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15 Challenges and Barriers in Conducting Cannabis Research

Several states have legalized cannabis for medical or recreational use since the release of the 1999 Institute of Medicine (IOM)[1] report *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999). As of October 2016, 25 states and the District of Columbia had legalized the medical use of cannabis, while 4 states and the District of Columbia had also legalized recreational cannabis use (NCSL, 2016; NORML, 2016a).[2] In November 2016, voters in California, Maine, Massachusetts, and Nevada approved ballot initiatives to legalize recreational cannabis, while voters in Arkansas, Florida, Montana, and North Dakota approved ballot initiatives to permit or expand the use of cannabis for medical purposes (NORML, 2016b).

Policy changes are associated with marked changes in patterns of cannabis use. In recent years, the number of U.S. adolescents and adults ages 12 and older who reported using cannabis increased by 35.0 percent and 20.0 percent for use in the past month and in the past year, respectively (Azofeifa et al., 2016). Revenue from the sale and taxation of cannabis can serve as a proxy measure for cannabis use and suggests that the scope of cannabis use in the United States is considerable. For example, the total estimated value of legal cannabis sales in the United States was $5.7 billion in 2015 and $7.1 billion in 2016 (Arcview Market Research and New Frontier Data, 2016). At the state level, the Colorado Department of Revenue reported that sales and excise taxes on recreational and medical cannabis sales totaled $88,239,323 in fiscal year 2015 (CDOR, 2016a, p. 29),[3] and in Washington, state and local sales taxes and state business and occupation taxes on recreational and medical cannabis totaled $53,410,661 in fiscal year 2016 (WDOR, 2016a,b).[4]

Despite these changes in state policy and the increasing prevalence of cannabis use and its implications for population health, the federal government has not legalized cannabis and continues to enforce restrictive policies and regulations on research into the health harms or benefits of cannabis products that are available to consumers in a majority of states. As a result, research on the health effects of cannabis and cannabinoids has been limited in the United States, leaving patients, health care professionals, and policy makers without the evidence they need to make sound decisions regarding the use of cannabis and cannabinoids. This lack of evidence-based information on the health effects of cannabis and cannabinoids poses a public health risk.

In order to promote research on cannabis and cannabinoids, the barriers to such research must first be identified and addressed. The committee identified several barriers to conducting basic, clinical, and population health research on cannabis and cannabinoids, including regulations and policies that restrict access to the cannabis products that are used by an increasing number of consumers and patients in state-regulated markets, funding limitations, and numerous methodological challenges. The following sections discuss these barriers in detail.

REGULATORY AND SUPPLY BARRIERS

Regulatory Barriers

Investigators seeking to conduct research on cannabis or cannabinoids must navigate a series of review processes that may involve the National Institute on Drug Abuse (NIDA), the U.S. Food and Drug Administration (FDA), the U.S. Drug Enforcement Administration (DEA), institutional review boards, offices or departments in state government, state boards of medical examiners, the researcher's home institution, and potential funders. A brief overview of some of these review processes is discussed.

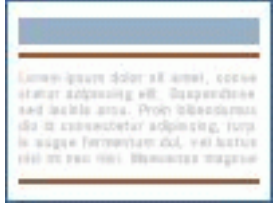
Researchers conducting clinical research on biological products such as cannabis must submit an investigational new drug (IND) application to the FDA. As a next step, the investigator may contact NIDA, an important source of research-grade cannabis, to obtain an administrative letter of authorization (LOA). An LOA describes the manufacturer's facilities, as well as the availability and pertinent characteristics of the desired cannabis product (e.g., strains, quality, strength, pharmacology, toxicology). To safeguard against the acquisition of cannabis or cannabinoids for non-research purposes, investigators must also apply for a DEA registration and site licensure before conducting studies involving cannabis or any of its cannabinoid constituents, irrespective of their pharmacologic activity.[5] The investigator must submit the IND and LOA to the FDA and the DEA for review (FDA, 2015).

After submitting an IND application, researchers must wait at least 30 days before initiating research, during which period the FDA reviews the application to ensure that research participants will not be exposed to unreasonable risk (FDA, 2016a). If the FDA determines that the proposed research would expose study participants to unreasonable risk or that the IND application is in some other way deficient, a clinical hold postponing the research may be imposed. This hold is not lifted until and unless the sponsoring researchers have resolved the deficiencies (FDA, 2016b).

It is important to note that the Controlled Substances Act of 1970 classified cannabis as a Schedule I substance, the highest level of drug restriction.[6] As defined by the Act, Schedule I substances are those that (1) have a high potential for abuse; (2) have no currently accepted medical use in treatment in the United States; and (3) have a lack of accepted safety for their use under medical supervision.[7] Other substances classified in Schedule I include heroin, LSD, mescaline, hallucinogenic amphetamine derivatives, fentanyl derivatives (synthetic opioid analgesics), and gammahydroxybutyrate (GHB).[8] By contrast, Schedule II substances—though they also have a high potential for abuse and may lead to severe psychological or physical dependence—are defined as having a currently accepted medical use and can be prescribed with a controlled substance prescription (DEA, 2006).[9]

In some states, researchers conducting clinical research on cannabis or cannabinoid products must also apply for and receive a controlled substance certificate from a state board of medical examiners or a controlled substance registration from a department of the state government in order to conduct clinical trials or any other activity involving Schedule I substances (Alabama Board of Medical Examiners, 2013; MDHSS, n.d.). Some state governments require additional approvals. For example, California requires that all trials involving Schedule I or II controlled substances be registered with and approved by the Research Advisory Panel of California (CADOJ/OAG, 2016). When the necessary approvals are secured, only then can the investigator apply for a DEA registration and site licensure to conduct research on a Schedule I controlled substance (see Box 15-1 for examples of research barriers).

BOX 15-1



Researchers conducting trials of Schedule I substances must additionally submit a research protocol to the DEA that includes details regarding the security provisions for storing and dispensing the substance.[10] Previously, nonfederally funded studies on cannabis were also required to undergo an additional review process conducted by the Public Health Service. This review process was determined to unnecessarily duplicate the FDA's IND application process in several ways and, as of June 2015, is no longer required.[11]

To ensure that controlled substances obtained for research purposes will be stored and accessed in accordance with DEA security requirements, local DEA officials may perform a preregistration inspection of the facility where the proposed research will take place (University of Colorado, 2016). DEA security requirements include storing cannabis in a safe, a steel cabinet, or a vault, and limiting access to the storage facility to "an absolute minimum number of specifically authorized employees.[12] The extent of the security measures required by DEA varies with the amount of cannabis being stored,[13] and among local DEA jurisdictions (Woodworth, 2011). Funders must bear the costs of meeting the necessary security requirements.

Additionally, as with any human clinical trial, approval from an institutional review board must be sought.[14] Obtaining this approval confirms that an appropriate plan to protect the rights and welfare of human research subjects has been outlined in the proposed research efforts. If a study is being conducted in a clinical research center, a separate review may be required by this entity's medical or research advisory committee.

In summary, basic and clinical researchers seeking to obtain cannabis or cannabinoids from NIDA for research purposes—including efforts to determine the value of cannabis or cannabinoids for treating a medical condition or achieving a therapeutic end need—must obtain a number of approvals from a range of federal, state, or local agencies, institutions, or organizations. This process can be a daunting experience for researchers. The substantial layers of bureaucracy that emerge from cannabis's Schedule I categorization is reported to have discouraged a number of cannabis researchers from applying for grant funding or pursuing additional research efforts (Nutt et al., 2013). Given the many gaps in the research of the health effects of cannabis and cannabinoids, there is a need to address these regulatory barriers so that researchers will be better able to address key public health questions about the therapeutic and adverse effects of cannabis and cannabinoid use.

> **CONCLUSION 15-1 There are specific regulatory barriers, including the classification of cannabis as a Schedule I substance, that impede the advancement of cannabis and cannabinoid research.**[15]

Barriers to Cannabis Supply

In the United States, cannabis for research purposes is available only through the NIDA Drug Supply Program (NIDA, 2016a). The mission of NIDA is to "advance science on the causes and consequences of drug use and addiction and to apply that knowledge to improve individual and public health," rather than to pursue or support research into the potential therapeutic uses of cannabis or any other drugs (NIDA, 2016b). As a result of this emphasis, less than one-fifth of

cannabinoid research funded by NIDA in fiscal year 2015 concerns the therapeutic properties of cannabinoids (NIDA, 2016c).[16] Because NIDA funded the majority of all the National Institutes of Health (NIH)-sponsored cannabinoid research in fiscal year 2015 (NIDA, 2016c),[17] its focus on the consequences of drug use and addiction constitutes an impediment to research on the potential beneficial health effects of cannabis and cannabinoids.

All of the cannabis that NIDA provides to investigators is sourced from the University of Mississippi, which is currently the sole cultivator of the plant material and has been since 1968 (NIDA, 1998, 2016a).[18] In the past, the varieties of cannabis that were available to investigators through NIDA were limited in scope and were not of comparable potency to what patients could obtain at their dispensaries (Stith and Vigil, 2016). Because of restrictions on production and vicissitudes in supply and demand, federally produced cannabis may have been harvested years earlier, is stored in a freezer (a process that may affect the quality of the product) (Taschwer and Schmid, 2015; Thomas and Pollard, 2016), and often has a lower potency than cannabis sold in state-regulated markets (Reardon, 2015; Stith and Vigil, 2016). In addition, many products available in state-regulated markets (e.g., edibles, concentrates, oils, wax, topicals) are not commonly available through federal sources (NIDA, 2016d). Since the products available through the federal system do not sufficiently reflect the variety of products used by consumers, research conducted using cannabis provided by NIDA may lack external validity. In July 2016, NIDA posted a formal request for information on the varieties of cannabis and cannabis products of interest to researchers (NIDA, 2016e). Reflecting the perceived shortcomings of cannabis and cannabis products currently provided by NIDA, a summary of the comments received in response to this request states that "the most consistent recommendation was to provide marijuana strains and products that reflect the diversity of products available in state dispensaries" (NIDA, 2016e).

Naturally, it is difficult for a single facility at the University of Mississippi to replicate the array and potency of products available in dispensaries across the country. It is worth noting, however, that NIDA has been increasingly responsive to the needs of clinical investigators. For example, NIDA has contracted with the University of Mississippi to produce cannabis strains with varying concentrations of Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (NIDA, 2016d), and NIDA has previously authorized development of cannabis extracts, tinctures, and other dosage formulations for research purposes (Thomas and Pollard, 2016). As mentioned above, NIDA has sought public comment on the needs of cannabis researchers in order to inform efforts to "expand access to diverse marijuana strains and products for research purposes" (NIDA, 2016e).[19] In addition, cannabis is made available to research investigators funded by NIH at no cost. Finally, the DEA has adopted a new policy that increases the number of entities that may be registered under the Controlled Substances Act (CSA) to grow (manufacture) marijuana to supply legitimate researchers in the United States.[20] Under this new policy, the DEA will facilitate cannabis research by increasing the number of private entities allowed to cultivate and distribute research-grade cannabis. As of December 2016, the University of Mississippi remains the sole cultivator of cannabis provided to researchers by NIDA (NIDA, 2016a).

Although new plans are being made to provide a wider array of more clinically relevant cannabis products for research, at present this issue is still a significant barrier for conducting comprehensive research on the health effects of cannabis use. How the proposed changes will affect cannabis research in the future remains to be seen.

CONCLUSION 15-2 It is often difficult for researchers to gain access to the quantity, quality, and type of cannabis product necessary to address specific research questions on the health effects of cannabis use.

Funding Limitations

Funding for research is another key barrier; without adequate financial support, cannabis research will be unable to inform health care or public health practice or to keep pace with changes in cannabis policy and patterns of cannabis use. NIH is responsible for funding research across a number of health domains. In 2015, NIH spending on all cannabinoid research totaled $111,275,219 (NIDA, 2016c). NIDA, a member institute of NIH, has as its mission to study factors related to substance abuse and dependence and conducts research on the negative health effects and behavioral consequences associated with the abuse of cannabis and other drugs (NIDA, 2016b). Because cannabis was historically perceived to have only negative effects, the majority of cannabis research has been conducted under the auspices of NIDA.

In fiscal year 2015, studies supported by NIDA accounted for 59.3 percent ($66,078,314) of all NIH spending on cannabinoid research; however, only 16.5 percent ($10,923,472) of NIDA's spending on cannabinoid research supported studies investigating therapeutic properties of cannabinoids (NIDA, 2016c).[21,22] As demonstrated in Chapter 4 of this report, a growing body of evidence suggests that cannabis and cannabinoids also have therapeutic health effects. In light of these findings, a comprehensive research agenda that investigates both the potential adverse and the potential therapeutic health effects of cannabis use is needed.

However, it may be unrealistic to expect NIDA to have the resources or interest to fund this broader research agenda, which could involve investigating the health effects of cannabis use on a diverse range of conditions (e.g., metabolic syndrome, cardiovascular disease, cancer, obesity and sedentary behavior, Alzheimer's disease) that are targeted by other institutes and centers of NIH. While it is not clear how these studies might be funded, almost assuredly the changing norms and the changing legal status of cannabis will have an impact on conditions that are targeted by institutes other than NIDA, and it will become increasingly important to have a funding mechanism to better understand the comprehensive health effects of cannabis so that consumers and policy makers can respond to changing trends accordingly.

CONCLUSION 15-3 A diverse network of funders is needed to support cannabis and cannabinoid research that explores the harmful and beneficial health effects of cannabis use.

METHODOLOGICAL CHALLENGES

Drug Delivery Challenges

Another challenge in investigating the potential health effects of cannabis and cannabinoids is the identification of a method of administering the drug that is accepted by study participants, that can be performed at most research sites, and that ensures standardized dosing. Smoking as a route of administration is particularly challenging, as some study participants may not view it as an acceptable method of drug administration, and academic medical centers or other locations where cannabis or cannabinoid research takes place may lack facilities where study participants can smoke under controlled conditions. Furthermore, variations among individuals in terms of

their cannabis smoking techniques make it difficult to ensure that study participants reliably receive the targeted dose of the drug. Devices for providing a metered dose of cannabis via inhalation exist (Eisenberg et al., 2014), but the FDA has not approved such devices for use. Standardized smoking techniques have also been developed (Foltin et al., 1988) but can be difficult to perform correctly. These difficulties are due, in part, to differences among individuals in their tolerance of the potential psychoactive effects of the drug (D'Souza et al., 2008; Ramaekers et al., 2009), which may prevent the receipt of equal doses by all study participants.

Researchers have also explored vaporization as a method for administering cannabis (Abrams et al., 2007). Cannabinoids vaporize at lower temperatures than the temperature at which pyrolytic toxic compounds are created through combustion; as a result, levels of some carcinogenic compounds are lower in cannabis vapor than in cannabis smoke (Eisenberg et al., 2014). However, there is a paucity of research on the effectiveness of these devices as a mode of drug administration. For example, data on the plasma concentrations of cannabinoids achieved through use of vaporizers exists, but they are limited (Abrams et al., 2007; Zuurman et al., 2008). In addition, even less is known about the long-term pulmonary effects of inhaling a vaporized liquid than about the effect of inhaling plant material. As vaporizing devices proliferate and evolve, researchers may benefit from advances in their portability and usability, but they will also have to account for clinically relevant differences in the functioning and the effectiveness of an increasingly wide range of models.

To circumvent the practical and methodological challenges involved in administration of cannabis through smoking or vaporization, investigators may choose to study the health effects of orally administered dronabinol or nabilone, which offer a more controlled method of drug delivery. However, the effects generated by these isolated cannabinoids might, at least in part, be different from those produced by the use of the whole cannabis plant, which also contains CBD and other cannabinoids, as well as terpenoids and flavonoids. As a result, extrapolating from the observed health effects associated with use of an isolated cannabinoid such as dronabinol or nabilone in order to predict the health effects associated with the use of cannabis may lead to erroneous conclusions.

The Placebo Issue

The gold standard of drug development is the prospective, randomized, double-blind, placebo-controlled clinical trial. Placebo cannabis produced by solvent extraction is available from NIDA and has a potency of 0.002 percent THC by weight and 0.001 percent CBD by weight (NIDA, 2016d).[23] The extraction process seems to retain the terpenoids and flavonoids so that the combusted placebo material smells similar to the true cannabis, thus helping to preserve the blinding to some extent. However, the psychoactive and vasoactive effects of cannabis pose a considerable challenge for effective blinding, since study participants who feel such effects will surmise that they are receiving cannabis or cannabinoids, and not a placebo.

Strategies to promote the effectiveness of blinding exist. For example, if the cannabis being studied has a very low THC content, study participants—especially those who, through regular use of more potent cannabis strains, are inured to the psychoactive effects of cannabis with low THC content—may not notice the psychoactive effects of the cannabis and therefore be unable to reliably determine whether they are using cannabis or a placebo. There is also a possibility that cannabis products with a lower ratio of the concentration of THC to the concentration of CBD may have less psychoactivity than products with a comparatively higher ratio of the

concentration of THC to the concentration of CBD (Hindocha et al., 2015; Jacobs et al., 2016). Using these strains with diminished psychoactive effects could promote more effective blinding. Researchers may also try treating both study arms in a placebo-controlled cannabis trial with a mildly psychoactive or sedating drug, the effects of which may help to ensure that study participants are unable to determine whether they are receiving a placebo or cannabis. However, by introducing another active agent, the investigators risk obfuscating the results of their study.

A potential method for assessing the effectiveness of blinding in a cannabis trial is to ask study participants to guess whether they are receiving true cannabis or a placebo. If most or all of the participants correctly guess their assignment, it can be inferred that the blinding was ineffective. Whether or not such methods are employed, investigators risk undermining their study results. On the one hand, conducting the test carries the risk of discovering that attempts at blinding were ineffective, thereby rendering the study results invalid. On the other hand, not conducting the test may lead journal reviewers aware of the challenges of blinding in cannabis trials to assume that blinding was ineffective and to discount the study results accordingly. Thus, research to address the challenge of achieving reliably effective blinding in a cannabis trial is of marked importance.

Exposure Assessment

In order to arrive at valid and meaningful results, population studies on the health effects of cannabis require as detailed an ascertainment of exposure to cannabis as possible. However, obtaining such a detailed exposure history can be difficult. This is especially true for recreational cannabis use due to the lack of a standardized dose and the existence of diverse routes of administration, including multiple modes of inhalation (Schauer et al., 2016). In addition, known pharmacological biomarkers of cannabis use may be unreliable in some circumstances, while population studies to identify novel pharmacological biomarkers of cannabis exposure are limited (Hartman et al., 2016; Schwope et al., 2011). Furthermore, the wide variety of different cannabis strains developed through a long and ongoing process of cultivation and the associated variation in the concentration of active substances in cannabis further complicate the characterization of cannabis exposure (ElSohly and Gul, 2014; Elsohly et al., 2016; Mehmedic et al., 2010). Finally, recreational cannabis may contain chemical contaminants or adulterants (Busse et al., 2008). Cannabis users may be unaware of the presence of these chemicals, making it unlikely that such chemicals would be identified through toxicological evaluation unless the user became involved in a forensic investigation.

Most observational studies, particularly case-control and cohort studies, depend on self-report in order to assess cannabis exposure. These reports may be incomplete, inaccurate, or imprecise due to failure on the part of investigators to ask cannabis users detailed questions about their cannabis exposure history, including the source of their cannabis exposure (e.g., smoking, edibles, vaping), or because users themselves may have limited knowledge of some aspects of their exposure or may be resistant to reporting some information. Personal recall of substance use may also be affected by other factors. For example, memory problems have been identified as a cause of inaccuracies in reporting drug use (Johnson and Fendrich, 2005; Pedersen, 1990). In other cases, study participants may not report illicit substance use in an attempt to conform to perceived social norms (Johnson and Fendrich, 2005). Similarly, individuals with substance dependency syndromes may have psychiatric comorbidity that affects the accuracy of reporting.

Finally, important information often missing from cannabis exposure histories is the extent of other substance use. As noted in Chapter 14, there is limited evidence that cannabis use is

associated with the use of other licit or illicit substances. Despite this association and the confounding effect of polysubstance use on evaluations of the health effects of cannabis use, surveys used to characterize cannabis exposure histories do not always assess for the presence of other substance use. Since secondhand exposure to cannabis smoke can have minor health effects, there may also be value in assessing for such exposure as part of larger assessments of cannabis exposure (Herrmann et al., 2015).

Cannabis-Related Study Designs

In researching the health outcomes of cannabis use, the committee identified a number of studies, particularly cohort studies, of general health outcomes such as all-cause mortality or important chronic illnesses such as cancers or cardiovascular diseases. For both cohort and case-control studies, a better assessment of cannabis use would offer more valuable information, such as years of use and age at first use. Particularly for cohort studies, this would offer better ascertainment of the duration and net burden of use as well as more insight into period and age effects. As discussed in the proceeding health outcomes chapters of the report, in many of the existing cohort studies cannabis use was often queried only at baseline, and thus there was little information on interval use over time or on the variation or cessation in that use. There was also very limited information on interval health events as the cohorts progressed, impeding a summarization of long-term use and the consequent health effects. Attention to these issues will likely improve the precision of study findings.

CONCLUSION 15-4 To develop conclusive evidence for the effects of cannabis use on short- and long-term health outcomes, improvements and standardization in research methodology (including those used in controlled trials and observational studies) are needed.

SUMMARY

The methodological challenges and the regulatory, financial, and access barriers described above markedly affect the ability to conduct comprehensive basic, clinical, and public health research on the health effects of cannabis use, with further consequences for the many potential beneficiaries of such research. In the absence of an appropriately funded and supported cannabis research agenda, patients may be unaware of viable treatment options, providers may be unable to prescribe effective treatments, policy makers may be hindered from developing evidence-based policies, and health care organizations and insurance providers lack a basis on which to revise their care and coverage policies. In short, such barriers represent a public health problem. See Box 15-2 for a summary of the chapter conclusions.

BOX 15-2

Summary of Chapter Conclusions.

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Footnotes

1 As of March 2016, the Health and Medicine Division continues the task of producing consensus studies and convening activities previously undertaken by the Institute of Medicine (IOM).

2 The count of states where cannabis is legalized for medical use includes Ohio and Pennsylvania, where medical cannabis laws were not operational as of October 2016 (NCSL, 2016).

3 $22,225,750 (Marijuana Sales Tax [2.9%]) + $42,017,798 (Retail Marijuana Sales Tax [10%]) + $23,995,775 (Retail Marijuana Excise Tax [15%]) = $88,239,323.

4 Medical Cannabis: $5,236,536 (State Retail Sales Tax) + $792,906 (State Business and Occupation Tax) + $ 2,084,323 (Local Retail Sales Tax) = $8,113,765. Recreational Cannabis: $30,017,823 (State Retail Sales Tax) + $4,050,212 (State Business & Occupation Tax) + $11,228,861 (Local Retail Sales Tax) = $45,296,896. $8,113,765 (Total Medical Cannabis Taxes) + $45,296,896 (Total Recreational Cannabis Taxes) = $53,410,661.

5 Code of Federal Regulations, Registration of Manufacturers, Distributors, and Dispensers of Controlled Substances, Title 21, § 1301.11 and Code of Federal Regulations, Schedules of Controlled Substances, Title 21, § 1308.11.

6 Code of Federal Regulations, Schedules of Controlled Substances, Title 21, § 1308.11; United States Code, Schedules of Controlled Substances, Title 21, § 812.

7 United States Code, Schedules of Controlled Substances, Title 21, § 812(b)(1).

8 Code of Federal Regulations, Schedules of Controlled Substances, Title 21, § 1308.11.

9 United States Code, Schedules of Controlled Substances, Title 21, § 812(b)(2).

10 Code of Federal Regulations, Registration of Manufacturers, Distributors, and Dispensers of Controlled Substances, Title 21, § 1301.18.

11 Office of the Secretary, Office of the Assistant Secretary for Health, U.S. Department of Health and Human Services. Notice. “Announcement of Revision to the Department of Health and Human Services Guidance on Procedures for the Provision of Marijuana for Medical Research as Published on May 21, 1999,” *Federal Register*, 80, no. 120 (June 23, 2015): 35960, https://www.gpo.gov/fdsys/pkg/FR-2015-06-23/pdf/2015-15479.pdf (accessed November 25, 2016).

12 Code of Federal Regulations, Registration of Manufacturers, Distributors, and Dispensers of Controlled Substances, Title 21, § 1301.72 (a) and (d).

13 Code of Federal Regulations, Registration of Manufacturers, Distributors, and Dispensers of Controlled Substances, Title 21, § 1301.71 (c).

14 Code of Federal Regulations, Institutional Review Boards, Title 21, § 56.103.

15 The committee was specifically directed in its statement of task not to comment on cannabis policy issues, such as regulatory options for legalization, taxation, or distribution. While the committee has identified the Schedule 1 classification of cannabis as posing a significant barrier to the conduct of scientific research on the health effects of cannabis, the committee is aware that any decision on the regulation of cannabis involves many factors far outside the committee's remit and expertise. Specifically, the committee did not comment on the abuse or dependency liability or accepted medical use of cannabis compared to other scheduled drugs.

16 In fiscal year 2015, NIDA's investment in cannabinoid research totaled $66,078,314, of which $10,923,472 was allocated for therapeutic cannabinoid research (NIDA, 2016c).

17 In fiscal year 2015, NIH's investment in cannabinoid research totaled $ $111,275,219, of which $66,078,314 was allocated to NIDA (NIDA, 2016c).

18 NIDA contracts with the University of Mississippi through an open solicitation process. Although the University of Mississippi is currently NIDA's only supplier of research-grade cannabis, other groups can compete for the contract (NIDA, 2015, 2016a).

19 In December 2016, cannabis provided by NIDA was generally free for NIH-sponsored research. For research not funded by the federal government, the cost of non-placebo cannabis was $10.96 per cigarette and $1,133 per pound ($2,497 per kilogram) (NIDA, 2016d).

20 DEA, U.S. Department of Justice. Policy Statement. "Applications to Become Registered Under the Controlled Substances Act to Manufacture Marijuana to Supply Researchers in the United States," *Federal Register*, 81, no. 156 (August 12, 2016): 53846, https://www.gpo.gov/fdsys/pkg/FR-2016-08-12/pdf/2016-17955.pdf (accessed January 7, 2017).

21 $66,078,314 (Total NIDA spending on cannabinoid research in fiscal year 2015)/$111,275,219 (Total NIH spending on cannabinoid research in fiscal year 2015) = 0.593. $10,923,472 (Total NIDA spending on therapeutic cannabinoid research in fiscal year 2015)/$66,078,314 (Total NIDA spending on cannabinoid research in fiscal year 2015) = 0.165.

22 By contrast, NIH spending on tobacco research totaled $300 million in 2015, and spending on research related to the harms and benefits of alcohol use totaled $473 million in 2015 (NIH, 2016).

23 In December 2016, placebo cannabis provided by NIDA was generally free for NIH-sponsored research. For research not funded by the federal government, the cost of placebo cannabis was $13.94 per cigarette and $1,133 per pound ($2,497 per kilogram) (NIDA, 2016d).

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