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Sweet flowers are slow, and weeds make haste: Leveraging methodology from research on tobacco, alcohol, and opioid analgesics to make rapid and policy-relevant advances in cannabis science

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Abstract

The legalization of medical and recreational cannabis use has occurred ahead of science. The current evidence base has poor utility for determining if cannabis products can meet the standards of safety, efficacy, and quality intrinsic to modern medicine, and for informing regulation of cannabis as a legal intoxicant. Individual jurisdictions that pass cannabis reforms may not have adequate resources to support the level of new scientific research needed to inform regulatory actions; this could make it difficult to keep a rapidly growing multi-billion-dollar cannabis industry in check. Further, the present lack of evidence-based regulatory oversight for cannabis parallels the climates that gave rise to the tobacco and prescription opioid epidemics, suggesting that continued omission may result in negative public health consequences. However, translating methodological framework developed through research on these compounds may promote rapid advances in cannabis science germane to regulatory knowledge gaps. The present review highlights specific advancements in these areas, as well as in alcohol regulation, that are prime for informing policy-relevant cannabis science, and also offers some recommendations for evidence-based regulatory policy. Resulting progress may directly inform both regulation of cannabis in both medical and licit recreational drug frameworks, and new cannabis-related public health initiatives.

Keywords

Cannabis; policy; behavior; medicine; legalization

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Recent changes in medical and recreational cannabis policy

Historical context

The widespread prohibition of cannabis by international drug treaties started in the 1920s, with signing of the International Opium Convention and the widespread national-level prohibition initiatives that followed. Prevalence of cannabis use increased in the 1960s, along with the public dissatisfaction with prohibition and associated legal penalties that gave rise to policy reform initiatives. Resulting legislation passed in the 1970s and 1980s ranged from bills that reduced penalties for simple possession in some jurisdictions, to official policies of 'no-prosecution' under certain conditions in others. As of March 2018, possession for personal use is decriminalized in ~30 nations, and many others have criminal laws that simply aren't enforced.

In the United States, advocacy for legal access to cannabis for medical use grew during the 1970s-1990s, with the state of California passing the first regional medical cannabis bill in 1996. As a result of continued legislative action at the state-level, over half the U.S. population currently has access to medical cannabis products with psychoactive levels of THC, and almost the entire remainder has access to at least some non-psychoactive products [e.g., oral tinctures containing cannabidiol (CBD), but almost no THC]. In 2001, Canada introduced a nationwide medical cannabis program, whereby physician recommendations allow individuals access directly through Health Canada-designated supplies and suppliers. Several other countries in the Americas (Argentina, Mexico, Peru) and Europe (U.K., France, Czech Republic, Romania, Poland) allow cannabis-based medicines, but the variety and types of products available are generally more restricted (Bifulco & Pisanti, 2015). Furthermore, after historically leaving cannabis policy up to individual territories, Australia federally legislated cultivation and use of medical cannabis in 2016.

Legalization of recreational cannabis use is a more recent phenomenon. Since 2013, Uruguay, and nine jurisdictions in the U.S. (five of which have functioning recreational dispensaries) have passed such legislation. Overall, roughly one-fifth of U.S. residents have access to recreational cannabis via legal dispensaries. Canada recently passed a bill supporting federal legalization and regulation (Government of Canada, 2017). Other countries (e.g., Spain, Colombia) have legalized possession for non-medical use, but not sale. Within each of these four legal status categories (prohibition, decriminalization, medical access, full recreational legalization), there is enough heterogeneity in specific policies, and how they are enforced, that direct comparisons within each category are difficult. Below, we provide a summary of existing cannabis policies.

Current medical cannabis policies

Medical cannabis policies are heterogeneous; the types of products made available, regulations related to their manufacture and sale, and lists of qualifying medical conditions that permit access all vary widely across jurisdictions. For example, in the U.S., New Mexico allows individuals access to whole plant-based formulations, extracts, edibles, topicals, etc., with no restrictions on THC content. Access requires a written recommendation from a licensed medical provider (i.e., psychologists, nurse practitioners,

M.D., D.O.). These patients can also get a license for home cultivation, with minimal restrictions. In contrast, New York State only allows non-combustible formulations with defined THC:CBD ratios, requires that providers be physicians (M.D or D.O) that have completed specialized training on product and dosing recommendations. Providers must also use the state Prescription Drug Monitoring Program to track patients' prescription drugs history, and report adverse events, and may revoke a patient's certification if necessary. Access in European countries is generally more restrictive, particularly in the U.K, where only one, highly refined plant-based cannabis formulation (1:1 THC:CBD; Sativex®) is approved for medical use.

The variability in qualifying medical conditions is equally as broad; Some jurisdictions limit access to mostly chronic and/or life-threatening illnesses, while others allow a broad range that includes less severe physical ailments. May also permit access for psychiatric conditions, with Post Traumatic Stress Disorder (PTSD) being the most common, and some allow access based on 'other conditions as determined in writing by a qualifying patient's physician' without formal oversight. For most of qualifying conditions, there is limited evidence supporting the efficacy of cannabis as a treatment. The most comprehensive report on cannabis in medicine conducted to date found significant supporting evidence for just three: nausea and vomiting associated with chemotherapy, multiple sclerosis related spasticity, and chronic pain (National Academics of Sciences, Engineering, & Medicine, 2017). Further, clinical prescribing guidelines are not available in most jurisdictions, and the heterogeneity of products makes accumulating evidence to support off-label prescribing practices difficult. Most physicians do not feel prepared to prescribe medical cannabis (Evanoff, Quan, Dufault, Awad, & Bierut, 2017).

The lack of consistency and objectivity in medical programs may stem from cannabis' ill fit for modern drug development regulatory framework. As a botanical, meeting the standards of dosing precision and formulation purity are significant challenges. All but the most highly-refined formulations (e.g., Sativex; GW Pharmaceuticals ®) are unlikely to result in patentable products that secure a return on costs required to conduct the level of clinical research required for an Investigational New Drug to garner approval. Further, in some countries, restrictions on research with investigational drugs have made studying the efficacy of cannabis for medical conditions challenging. The legislative actions underlying medical cannabis approval to date have been driven largely by low-quality evidence that cannabis provides symptom relief for a variety of conditions. Most studies providing hypothetical 'support' for this legislation are not randomized, controlled efficacy trials. The rigor of clinical research has increased, but is hindered by the very nature of cannabis' psychoactive effects: Maintaining placebo blinding is difficult (Cabaret, 2018), and cannabinoid agonists (e.g., THC) may directly enhance the strength of placebo responses (Di Marzo & Centonze, 2015), tempering interpretation of results. Finally, 'symptom relief' does not necessarily equate to medical efficacy, and compounds that provide short-term relief may have negative clinical impacts long-term (e.g., alcohol is an acute anxiolytic, but it is not an effective treatment for Anxiety Disorders, and regular use may make these disorders worse). Overall, the current policy of 'approval first, evidence second' is essentially backward relative to the standard medications development process. This approach leaves medical cannabis research

susceptible to a unique set of confirmation biases that only advanced clinical research methodology can address

Current recreational cannabis policies

Recreational use policies are equally variable. About half of the U.S. jurisdictions with legal recreational cannabis have functioning dispensaries, and, like medical dispensaries, most staff have little formal training (Haug et al., 2016). Furthermore, although most jurisdictions with recreational access have restricted traditional advertising (e.g., banned television ads), most adults in populated areas in legalized states may still be exposed to advertising via other forms (storefronts, street side, and billboards), including young adults who are not current cannabis users (Fiala, Dilley, Firth, & Maher, 2018). Individuals initiating use through purchases at these dispensaries may receive no more relevant product use information than if they had purchased illicitly.

Most legalized jurisdictions mandate specific testing and labeling standards for recreational cannabis products, but the appropriateness of these standards is based on scant data. For example, several states have mandated that all products be tested and labeled for THC and CBD content. Whole plant formulations are to be labeled as % THC and % CBD by weight, and prepared edibles labeled as total THC and CBD content per dosage unit. In Colorado, early oversights about packaging and labeling regulations on edible products (e.g., total allowable THC content per dosage unit, multiple dose-unit packaging, and child-resistant packaging) resulted in an influx of emergency department admissions for excessive cannabis intoxication (Ghosh et al., 2017).

Although these policies have been corrected, labeling and packaging standards adherence monitoring programs have proven difficult to implement. Studies examining the labeling accuracy of cannabis products distributed as recreational (e.g., THC-containing edibles), via medical cannabis programs (CBD extracts), demonstrate poor content and concentration labeling accuracy (Vandrey et al., 2015; Bonn-Miller et al., 2017). This is especially concerning because some products labeled as CBD-only were found to contain enough THC to cause intoxication (Bonn-Miller et al., 2017), and such accidental intoxication has occurred (Crippa, Crippa, Hallak, Martín-Santos, & Zuardi, 2016). Another issue is that product labeling may inadvertently substantiate unproven claims. For example, the retail cannabis industry often reports that CBD augments the subjective effects of cannabis independent of total THC content, while data from controlled human drug administration studies suggest CBD has no such effects (Hill et al., 2015; Haney et al., 2016). Thus, mandating that recreational products be accurately labeled for CBD may be interpreted by consumers to mean that industry claims are legitimate.

Putting the scope of changes in cannabis regulation into context

Medical cannabis; a 'first' in the era of modern biomedical science?

The widespread legalization of cannabis for medical use is a unique set of events: (1) a psychoactive compound with demonstrated abuse liability has gone from an illicit substance with no accepted medical use to a drug with permitted medical use, (2) these changes have

occurred as a function legislative action driven by public opinion, and (3) largely without the guidance of scientific data. Imagine the public response if a large pharmaceutical company was found to have, somehow, pushed a product into a medical market in this manner? It is likely that cannabis use will continue to increase in the long-term (Hall & Lynskey, 2016a, Hall & Lynskey, 2016b), and we should work proactively to catch science up with policy.

The absence of data on regulating cannabis as a licit recreational drug of abuse is also in part a function of federal policy. The U.S. National Institutes of Health (NIH) is the largest funder of biomedical research, globally. As a Schedule I drug at the federal level, most of NIH-funded research has historically approached cannabis use as a behavior that is explicitly problematic at all levels, with little focus on identifying criteria for responsible use, harm reduction-type approaches. There is also little known about how various regulatory policies related to cultivation, sale, and use might affect consumption patterns and influence cannabis-use related harms. Indeed, much of the data used to guide policy related to other medical and licit recreational drugs of abuse was garnered via close monitoring of the effects of policy changes on health outcomes and behavior (World Health Organization, 2012). The issue with relying on these approaches is that they often require waiting for mistakes to happen to develop measures of policies to remedy them, with edibles labeling in Colorado being a prime example. This problem is compounded by the fact that legalization has driven rapid increases in the overall size and value of the medical and recreational cannabis markets, as well as the emergence of cannabis-specific investment, market research, and lobbying firms to promote the financial interests of the cannabis industry.

Recreational legalization; sowing seeds for ‘big cannabis?’

The parallels between these changes and the growth of the U.S. tobacco industry in the first half of the 20th century is concerning. Mechanization of cigarette production permitted industry centralization, that in turn drove explosive growth in cigarette smoking. The industry began directing messaging and advertisement to selected racial and ethnic groups, and performed market and sales research to identify new consumer populations, their product preferences, and their risk perceptions. These data were used to inform targeted advertising strategies aimed at increasing cigarette consumption. Tobacco companies continue to invest heavily in advertising, and have vigorously protected their interests through campaigns of misinformation, legislative manipulation, fake science, and assertions of protections of individual freedom. There are documented cases of perjury and systematic obfuscation about the dangers of tobacco, its addictiveness, and the use by minors (Bero, 2003).

Some cannabis product distributors have already adopted product manipulation techniques used by the tobacco industry to increase use initiation and abuse liability of tobacco cigarettes (e.g., selling single, pre-rolled joints that include flavoring, filters, and modifications to increase potency). The industry is also using marketing strategies aimed at altering public perceptions about the risks and benefits of cannabis use, and increasing public support for legalization (Krauss et al., 2017). This is problematic because many individual states do not have adequate resources to support the level of scientific research needed to determine how these activities affect consumer behavior and public health – a

problem further complicated when members of state cannabis advisory boards may also be cannabis industry entrepreneurs (Caulkins, 2018). The belief that cannabis has broad and significant medical benefits, and low levels of risk, drives public support for legalization (Sznitman & Bretteville-Jensen, 2015). Without independent data, it will be difficult to counter ‘industry science,’ and sustain the level of regulatory action necessary to protect public health.

During the 20th century, one of the most vexing problems of studying the effects of tobacco smoking on health was the long latency between regular use and the development of tobacco-related morbidities, that some smokers never develop smoking-related diseases, and that many deaths attributed to smoking are from causes that also kill non-smokers (e.g., heart disease, stroke). Although smokers develop these diseases sooner than non-smokers, on average, there is enough overall variance that large sample are required to detect these differences. Even when considering conditions that generally only effect smokers, the lag between smoking and disease onset is often decades, and it may occur years after smoking cessation. Elucidating the causal relations between smoking and disease required decades of careful data collection to determine how cumulative exposure (‘pack-years’) and other time-related variables interact to determine overall risk (Thomas, 2013).[TQ2] This provides an illustration of why a ‘wait and see’ approach to cannabis regulatory science hasty.

Growing a cannabis regulatory science; where do we start? what are we lacking?

Cannabis science dates to the mid-1960s, when the discovery of the endocannabinoid system and that THC is the primary psychoactive compound in cannabis primed research on the behavioral pharmacology of cannabis and other cannabinoids. Since then, human drug administration studies have shown that cannabis self-administration, and the resulting psychoactive effects, are primarily driven by THC’s activity at the CB1 receptor (Huestis et al., 2007). The physiological, subjective, and psychomotor effect of cannabis are dose-dependent (Azorlosa, Heishman, Stitzer, & Mahaffey, 1992), and repeated exposures can produce acquired tolerance (e.g., Gorelick et al., 2012). Frequent, heavy use may produce alterations to the endocannabinoid system (Ceccarini et al., 2015), a finding consistent with clinical laboratory studies demonstrating that abrupt cessation can produce a pharmacologically-specific withdrawal syndrome that does not qualitatively differ from that of other drugs (Budney, Hughes, Moore, & Vandrey, 2004; Budney, Vandrey, Hughes, Moore, & Bahrenburg, 2007; Haney et al., 2013). Orally-administered cannabinoid agonists (nabilone) have been shown to cannabis withdrawal and self-administration in problematic users (Haney et al., 2013), but no FDA approved treatments for Cannabis Use Disorder have been developed.

Since most cannabis research has focused on addiction and treatment, the science is lacking in several policy-relevant areas. First, while the average potency or illicit recreational cannabis has quadrupled in the past two decades (from 4% to 12%; ElSohly et al., 2016), most human drug administration research conducted in the U.S. used cannabis containing 7% THC. If, and to what extent, potency influences psychoactive effects beyond absolute dose of THC delivered has not been fully tested (e.g., Ramaekers et al., 2006). Second, although preclinical studies examining the role cannabinoid/opioid interactions in pain

response and drug-induced analgesia have long shown promise (Ledent et al., 1999; Welch & Eads, 1999), data from human studies examining the analgesic efficacy and abuse liability of cannabinoid/opioid combinations are just now emerging (Haney et al., 2015; Cooper et al., 2018), and there are no controlled data on how chronic pain states affect risk for developing Cannabis Use Disorder. Third, there is little data on what types of harm are associated with specific patterns of use to inform harm-reduction education and guidelines. These are critical concerns about regulating and monitoring medical cannabis use in jurisdictions that permit it, but the science is moving slow. Identifying and adapting methodological advances from related areas may be an effective way to make rapid progress and close the current gaps between science and policy.

Opportunities to leverage methodological advances from opioid science

Methods of comparative abuse liability assessment

Medical research on opioids has a long and rich history, including the development of rigorous behavioral pharmacology methods to assess the abuse potential of drugs (Walsh & Babalonis, 2017). These methods are gold standards in drug approval processes (Carter et al., 2009; Carter & Griffiths, 2009; Henningfield & Keenan, 1993). Comparative abuse liability assessment methodology can accommodate multiple compounds and formulation types (e.g., Vansickel, Weaver, & Eissenberg, 2012; Walsh, Nuzzo, Lofwall, & Holtman, 2008), and results from studies on opioids have demonstrated predictive validity with regard to community rates of non-medical use, and associated health care costs (White et al., 2015). The hallmark of these methods involves double-blind, placebo-controlled comparisons of several related compounds, multiple doses, or formulations, including a well-studied variant as a reference compound. These procedures are ideally suited to characterize and compare cannabis products along several dimensions including potency, route of administration, THC:CBD ratio, cannabinoid/terpene content, etc. The utility of this model lies in its ability to screen multiple novel compounds simultaneously, making it well suited for a climate where novel cannabis products are being rapidly introduced into the market (Berg, Henriksen, Cavazos-Rehg, Schauer, & Freisthler, 2017).

Clinical use guidelines

While research characterizing the relative abuse liability of emerging products or formulations is critical first step to understanding how changes in cannabis policy may influence the etiology of problematic cannabis use, the ongoing opioid analgesic epidemic in the United States (Kolodny et al., 2015) and increasing problems in Australia (Larance et al., 2017) and Canada (Fischer, Rehm, & Tyndall, 2016) have shown that structural factors also apply. The President's Commission on Combating Drug Addiction and the Opioid Crisis (2016) identified several, including: (1) unsubstantiated claims that oral formulations of opioid agonists have low abuse potential and are effective treatments for long-term pain, (2) increased pressure in the healthcare community to identify and treat chronic pain conditions, (3) inappropriate levels of 'pain patient' advocacy focused almost entirely on increased access to opioids, (4) deficient pain management education for prescribers and patients (5) aggressive marketing from the pharmaceutical industry supply chain, and (6) poor post-marketing surveillance and oversight of medications. The opioid crisis also fostered a new

area of research; science focused on identifying factors the influence transitions from medically appropriate use to disordered use in chronic pain patients, and how this may be prevented. Differences in relative risk aside, the data on medical cannabis reviewed in the sections above show parallels to all of the Opioid Commission's points. Thus, collection of data on clinical prescribing, and clinical outcomes among cannabis patients by health sciences researchers without financial stake in the cannabis industry is critical. This type of objectivity will require funding from non-industry-tied sources.

Comprehensive clinical guidelines for the use of opioids to treat chronic pain were developed to ensure assessment of patient need, treatment courses (e.g., compound, dose), follow-up assessments, and discontinuation strategy all occur in the context of thorough evaluation of the potential risks and benefits (Dowell, Haegerich, & Chou, 2016). Again, although the risks associated with opioids vs. cannabis in the treatment of chronic pain differ, they offer a much-needed roadmap for future research given that pain is the most prevalent indication for medical cannabis (Park & Wu, 2017). As research on the efficacy of medical cannabis for chronic conditions continues, the missteps from clinical trials involving opioids should be considered when interpreting results. Namely, that short-term trials with limited duration of medication exposure are inadequate to detect some meaningful adverse outcomes (e.g., problematic use, loss of efficacy via tolerance), and thus cannot be used as a basis for inferring long-term benefits.

Medical cannabis monitoring programs

Since long-term clinical trials of sufficient duration and size may not be feasible, logistically or financially, an alternative may be to develop surveillance systems to track both efficacy and long-term consequences. These extra steps that were not taken in some regions, and could have more quickly identified opioid-related problems before they became public health emergencies. Many regions regulating cannabis as medicine already require patient registration. These registries could be further linked to general medical databases (e.g., electronic health records) and other systems created specifically for medical cannabis to track outcomes. Prescription Drug Monitoring Programs (PDMPs), which have been successful in reducing some but not all aspects of opioid misuse (Finley et al., 2017) could be more widely adapted for medical cannabis and integrated to monitor appropriate prescribing, use, and diversion.

Opportunities to leverage methodology from tobacco science

Toxicology assessment

Research combining behavioral pharmacology approaches (e.g., abuse liability) together with analytical toxicology aimed at quantifying relative harm potential is another area prime for transition to policy-related cannabis science. Tobacco science has identified approximately 600 ingredients in cigarette tobacco which create more than 7,000 identified chemicals during the combustion processes (Tobacco.org, 2018). Many of these chemicals are known to be toxic or harmful to humans. In 2012, the United States Food and Drug Administration (FDA) released the most comprehensive report on tobacco-related toxicants compiled to date, which identified 93 harmful and potentially harmful constituents (HPHCs)

in tobacco products and tobacco smoke that have been linked to tobacco-related disease (FDA, 2012). The FDA requires tobacco manufacturers and importers to report on levels of HPHCs present in both products as-manufactured, and as constituents in smoke resulting from product use.

Since research on the toxicology of cannabis products is skim, there is no list of HPHCs for cannabis products. However, the list of tobacco HPHCs could be potentially used as a starting point for assessing cannabis products and cannabis smoke emissions. Expansive analytical chemistry methodologies developed over the last few decades via tobacco product characterization research can be easily adapted to assess cannabis product toxicity. Some of the most relevant questions for cannabis users' safety and public health protection that could be addressed by using analytical assays and methodologies routinely used for tobacco, including those that:

- Characterize the organic and inorganic content of cannabis products, and examine how physical and chemical variations in these components affect toxicant exposure
- Examine the chemical composition of mainstream smoke for various cannabis products. What toxicants are present? and in what levels? What are the exposure levels of harmful and potentially harmful constituents in main-, side-stream, and environmental cannabis smoke and aerosol?
- Assess how smoking behaviors (e.g., puff size, inter-puff-interval) impact smoke emissions and exposure, and how product physical and chemical design characteristics influence this puffing behavior, and in turn exposure.
- Determine what particle types and sizes are present in the main- and side-stream smoke emissions from different cannabis products, and in what concentrations, including comparisons across various classes of cannabis products and within a class of cannabis products with different design features (filters, ventilation, wrapping paper, flavors and other additives).
- Examine if, and how product storage conditions impact the levels of toxins in cannabis
- Assess the impact of cannabis on the general environment - from cultivation (water and energy consumption, fertilizers and pesticides use) to discarded and used products (dumped waste water from bonds, discarded batteries from electronic vaporizers, etc).

Effects of non-pharmacological product characteristics on use behavior

Behavioral pharmacology has shown that design characteristics of tobacco products other than nicotine impact tobacco use behavior, including flavoring (e.g., menthol), physical properties (e.g., filter ventilation), and route/formulation (e.g., combustible vs. vaporized vs. edible vs. transdermal). This area has been largely overlooked; most studies involving experimental cannabis administration to humans have used pre-rolled cannabis cigarettes provided by the NIDA Drug Supply Program, which do not capture the amount of non-pharmacologically-related variability offered in legal cannabis markets.

While cannabis is commonly identified by consumers and dispensary staff using various distinctions, i.e., 'indica', 'sativa', hybrid,' these terms have no meaningful relations to the average chemical composition of the end product (Sawler et al., 2015). The same is true about 'strains,' e.g., 'OG Kush', 'Northern Lights', 'Super Lemon Haze'. The most accurate way to characterize cannabis products is by percentage by weight of discrete organic compounds, including cannabinoids (e.g., THC, CBD), terpenes, and others. It is unclear if the subjective effects of THC are altered by these other components in a manner that effects abuse liability via pharmacological mechanisms, but they can clearly alter sensory characteristics (taste, smell). Given that these characteristics can alter tobacco use behavior independent of pharmacological action (Caggiula et al., 2008), effects on cannabis use should also be examined. Further, interactions between abuse liability and toxicant yield may drive the overall physical harm potential of a given product or formulation. For example, vaporization of cannabis appears to produce similar pharmacokinetic delivery of THC and other cannabinoids as smoking, making it desirable to users while also reducing exposure to toxicants, making it more desirable than smoking from a harm-reduction standpoint. Thus, regulatory efforts that encourage use of less toxic delivery methods may be an effective way to reduce the overall public health burden of increased cannabis use that may result from these policy changes.

How can we leverage research on alcohol inform harm reduction?

Identify and define consumption patterns that align with relative risk

The scientific understanding of relations between patterns of alcohol use and relative harm potential has been well-characterized, and provides methodology prime to be leveraged to cannabis science. Harms associated with alcohol consumption are determined primarily by the volume of alcohol consumed and drinking patterns. The percent of alcohol is expressed as alcohol by volume and this varies by beverage type, and blood alcohol concentration (BAC) refers to the ratio of alcohol in the blood to the total volume of blood (percent). Several US federal agencies, and the World Health Organization use evidence-based guidelines for defining various drinking patterns: moderate drinking (up to 1 drink per day for women, 2 drinks per day for men), low-risk drinking, binge drinking, extreme binge drinking, alcohol misuse, and heavy drinking.

Although definitions vary across agencies, low-risk drinking is generally defined as no more than 3 drinks in any one day, and no more than 7 drinks per week for women; or no more than 4 drinks/day and 14 drinks/week drinks per week for men [US Department of Health and Human Services (USDHHS), 2017]. Individuals who drink within these limits have a very low risk of being diagnosed with an Alcohol Use Disorder (USDHHS, 2017). Binge drinking (also referred to as heavy episodic drinking) is defined as 4 standard drinks within a 2-hour period for women; 5 over 2-hours for men, and generally produces a BAC 0.08%. Binge drinking is associated with a unique set of harms relative to heavy drinking; heavy drinkers are more likely to develop physical problems resulting from alcohol exposure, whereas binge drinking-related harms are associated with the effects of acute intoxication (e.g., violence, automobile accidents, etc.; Miller, Naimi, Brewer, & Jones, 2007).

The increasing movement by states and countries to legalize the recreational use of cannabis for adults highlights the importance of setting consumption standards relative to the potential harm resulting from specific patterns of use, but is not currently possible for several reasons. First, there is no U.S. federal or global regulation to create product testing and labeling standards for cannabis that would allow similar guidelines, akin to the standard drink (e.g., total THC content). Second, these equivalents would need to account for variation in bioavailability and drug effects across different routes of administration. Third, individual differences in cannabis pharmacokinetics (e.g., drug metabolism) and pharmacodynamics (e.g., development of tolerance) are poorly understood, but critical factors to consider in setting cannabis consumption standards. The standardization of alcohol units has allowed for the development of evidence-based criteria to separate low-risk vs. heavy drinking patterns and binge-use from non-binge use because of differential harms and health outcomes associated with each. Yet, there have been no population-based studies that have collected sufficient data to determine cut-offs for low-risk and high-risk cannabis use, and associated consequences. This is because existing studies of this size have focused primarily on frequency of use, omitting other important factors (e.g., quantity, potency) that are more difficult to collect such detailed data on.

Assessing regulatory impact in an evolving marketplace

A variety of US and international policies and laws have been developed to reduce the public health effects of alcohol consumption across the age continuum, several of which could be applied to the regulation of cannabis in the marketplace. There are four primary areas of alcohol policy that may be translatable to cannabis: increasing the price through taxation, limiting access to the product through zoning laws and limiting days and hours of sale, reducing or banning advertising, and mandating employee training and regulation enforcement programs.

Taxation: Research has consistently shown that as the price of alcohol increases, consumption and related harms decreases (Babor, Mendelson, Greenberg, & Kuehnle, 1978; Chaloupka, Grossman, & Saffer, 2002; Elder et al., 2010), and higher alcohol prices are associated with fewer instances of alcohol-impaired driving, fewer motor vehicle crashes and fatalities, lower mortality from liver disease, lower rates of violence, and less all-cause mortality (e.g., Chaloupka et al., 2002). Findings ways to regulate the cost of cannabis and emerging products may reduce problematic use. However, there is also potentially a very nuanced association between regulatory actions that effect cannabis price, and individual purchasing behavior. Taxes that increase price per gram may incentivize individuals to purchase stronger concentrations or products, which may increase abuse liability. All of these factors need to be empirically evaluated to maximize regulation effectiveness.

Outlet density restrictions: Harms can also be reduced by limiting access through controlling retail outlet density, and hours of sale, a practice demonstrated effective for alcohol (World Health Organization, 2012). The presence of a large number of alcohol retail outlets in a given geographical area has been associated with increases in alcohol consumption patterns that result in negative health outcomes, including Alcohol Use Disorder, domestic violence, drunk driving offenses, and alcohol-related traffic accidents

(Campbell et al., 2009). There could be several options for reducing density of cannabis outlets in a community, including Conditional Use Permits (CUP) and Deemed Approved Ordinances (DAO; Jernigan, Sparks, Yang, & Schwartz, 2013). A CUP subjects certain land uses to special conditions to ensure compatibility with other, nearby land uses, while DAOs primarily target businesses that have been grandfathered into existing license restrictions. These permits, among other things, can require operational conditions such as spacing between cannabis outlets and distance limits between places of special considerations and outlets, such as churches, schools, or daycares.

Hours of sale restrictions: Restrictions on hours of sale have been associated with decreases in alcohol consumption, alcohol-related assault and injury, emergency room admissions, and motor vehicle crash injuries (Hahn et al., 2010). Research on the effects of hours of sale restrictions on problematic cannabis use and associated harms would directly inform evidence-based regulation of cannabis sale hours, but unfortunately, collecting such data often requires regulations to change because of negative consequences that have already occurred. However, detailed examination of the effects of hours-of-sale changes in given jurisdictions could be used to preemptively inform policy for others. This could be particularly useful in the U.S., where cannabis laws are changing on a regional basis.

Restrictions on marketing and advertising: The relationship between alcohol advertising and consumption has most clearly been seen in youth and young adults (Anderson, De Bruijn, Angus, Gordon, & Hastings, 2009; Jernigan, 2010), and shown that reductions in alcohol marketing can decrease the prevalence of adolescent drinking (Saffer & Dave, 2006). Unlike tobacco, alcohol advertising is voluntarily regulated by the industry itself in most countries, despite calls for a more comprehensive and public health-oriented approach that would provide state or federal oversight (Casswell, 2012; Casswell & Maxwell, 2005). The association between exposure to cannabis marketing and consumption is also growing, with recent research finding that exposure to medical cannabis advertisements in California was associated with increased cannabis use intentions among adolescents (D'amico, Miles, & Tucker, 2015). After recreational cannabis was legalized in Oregon, a study found that over 50% of the adults statewide reported being exposed to cannabis advertising in the past month, including via storefront, billboards, and street side advertisements (Fiala, Dilley, Firth, & Maher, 2017)[TQ3]. Considering legalization trends, the American Public Health Association has recommended limiting and restricting advertising at the federal, state, and local levels (American Public Health Association, 2014).

Mandated employee training and regulation enforcement: Lastly, requiring responsible beverage service training for employees that serve or sell alcohol is demonstrated to be effective in reducing alcohol consumption and related problems (e.g., Saltz 1997), and decreasing sales to underage decoys (Elder, Lawrence, Janes, et al., 2007). Enforcing existing restrictions is also critical: The Community Preventive Services Task Force, an independent panel of 15 public health and prevention experts, has recommended enhanced enforcement of laws prohibiting the sale of alcohol to minors (Community Preventive Services Task Force, 2006), which is already being done with cannabis

regulation. Regulations that apply directly to products, and related sale restrictions (e.g., ‘bundling’ cannabis products together with snacks, tobacco, etc.) also require compliance monitoring. Currently, this often falls under the purview of local law enforcement, but a specialized agencies may be more effective.

These regulatory impact assessment recommendations must be considered in the context of several important caveats. Perhaps most importantly, direct application of alcohol regulatory policy to cannabis is problematic because alcohol does not currently have a thriving illicit market in most nations. In this regard, regulations that increase the price of licit cannabis, and decrease access via and limiting outlet density and hours of sale, may simply shift purchasing from licit to illicit markets in some instances. Such shifts may also impact consumption level monitoring, i. e., illicit purchase and related consumption is more likely to remain ‘hidden.’ Thus, research on the effects of these types regulations on patterns of problematic cannabis consumption will require sophisticated methodology sensitive to shifts between licit and illicit marketplace sourcing.

Developing recreational cannabis use surveillance platforms

Beyond policies, alcohol control research relies heavily upon national, probability-based annual surveys (e.g., Population Assessment of Tobacco and Health, National Epidemiological Survey of Alcohol and Related Conditions, National Survey of Drug Use and Health) to monitor historical and current, and attitudes, beliefs, and intentions regarding current and future use. While essential, these studies are limited in several important ways: They often neglect a fine-grained assessment of cannabis use behaviors, emerging use patterns, and attitudes, and cannot keep pace with rapid developments in new cannabis use behaviors, marketing, and legalization activities. Understanding the interactions among trends in use, changing attitudes, and policy developments is imperative to prevent uptake among younger users and deter problematic use among current users. The World Health Organization developed the Global Information System on Alcohol Health, a surveillance and data repository tool to present information on levels and patterns of alcohol consumption, alcohol-related health and consequences, and policies at the global level. This type of surveillance system and data repository is critical to developing policies, prevention campaigns, and interventions that are empirically-based and grounded in recent behavioral trends.

Discussion

The development of cannabis science in areas necessary to inform regulation of cannabis, both as a medicine and as a licit recreational drug, has not kept pace with recent policy changes. Although the reasons for this can be debated from numerous standpoints, what is most important is that we close these gaps as quickly as possible to protect public health. Tobacco, alcohol, and opioid sciences are advanced in the some of the very areas cannabis science is woefully lacking. Cannabis shares non-overlapping similarities with each of these three compounds for both features of direct scientific relevance (abuse liability, toxicology, etc.), and in historical parallels that serve as valuable cautionary tales. Thus, prior developments in these areas should be directly leveraged and integrated into programmatic

efforts to develop a field of cannabis regulatory science. These methodological advances might also be particularly well-suited for cross-combination when applied to cannabis. For example, it may be possible to integrate the comparative abuse liability assessment models developed through opioid research with analytical toxicology methods from tobacco science to collect data on abuse liability and toxicant delivery simultaneously. These data could eventually be used to develop ‘relative harm indices’ to compare products that differ on multiple characteristics.

Overall, there is a need for studies that: (1) compare the abuse liability of cannabis products across multiple doses and routes of administration, (2) examine relations between medical conditions that are commonly used as indications for medical cannabis use (e.g., pain) and individual differences in abuse liability, and risk for developing Cannabis Use Disorder. This research could support the development of clinical use guidelines, (3) characterize the toxicology profiles of commercially-available products, (4) examine the influence of non-pharmacological product characteristics on measures associated with abuse liability. This research may inform additive and packaging restrictions for some cannabis products. Indeed, given the current trends in public opinion, we must shift more of our focus to research that informs harm reduction. This includes developing an evidence bases that (5) provide guidance on the relative risk of different amounts or types of consumption patterns in order inform use guidelines. The NIAAA guidelines for low risk drinking may serve as a parallel. Finally, we need to develop science that (6) informs smart regulatory action with regard to instituting restrictions on sale hours, retail outlet density, etc. and, and (7) monitors the impact of these policies on licit and illicit markets using sophisticated methodology so that interplay between licit and illicit markets are captured.

Although there are qualitative differences between cannabis and these other substances, we should probably err on the side of caution, and assume that the cannabis industry will resemble these other three industries in at least some manners; centralized, sophisticated, and financially-motivated. Second, the data reviewed above suggest that that a single regulatory framework could not accommodate cannabis a recreational drug and a medicine; the standards are too different, Finally, although individual jurisdictions may earmark funding for cannabis research agendas like those described above (e.g., California, Colorado, and Washington in the U.S.), policy reforms have spillover effects across political boundaries Hao & Cowan, 2017). Further, it is unclear as to whether this level of funding appropriation will be adequate to address such dramatic changes in drug policy. If the historic data on tobacco, alcohol, and opioids reviewed above yield one *onus*, it is that omission can breed catastrophe. The authors urge national and international organizations responsible for the protection of human health to provide support for research aiming to make rapid, and policy-relevant, advances in cannabis science.

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