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Necessity of Addressing Motivations for Cannabis Use to Guide Research

Ziva D. Cooper[1,2], **Bryon Adinoff**[3]

[1]UCLA Cannabis Research Initiative, Jane and Terry Semel Institute for Neuroscience and Human Behavior, Department of Psychiatry and Biobehavioral Science, University of California, Los Angeles

[2]Department of Psychiatry, Columbia University Medical Center and New York State Psychiatric Institute, New York, NY, USA

[3]Department of Psychiatry, University of Colorado School of Medicine

Introduction:

Over the last two decades, rapid changes in legal cannabis regulation have occurred in the United States and across the globe. Alongside these developments, accessibility and availability of cannabis and cannabis-derived products (CDPs) have increased and perceptions related to the medicinal value and harms of cannabis have transformed. There have been shifts in demographic subgroups of people who use cannabis and changing motivations for use, now incorporating a sizable proportion of people using cannabis of CDPs solely for medical reasons [1]. A booming cannabis industry has developed to meet the needs of various consumers, introducing novel cannabis-based products with unknown health effects. With these changing laws and attitudes, data related to both therapeutic and adverse effects of cannabis exposure are urgently needed to prevent hazardous use and maximize potential medical benefits. The objective of this Special Issue on the "Benefits and Consequences of Cannabis Legalization" is to provide a translational understanding of both the positive and negative consequences of cannabis and cannabinoids on health and behavior, and, from the policy perspective, the pros and cons of implementing cannabis legalization. To accomplish this goal, each article of the Special Issue discusses evidence for both the benefits and harmful effects of cannabis use [2-7] and policies that guide legal regulation [8-10] and social justice considerations [11].

Benefits and Negative Consequences: From Preclinical Science to Population Statistics

A holistic understanding of the health effects of cannabis and cannabinoids requires a translational approach, where preclinical work guides clinical studies and provides hypotheses for the impact of cannabis use at the population level. Conversely, trends in use

CORRESPONDING AUTHOR: ZIVA D COOPER, PH.D., UCLA Cannabis Research Initiative, Semel Institute for Neuroscience and Human Behavior, Department of Psychiatry and Biobehavioral Science, 760 Westwood Plaza, 37-418, Los Angeles, CA 90024, Phone (646) 221-2346, zcooper@mednet.ucla.edu.

and population health outcomes related to cannabis exposure often inform and direct preclinical research to identify mechanisms for observed consequences. For clinical and epidemiological studies, considerations associated with motivations for use (i.e., medical versus personal) are critical in developing conclusions related to the context-dependent effects of cannabis on health and society. As such, assessing both the potential therapeutic and negative effects of cannabis and cannabinoids by incorporating findings from preclinical research, controlled clinical studies, population level findings and considering intentions of use are important bridges to developing optimal approaches to direct legal cannabis regulation.

As pharmacological agents, phytocannabinoids, the unique chemical constituents of the cannabis plant, have been studied preclinically for close to a half century for both their positive and negative effects on brain and behavior. The cognitive impairing effects of delta-9-tetrahydrocannabinol (THC), the primary psychoactive and intoxicating component of the cannabis plant, are well known and reliably observed under many conditions across species and laboratories. These effects occur with repeated exposure to high and even low THC doses. The Special Issue highlights intriguing preclinical findings probing variables that augment and even oppose these detrimental effects [2]. Understanding how these opposing effects of THC on cognition may translate to humans, it is important to consider use patterns that are shaped by motivations for use to guide hypotheses related to the neurocognitive impact of cannabis exposure.

Another article in the issue features the impact of cannabis use on cognition and the brain, which is based overwhelmingly on decades of work assessing the impact of adolescent, recreational and heavy cannabis users [3]. To date, little work has been directed toward understanding the impact of cannabis use on these endpoints in patients using medical cannabis. These effects will likely differ in populations using cannabis and cannabinoids for medical purposes as has been shown in recent reports [12]. Understanding neurocognitive consequences in addition to other negative effects, such as intoxication and abuse liability, are critical endpoints to assess within the context of medical use to optimize cannabinoids' clinical utility and mitigate undesirable outcomes. This is an area explored in the Special Issue in a review of randomized clinical studies of cannabis and CDPs for pain. An analysis of variables that either minimize or contribute to abuse liability and cognitive effects across studies is discussed [7]. Moving forward, assessing these effects within the framework of motivations of use will be integral in providing a comprehensive perspective of the context-related impact of cannabis and cannabinoid use on outcomes.

Evaluating findings from an epidemiological perspective provides a basis for understanding the population-level impact of the changing cannabis laws [6,13]. Specifically, these data shed light on whether increased availability and accessibility of cannabis has resulted in negative effects on health and behavior, or alternatively, a potential positive contribution to certain public health concerns, such as defraying opioid-related harms and use of other substances (i.e., [13,14]). Analyzing associations between rates of cannabis use and cannabis use disorder (CUD) across demographic subgroups as a function of state cannabis laws [6] is instrumental in guiding future policy decisions. Furthermore, tracking changes in use among specific at-risk populations including emerging adults, pregnant women, and older

individuals will inform a public health response to vigilantly attend to the impact of use in these populations and educate these groups on the known harms and unknown consequences to prevent hazardous use. With respect to cannabis-associated consequences in some of these at-risk populations (i.e., older adults), defining motives for use will be critical in studying and interpreting outcomes. Another area of interest relates to earlier findings demonstrating decreases in opioid fatalities in medical cannabis states (i.e., [15]) and later data pointing to decreases in opioid and other drug prescribing in medical cannabis states [16,17]. These early findings provided some promise that increased availability of cannabis may decrease other drug use. In this Special Issue, a synthesis of the available data connected to the impact of cannabis laws on other drug use illustrates that the relationship is complex [13]. Developing standardized methods to define respondents' motives for cannabis use and other drug use (i.e., illicit versus therapeutic opioid use) will improve understanding of the impact of changing cannabis laws on behaviors and health outcomes.

Dual Nature of Cannabis Use and Commerce: Public Health and Research Considerations

With developing policy and national awareness of the potential therapeutic effects of cannabis and cannabinoids, motivations for use are shifting. A growing population of people are using cannabis and CDPs solely for medical reasons, with the majority of people using medical cannabis also engaging in personal use [1]. In the past, only a small proportion of cannabis-related human research was dedicated to understanding the potential benefits or therapeutic effects of cannabis and cannabinoids. As such, there is a paucity of rigorous research to draw from providing evidence supporting the safety and utility of cannabis or CDPs for the tens of medical indications for which cannabis is now permissible in the majority of the United States (i.e., [18]). Despite having decades of research related to the negative impacts of cannabis use, there are significant unknowns related to emerging issues including the acute and long-term effects of novel methods of cannabis use for both therapeutic and personal reasons.

Changes in policies related to medical and adult cannabis laws and increases in use across sociodemographic subgroups has lent itself to a burgeoning market for emerging cannabis-related product types that vary according to several features, **1)** mode of delivery, **2)** predominant cannabinoid constituents (THC, cannabidiol [CBD], THC combined with CBD, other minor cannabinoids and terpenes), **3)** product strength, and **4)** targeted consumer. While smoking cannabis used to be the predominate mode of use, there are now diverse methods by which cannabis can be administered. Multiple methods and devices for inhalation now include vaporizers used with plant material and cannabis oils, devices for ultra-high strength products that can contain > 90% THC, and metered-dose inhalers. For oral and sublingual administration, products include extracts, tinctures, capsules, and cannabis-infused edible products. Other types of preparations include topicals, suppositories, and cannabinoid-infused fabrics. Many of these products are marketed to specific consumers and motivations for use. For those seeking cannabis-based products for health, wellness, symptom relief, and treatment for diseases, cannabis-infused suppositories for menstrual pain relief, cannabidiol-infused athleticwear to improve muscle recovery, topical

cannabinoids for arthritis, cannabis suppositories for ulcerative colitis, and several others now exist. Many products geared toward health and wellness contain little to no THC and are predominantly cannabidiol (CBD) based. Whereas ultra-high strength THC preparations like dabs and waxes (up to 90% THC) are promoted as fast and efficient intoxicants.

In understanding the acute and long-term health consequences of these various products, motivations for use will have a significant impact on health outcomes. To date, this has not been an area of rich data analysis. Because of the growing market and increased attention to the potential medical benefits of cannabis and cannabinoids, it is likely more people will be drawn to cannabis and CDPs for therapeutic use. Evolving products and high strength cannabis geared towards enhanced intoxication will also lead to increased exposure with potential negative consequences. The differences in motives for use not only has ramifications for health outcomes but is also integral in the discussion of public policy related to cannabis. Many approaches to regulatory policies take into account the dual nature of motivations for use and cannabis marketplace (i.e. medicinal products versus products tailored for adult use). Evaluating the implementation and impact of these policies on long term public health will be critical in identifying the optimal model for legal regulations.

Advancing the Field:

Progress in cannabis and cannabinoid research is contingent upon forward and back translational approaches; preclinical evidence informs the impact of cannabinoids on health and behavior in humans and epidemiological outcomes provide a roadmap of the important trends that must be evaluated under controlled conditions either in the clinical laboratory or via preclinical investigations. Recent public policy has not been guided by scientific evidence. However, as evidence accumulates related to the potential therapeutic effects and harms of cannabis and emerging products, these data should be instrumental in strategic policy development to optimize regulations that ensure public health and safety. Several barriers exist to expeditiously address some of the most critical public health concerns related to expanded cannabis access through translational research. These barriers include the regulatory requirements for studying cannabis, a Schedule I drug, difficulty in obtaining funding to study the therapeutic effects of cannabis and cannabinoids, and the need for study drug to be manufactured according to Good Manufacturing Practices (GMP) for clinical investigations. Over the last year, some reprieve of these barriers has signaled a positive direction in opening up pathways for cannabinoid study In the US. For instance, the 2018 Farm Bill removed hemp (cannabis with < 0.3% THC) from the Controlled Substances Act, eliminating federal restrictions related to hemp-derived cannabidiol. This change significantly eases challenges of studying CBD and broadens potential sources for study drug. In order to increase funding specifically targeting the therapeutic effects of cannabis, the National Center for Complimentary and Integrative Health (NCCIH) awarded 3 million dollars in 2019 to investigations exploring the potential pain-relieving effects of the lesser-studied chemical constituents of the cannabis plant, including minor cannabinoids (i.e., not THC) and terpenes [19]. Finally, The Drug Enforcement Administration (DEA) announced in August, 2019 support in facilitating and expanding scientific and medical research of cannabis [20].

The growing appreciation by federal regulators and funding agencies of the urgent need for cannabis and cannabinoid investigations coupled with the burgeoning public interest has set the stage for high impact research from preclinical study to public policy. Moving forward, this work must attend to the dual nature of the motivations underlying cannabis use and to both the potential benefits and negative consequences of use. The areas reviewed in this Special Issue exquisitely highlight the knowns related to the positive and negative consequences of 1) cannabis exposure on health, and 2) cannabis-related policies on society. These reviews also underscore the significant gaps in knowledge that future work must address to elucidate the many variables that impact individual and community outcomes. The evidence presented in this Special Issue and recommendations for future investigations are integral in developing a nuanced understanding of the impacts of cannabis and cannabinoids on health and society. This information is necessary to educate the public, guide patients and health care providers, inform policy, and provide a roadmap for future research.

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