many reviews of this issue are available (Hamilton, 2017; Rabin & George, 2017; Radhakrishnan, Wilkinson, & D'Souza, 2014; Schoeler et al., 2016). THC and other synthetic CB1 receptor agonists have the potential to elicit the onset of acute transient psychotic symptoms and produce cognitive dysfunction. THC appears to exert a dose-dependent risk (albeit a relatively small risk) for increasing the probability of developing a psychotic disorder, particularly among those with an initial increased risk (e.g., genetic vulnerability, exhibiting prodromal signs or symptoms, earlier onset cannabis use). Regular use of high potency cannabis (i.e., high THC content) appears to confer markedly higher risk. Cannabis use has also been associated with worsening of symptoms of schizophrenia, as well as adversely impacting the clinical course (i.e., trigger relapse, and outcomes for those with psychotic disorders).

Some preclinical and clinical data, however, suggest that some cannabinoid compounds, most notably CBD, might have potential for exerting positive effects on schizophrenia (Gururajan & Malone, 2016; Leweke, Mueller, Lange, & Rohleder, 2016). A double-blind, randomized controlled trial testing CBD against amisulpride reported that both compounds reduced symptom severity, and CBD caused fewer extrapyramidal symptom side effects

(Leweke et al., 2012). Another recent double-blind placebo-controlled trial of CBD used in conjunction with treatment as usual, demonstrated that CBD helped significantly reduce positive psychotic symptoms and improved scores on the Clinical Global Impressions Scale (McGuire et al., 2017). There do not appear to be any published clinical trials evaluating the cannabis plant as a treatment for psychosis (Walsh et al., 2017). Interestingly, while individuals with schizophrenia who use cannabis have worse symptoms of psychosis, there is some evidence to suggest that they have better cognitive functioning (e.g., attentional control, visuospatial abilities) than individuals with schizophrenia who do not use cannabis (Rabin, Zakzanis, & George, 2011). However, methodological differences across studies, such as poorly defining cannabis use or inadequate control groups, warrant cautious interpretation of this observation (Rabin et al., 2011; Segev & Lev-Ran, 2012). Moreover, selection biases may explain these observations; that is, persons with schizophrenia who are able to obtain and use cannabis may generally be higher functioning than those with schizophrenia who cannot and don't (Rabin et al., 2011; Segev & Lev-Ran, 2012).

In sum, there is convincing evidence from studies examining the use of cannabis plant material that cannabis use is related to an increased likelihood of developing psychosis in subgroups of the population and worsens existing symptoms of psychosis. Nonetheless, the literature highlights the complexity of the problem and the need to consider the effects of various compounds in the cannabis plant. Preclinical and clinical data on CBD suggest that additional research is warranted to examine the potential for CBD to reduce the risk of developing schizophrenia or for use as a medication for schizophrenia.

Bipolar Disorder—To date, we are not aware of any data from controlled studies which suggest that either the use of the cannabis plant in its entirety or CBD has potential as an effective therapeutic agent for bipolar disorder. One published case study of two adults with bipolar disorder who were given up to 1200 mg CBD over the course of 25 days reported no significant improvement in symptoms (Zuardi et al., 2010). As with schizophrenia, there are data to suggest that cannabis either has no effect or improves cognition among individuals with bipolar disorder (Braga, Burdick, Derosse, & Malhotra, 2012; Sagar et al., 2016). Again, however, such results could reasonably be ascribed to selection biases stemming from higher functioning individuals' greater likelihood of using cannabis.

Clinical survey data suggest an association between use of cannabis and both the development of bipolar disorder as well as negative course and outcomes among those with bipolar disorder, although some studies have found no directional relationship. For example, data from the Netherlands Mental Health Survey and Incidence Study indicate that cannabis use at baseline increased the risk for bipolar disorder at follow up (van Laar, van Dorsselaer, Monshouwer, & de Graaf, 2007), and according to analyses of NESARC data, a diagnosis of Bipolar Disorder at baseline is not associated with subsequent cannabis initiation (Feingold et al., 2015). As with other mental disorders, the risk of experiencing the onset of bipolar disorder at a younger age may increase in relation to lifetime severity and frequency of cannabis use (Lagerberg et al., 2014; van Laar et al., 2007).

Additional data from several other large longitudinal studies have shown that individuals with bipolar disorder who use cannabis do not fare well. Among individuals with bipolar

disorder, those who use cannabis experience worse clinical outcomes (disorders severity, mania, and psychosis) (van Rossum, Boomsma, Tenback, Reed, & van Os, 2009), are less likely to have their symptoms go into remission (Kim et al., 2015), and have a significantly shorter time to recurrence of bipolar disorder symptoms (Zorrilla et al., 2015) than those who do not use cannabis. Meta-analyses of experimental and prospective observational studies lend further support to the relationship between cannabis use and subsequent onset of bipolar disorder or worsening of existing symptoms of bipolar disorder (Gibbs et al., 2015).

Summary: cannabis and mental disorders

A few points of emphasis on the relationships between cannabis and mental disorders are worthy of note:

1. The scientific and clinical literature has yet to adequately differentiate the cannabis plant from isolated compounds of the plant or from synthetic cannabinoid compounds. Summaries of information that do not account for these differences provide a poor representation of how “cannabis” interacts with mental disorders. Such unreliable information has great potential for misleading policymakers and the public about the therapeutic potential and efficacy of the cannabis plant or isolated cannabinoid compounds.

2. Currently, there are little to no controlled data from clinical science that support the use of the cannabis plant containing effective doses of THC for any of the psychiatric conditions reviewed above (National Academies of Sciences Engineering Medicine, 2017). Indeed, there are fairly strong clinical data to indicate that use of the cannabis plant containing effective doses of THC may cause or worsen many of these conditions. However, there are no clinical data to suggest that CBD has a negative effect on psychiatric conditions; and there are some preliminary clinical data to suggest that CBD warrants more controlled study as a potential therapeutic agent for some psychiatric conditions. Moreover, basic and laboratory research suggest that compounds that target the endogenous cannabinoid system should be explored as potential therapies for psychiatric conditions. That said, such observations do not indicate that use of the cannabis plant has utility in treating such disorders.

3. Those with mental disorders are most vulnerable to the negative effects of cannabis use and the development of CUD. As legal cannabis laws are considered or enacted, regulatory provisions and public health initiatives are sorely needed to prevent even greater health disparities related to cannabis use and CUD among those at risk for or that have a mental disorder. We discuss these concerns in more detail below.

The potential impact of cannabis laws and regulations on individuals with mental disorders: lessons from pharmaceutical, tobacco, and alcohol regulation

Legally deeming cannabis as both a commercial and medical product makes effective regulation even more difficult than that of traditional commercial-only substances like tobacco and alcohol. This difficulty is especially pronounced in regards to protecting those with mental disorders. Medical cannabis laws that legitimize the use of cannabis for multiple, diagnostically ambiguous health conditions including some psychiatric conditions, have the potential to further increase the prevalence, frequency, and dose of cannabis use among those with or at risk for mental disorders. Thus, when considering optimal regulatory strategies for cannabis, it would seem prudent to start by examining not only the U.S.'s history of regulatory efforts to mitigate the harms of tobacco and alcohol, but also the concepts and systems that guide pharmaceutical industry regulation. Below, we provide examples of several parallels between the emerging cannabis industry and the pharmaceutical, tobacco, and alcohol industries. We believe these parallels can inform preliminary designs of public health-oriented regulatory approaches to cannabis that may help prevent escalation of the risk of harm among those with mental disorders.

Making scientifically unsubstantiated medical claims and using them for promotional purposes

For-profit companies benefit from selling as much of their products as possible, to as many people as possible. However, when the product being sold is a medication, there is a unique tension to consider. The revenue generated by a medication is bound to the incidence and prevalence of the medical condition that the medication has been approved to treat. It is largely for this reason that pharmaceutical companies have often sought to expand the use of a medication in the population by attempting to promote "off-label" use of that medication. Briefly, off-label use denotes the use of a medication for indications not approved by FDA (i.e., treatment of conditions for which there are few if any data supporting the use of that medication). Psychiatry is particularly vulnerable to the influence of off-label promotion (Moncrieff, 2011; Moncrieff, Hopker, & Thomas, 2018). It is not difficult to find instances in which pharmaceutical companies have attempted to increase off-label prescribing of psychiatric medications to treat non-approved mental disorders (Kesselheim, Mello, & Studdert, 2011; Mack, 2003; McKean & Monasterio, 2012; Mello, Studdert, & Brennan, 2009; Vedula, Bero, Scherer, & Dickersin, 2009), and not surprisingly, off-label prescribing of psychiatric medications is common (Alexander, Gallagher, Mascola, Moloney, & Stafford, 2011; Eguale et al., 2012; Stafford, 2008). However, this tactic is not limited to pharmaceutical companies. There is evidence that the tobacco industry promoted the idea that smoking and nicotine helped reduce anxiety and regulate emotions (Hirshbein, 2012), and that nicotine provided a means for individuals with schizophrenia to self-medicate (Prochaska et al., 2008).

Similarly, few U.S. legal cannabis laws have explicitly deemed anxiety or depressive disorders as qualifying conditions for medical cannabis. Yet survey data clearly indicate that

anxiety and depression are consistently two of the most common reasons for using medical cannabis (Aggarwal et al., 2013; Bonn-Miller, Boden, et al., 2014; Lankenau et al., 2018; Nunberg et al., 2011; Reinarman et al., 2011; Sexton, Cuttler, Finnell, & Mischley, 2016; Troutt & DiDonato, 2015). Understanding why this is happening is critical. As mentioned above, many positively rewarding psychoactive substances also produce acute relief from current negative emotional states. Such negative reinforcement is a likely contributor to the high prevalence of cannabis (and other substance) use among those with mood disorders.

Because a substantial amount of the cannabis consumed in the United States is consumed by individuals with mental disorders (Lev-Ran, Le Foll, et al., 2013), it is in the interest of the cannabis industry to continue to promote the idea that cannabis is a useful “treatment” for mental disorders. Indeed, cannabis product distributors are now making scientifically unsubstantiated claims about using cannabis to treat depression and anxiety (Bierut, Krauss, Sowles, & Cavazos-Rehg, 2017; Caulkins, 2018; U.S. Food and Drug Administration, 2016), and it is easy to find examples of legally-registered dispensaries in states like Colorado (The Clinic Marijuana Center, 2017), New Jersey (Garden State Dispensary, 2017), Delaware (First State Compassion Center, 2018), Rhode Island (Summit Medical Compassion Center, 2017), Nevada (Deep Roots Medical, 2017), and New Hampshire (Sanctuary Alternative Treatment Center, 2017) tacitly or explicitly promoting the use of cannabis or cannabinoids to treat mental disorders on their websites even though such disorders are not on the list of state-approved conditions. Furthermore, many dispensaries are staffed by budtenders who provide point-of-sale verbal recommendations or written materials concerning which type of cannabis (%THC, %CBD) can be used to treat various mental disorders and negative moods states (Haug et al., 2016).

What makes these observations concerning is that information that “legitimizes” or provides messages of hope related to cannabis’ proclivity for relief from mental disorders has great potential for increasing initiation and possibly maintenance of cannabis use among those with mental disorders. Potential for this impetus to cause such harm can manifest in at least two ways: (1) use of cannabis rather than or in addition to known effective medications, and (2) facilitating rationalization of use of a substance (cannabis) with known potential for addiction and likely long-term adverse effects on psychiatric conditions.

Despite such industry behavior, one is hard-pressed to find any provisions of legal cannabis laws requiring that cannabis product labels, dispensary websites, or dispensary staff, detail the fact that the scientific literature does not support cannabis as a treatment for mental disorders, and that cannabis use has potential for adversely impacting such conditions.

Cannabis sales outlets (i.e., dispensary) location and density

The disproportionately large prevalence of alcohol and tobacco use disorders among those with mental disorders may be attributed, in part, to the fact that mental disorders and outlets for selling alcohol and tobacco are both highly concentrated in the same geographic areas – primarily socioeconomically disadvantaged neighborhoods (Pearson, Bowie, & Thornton, 2014; Pereira, Wood, Foster, & Haggar, 2013; Young-Wolff, Henriksen, Delucchi, & Prochaska, 2014). It is well known that systems-level contextual variables such as the location and density of tobacco and alcohol outlets are strongly related to having a tobacco

or alcohol use disorder and having a more difficult time discontinuing use (Campbell et al., 2009; Chuang, Cubbin, Ahn, & Winkleby, 2005; Reitzel et al., 2011).

Again, as might be expected, a growing body of literature examining the location and density of cannabis dispensaries reveals patterns similar to those for alcohol and tobacco. Often, states pass non-preemptive legal cannabis laws, letting municipal governments decide whether or not to permit sale of cannabis in their particular jurisdiction. Consequently, dispensaries have become more concentrated in socioeconomically disadvantaged areas (Morrison, Gruenewald, Freisthler, Ponicki, & Remer, 2014; Nemeth & Ross, 2014) that also have high densities of alcohol outlets (Morrison et al., 2014; Shi, Meseck, & Jankowska, 2016; Thomas & Freisthler, 2016). By some estimates, for each additional dispensary per square mile, the annual number of cannabis use disorder-related hospitalizations increases by 7% (Mair, Freisthler, Ponicki, & Gaidus, 2015). Individuals living in states with a greater number of dispensaries per person are also more likely to have used alternative methods of cannabis administration (e.g., edibles and vaping), illustrating the influence that dispensary proliferation may have on use patterns (Borodovsky, Crosier, Lee, Sargent, & Budney, 2016).

Some efforts have been made to prevent dispensaries from being located near mental health treatment clinics (Freisthler, Kepple, Sims, & Martin, 2013). However utilization of mental health treatment is extremely low (most notably among socioeconomically disadvantaged individuals) (P. S. Wang et al., 2005). Thus this solution, although well-meaning, targets locations where only a fraction of this vulnerable population is found.

Cannabis products: potency, content, and diversification

At the turn of the 20th century, the mechanization of the tobacco industry brought about increased product development and alterations (Richter & Levy, 2014). Given that those with mental disorders are more likely than the general population to become and stay addicted to nicotine (Prochaska, Das, & Young-Wolff, 2017) and have the highest prevalence of nicotine use disorder (Grant et al., 2004; Hurt & Robertson, 1998), one could reasonably argue that tobacco company efforts to develop products that increased the amount of nicotine delivered to the user affected those with mental disorders more than any other subpopulation. A similar dynamic appears to be taking place with regard to the nascent legal cannabis industry (ArcView Market Research, 2016; Richter & Levy, 2014). Since the mid-1990's, the average potency (i.e., %THC) of street cannabis seized by the DEA has increased from 4% to 12% THC (ElSohly et al., 2016). Remarkably, the cannabis products sold in dispensaries can exceed these levels by up to 7-fold (Carlini et al., 2017). Moreover, these high potency THC concentrates are being consumed using new rapid and efficient methods of administration (M. Loflin & Earleywine, 2014). Survey data have begun to link the use of these high-potency products to increased risk of depression, anxiety, and psychosis (Chan et al., 2017; Daniulaityte et al., 2017; Keller, Chen, Brodsky, & Yoon, 2016) - supporting prior findings from the United Kingdom that indicate similar relationships (M. Di Forti et al., 2009; Marta Di Forti et al., 2014). Despite this, few states have attempted to regulate the potency of cannabis concentrate products, and additionally, to

our knowledge, there are no regulatory requirements to warn consumers about the concerns associated with use of high potency cannabis concentrate products.

Historically, tobacco companies also have profiled the product preferences of subgroups of tobacco users, and in doing so learned about the potential reinforcing effects of product flavoring (Ahijevych & Garrett, 2010; Cook, Wayne, Keithly, & Connolly, 2003). For example, those with mental disorders are more likely than other groups of smokers to be using menthol-flavored cigarettes (Cohn, Johnson, Hair, Rath, & Villanti, 2016; Prochaska et al., 2017). Menthol flavoring enhances the reinforcing effects of nicotine (Ahijevych & Garrett, 2010), leads individuals to believe that tobacco is less harmful (Anderson, 2011), and is associated with more difficulty quitting (D. T. Levy et al., 2011). Similar tactics and associated concerns are apparent with cannabis product design and flavoring. There has been an unprecedented diversification of attractive cannabis edible products (e.g., baked goods, drinks, lollipops, gummies)(Barrus et al., 2016). Such products may reduce risk perceptions of cannabis use and increase the reinforcing potential of cannabis because they are highly palatable and allow users to avoid the unpleasant sensations associated with smoking. Additionally, different strains of cannabis are known to smell and taste different putatively in large part because they contain different profiles of a class of compounds called terpenes. Terpenes found in the cannabis plant have also been touted for their potential anti-anxiety properties (Russo, 2011). The cannabis industry has now begun filing patents for methods to create cannabis plants with terpene profiles that they believe are useful for treating anxiety and depression (Lewis, Backes, & Giese, 2015; Weed, 2017). In summary, effective regulation of cannabis will need to focus on various aspects of cannabis product design. This includes not only THC and CBD content, but other product constituents that may alter the reinforcing effects of cannabis (e.g., edible flavors and terpenes).

Recommendations for legislative and regulatory actions

Based on extant literature and historical knowledge of the for-profit sale of psychoactive substances, the following recommendations may help prevent or reduce legal cannabis-related harms among those with mental disorders.

1. States with medical cannabis laws should remove any psychiatric conditions from their list of qualifying conditions.
2. States with medical cannabis laws should remove any clauses in their legislation that provide medical condition loopholes (i.e., allowing use for any conditions that a physician deems appropriate).
3. Medical and commercial cannabis dispensary personnel, product labels, publications, on-site display materials, websites, and social media profiles should:
    - not be permitted to tacitly or explicitly make scientifically unsubstantiated claims about the therapeutic utility of the cannabis plant for mental disorders (or any other medical disorders).

- not be permitted to use psychiatric proxy terms such as “stress,” “happy,” or “relaxed” to describe the effects of consuming cannabis products.
- clearly inform consumers that cannabis may contribute to the onset of mental disorders.
- clearly inform consumers that cannabis may worsen symptoms of a mental disorder and adversely impact its course.
- not be permitted to use terms referring to the cannabis plant (e.g., “marijuana” or “cannabis”) when describing published scientific investigations of isolated cannabinoid compounds (e.g., THC or CBD).

4. States with medical and commercial cannabis laws should actively enforce licensed dispensaries’ adherence to regulations via compliance checks and audits similar to those used for tobacco (Jason, Ji, Anes, & Birkhead, 1991) and alcohol (Wagenaar, Toomey, & Erickson, 2005). Failure to comply with regulations would result in heavy, financially-related penalties. Compliance checks might involve active monitoring of dispensaries’ online behavior (e.g., dispensary website or social media page)(Peiper et al., 2017) or having government personnel attempt to purchase cannabis explicitly for psychiatric purposes.

5. Regulations should limit THC potency in all cannabis products. Data are not available to inform a specific %THC limit, thus setting this limit would be partially, but not completely arbitrary. A growing literature raises concern about the association between the use of high-THC products and development of mental disorders, and in the last few years we have seen an escalation in hospitalizations associated with excessive intoxication from consumption of high-THC products (particularly edibles and concentrates)(Pierre, Gandal, & Son, 2016; G. S. Wang et al., 2016). There is little justification for selling and consuming cannabis products with THC levels over 15%, particularly for “medical” use. Such limits would help curb industry attempts to devise cannabis formulations with greater reinforcing effects that might be especially harmful to those with mental disorders.

6. Legal cannabis laws (medical or commercial) or the regulations enacted by municipalities in states with non-preemptive legal cannabis laws should restrict the total number of dispensaries permitted within the state or specific municipalities, with special consideration for the location of dispensaries. For example, states could limit the total number of dispensaries located in neighborhoods with average household incomes at or below the federal poverty level.

7. Develop a research agenda that allows regulatory agencies to implement cannabis product standards–analogous to FDA’s tobacco product standards–that protect public mental health. The core mission of this research agenda should be to determine if potential new product standards could (1) increase the likelihood that current cannabis users who have or are at risk for developing a mental

disorder discontinue cannabis use, and (2) decrease the likelihood that individuals who are not using cannabis and either have or are at risk for developing a mental disorder, start using cannabis (Villanti et al., 2011).

8. States with both a commercial and medical cannabis law should tighten restrictions in their commercial law and, although highly improbable, repeal their medical cannabis law to allow time for clinical science to develop and test cannabinoid compounds that are safe and effective for treating mental disorders.

9. States with only a medical cannabis law should replace their law with either a restrictive commercial cannabis law or decriminalization.

Future directions: research and data infrastructure

Research

It is necessary to begin building a body of scientific knowledge that can be used to design cannabis regulations that protect those with or predisposed to developing mental disorders. The question is: where do we start? Perhaps the best place to look for the types of research questions that must be addressed is in the tobacco, alcohol, and pharmaceutical regulation and control literature (Ashley & Backinger, 2012; Ashley, Backinger, van Bemmel, & Neveleff, 2014; Barry & Glantz, 2016; Pacula, Kilmer, et al., 2014). For example, in the same way that tobacco product content has been evaluated for its impact on those with or at risk for mental disorders (Cohn et al., 2016), it will be essential to evaluate the impact of cannabis product content (e.g., THC, CBD, other cannabinoids, terpenes) on one's risk for developing a mental disorder or the course of an existing mental disorder. Similar thinking should apply to various product labeling and marketing tactics that the cannabis industry is likely to employ. More broadly speaking, perhaps one of the most fundamental concepts for cannabis regulatory scientists to consider is the interaction between the medical and commercial cannabis industries. Well-designed research that results in effective regulation of the medical cannabis industry may have suboptimal impact if similar regulations cannot simultaneously be applied to the commercial industry.

Data infrastructures

Permitting the for-profit sale of addictive substances creates a unique set of public health concerns - particularly when the substance is sold both as a medicine and a commercial product. As cannabis transitions from illicit to licit substance in the U.S., our ability to monitor and isolate potential causes of acute and long-term benefits and adverse effects of cannabis use on a population-level scale must keep pace. Although some states have created medical cannabis patient registration systems, the resulting data fall short of what will be necessary for creating effective regulations. Several researchers have noted that effective monitoring will be impossible unless there is a concerted effort to create new local, state, and federal cannabis data collection systems (Freeman & Swift, 2016; Hoffman, Terashima, McCarty, & Muench, 2017; Kilmer & Pacula, 2017a, 2017b; Lenton & Subritzky, 2017; S. Levy & Weitzman, 2016; Pacula, Kilmer, et al., 2014; van Ours, 2017).

The Sentinel System currently utilized by FDA for pharmacovigilance provides an excellent first step towards conceptualizing a cannabis data system. Launched in February 2016, the Sentinel System allows FDA to query de-identified, individual-level data from a diverse but synchronized network of relevant partners (i.e., hospitals, insurance companies, pharmacies) to answer questions concerning medication safety (Behrman et al., 2011; U.S. Food and Drug Administration, 2018). State-specific sentinel initiatives (or perhaps even collaborative inter-state systems) for cannabis could require all registered dispensaries and relevant healthcare entities to comply with standardized, individual-level, data collection and reporting procedures. Such data systems could provide the vital information necessary for creating more nuanced cannabis exposure variables and uncovering links to important health outcomes. For example, states could classify types of products based on cannabinoid concentrations (e.g., CBD-oils, THC concentrates) and monitor the number of units and total volume of each type of product sold in particular jurisdictions. These data could then be linked with local-, county- and state-level mental disorder incidence and prevalence data. The combined dataset could be used to detect correlative relationships worthy of further investigation and possible intervention.

Concluding thoughts

The extant data indicate that those with mental disorders are negatively and disproportionately impacted by cannabis use, and are decidedly vulnerable to poorly regulated for-profit industries that market addictive substances such as cannabis. Policy-makers must recognize and consider these facts when developing or modifying cannabis laws and regulations. By building a robust Cannabis Regulatory Science, scientists will generate knowledge that can be translated into novel evidence-based regulations. As part of this effort, cannabis regulatory scientists should remain sensitive to the clear vulnerability of those with mental disorders and aim to discover and implement evidence-based policies that protect this and other vulnerable populations.

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