

Evaluating the Therapeutic Potential of Cannabinoids: How To Conduct Research Within the Current Regulatory Framework

Workshop Proceedings
December 8, 2018

The National Center for Complementary and Integrative Health (NCCIH) at the National Institutes of Health (NIH) sponsored a workshop on December 8, 2018, to discuss the processes and issues related to conducting cannabinoid research within the current regulatory environment. The conference brought together researchers, government officials, and industry representatives to:

- Gain an understanding of how best to navigate the regulatory environment
- Discuss NIH research interests and resources available to the scientific community
- Explore research strategies and approaches
- Receive updates from industry on resources, challenges, and progress in cannabinoid research
- Discuss future research opportunities
- Foster collaborations.

The focus of the workshop was on the state of the science and working within current regulations.

Background

People have used marijuana, also called cannabis, for a variety of health conditions for at least 3,000 years. The cannabis plant (*Cannabis sativa* L.) is unique source of phytochemicals, containing over 100 cannabinoids and terpenes, each with its own pharmacology. Of these phytochemicals, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most abundant and extensively studied. Marijuana is a Schedule I controlled substance according to the U.S. Federal Government. This classification is given to chemicals with high abuse potential and no recognized medical benefit. This classification extends to any phytochemical extracted from the plant. Whether marijuana has therapeutic benefits that outweigh its health risks remains uncertain, requiring more clinical studies to be conducted.

It is Federally illegal to sell/possess marijuana or cannabinoids outside of a U.S. Food and Drug Administration (FDA)- and Drug Enforcement Administration (DEA)-approved context. However, some states and the District of Columbia allow marijuana use for specific health purposes as well as for recreational use. As a result, more than two-thirds of U.S. citizens have access to state-regulated cannabis markets. States with medical marijuana laws show variability in allowable products, conditions for which marijuana is approved, and routes of administration, as well as whether they allow dispensaries, home growth, or registries. States with adult use laws vary on marketing issues, product labeling, distribution, and taxation. States also vary on testing and regulatory requirements. As a result, there is a patchwork of laws and regulations governing use, including research use, that must be understood. In addition, a growing number of people

are turning to cannabis with hope that it can provide therapeutic benefit for a wide range of conditions ranging from managing cancer chemotherapy side effects to treating epilepsy to addressing chronic pain. Despite the rapidly changing cultural, political, and legal landscape for cannabis in the United States and around the globe, the science is lacking with respect to informing public policy, public health, and personal decisions regarding the potential benefits and harms of cannabis use.

The FDA has not approved marijuana (the plant) for treating any medical conditions. However, the FDA has approved three cannabinoids as drugs. In 2018, the agency approved Epidiolex® (CBD) oral solution for the treatment of seizures associated with two rare, severe forms of epilepsy. This drug is derived from marijuana. The FDA has also approved the synthetic cannabinoids, dronabinol and nabilone, to treat nausea and vomiting associated with cancer chemotherapy in people who have already taken other medicines to treat these symptoms without good results. Dronabinol is also approved to treat loss of appetite and weight loss in people with AIDS. Dronabinol contains synthetic THC, and nabilone contains a synthetic substance with a similar chemical structure. In 2016, the FDA approved Syndros®, a liquid form of dronabinol. The FDA has determined that it is illegal to sell products that contain THC or CBD as dietary supplements or to sell foods containing THC or CBD in interstate commerce.

In January 2017, the National Academies of Sciences, Engineering, and Medicine (NASEM) published a report on the health effects of marijuana and products derived from it.¹ The report summarizes the current evidence on both therapeutic effects and harmful effects, recommends that research be done to develop a comprehensive understanding of the health effects of marijuana, and recommends that steps be taken to overcome regulatory barriers that may make it difficult to do research on marijuana's health effects. The December 8, 2018, workshop convened by NCCIH was a continuation of ongoing discussions in the scientific and policy communities focused on strategies for conducting research on the therapeutic potential of cannabinoids within the current U.S. regulatory and legal framework.

Evaluating the Risks and Potential Benefits of Cannabinoids: The State of the Science

Two speakers provided an overview of the state of the science for cannabis and cannabinoid research, including evidence, systematically obtained through controlled clinical trials, of some therapeutic benefit for specific conditions. The discussion also addressed the need to conduct research “in the field,” that is, studying cannabis and cannabinoid use as they occur in the general population.

Cannabinoids for Medical Use: A Systematic Review and Meta-Analysis

Penny Whiting, Ph.D., University of Bristol

¹ National Academies of Sciences, Engineering, and Medicine. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. Washington, DC: The National Academies Press; 2017.

In June 2018, Dr. Whiting and colleagues published a systematic review “Cannabinoids for Medical Use: A Systematic Review and Meta-Analysis.”² They reviewed randomized trials that had evaluated medicinal cannabinoids for the treatment of any of the following indications: nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDS, chronic pain, spasticity due to multiple sclerosis or paraplegia, depression, anxiety disorder, sleep disorder, psychosis, glaucoma, or Tourette’s syndrome. If no randomized controlled trials (RCTs) were available for a particular indication or outcome (e.g., long-term adverse events such as cancer, psychosis, depression, or suicide), nonrandomized studies including uncontrolled studies (e.g., case series) with at least 25 patients were eligible for consideration.

Twenty-eight databases and gray (not generally accessible) literature sources were searched with publication dates from 1975 to April 2015. All review stages were conducted independently by two reviewers. Where possible, data were pooled using random-effects meta-analysis. The review followed guidance published by the Centre for Reviews and Dissemination and the Cochrane Collaboration. Ultimately, the meta-analysis included 79 human clinical trials (6,462 participants), the majority of which evaluated nausea and vomiting due to chemotherapy or chronic pain and spasticity due to multiple sclerosis and paraplegia. Of these, 45 used a crossover design and 34 used parallel groups; almost all were placebo controlled. Where data were reported, the median proportion of male subjects was 50 percent, and the mean proportion of white subjects was 78 percent.

The cannabinoid types reviewed were primarily synthetic formulations or natural product extracts such as nabilone capsules; nabiximols spray; dronabinol capsules; THC in capsule, smoked, and spray forms; THC/CBD capsules; levonantradol in capsule or intramuscular form; CBD as capsules or spray; or ajulemic acid (CT3) in capsule form. Few studies focused on natural forms such as vaporized or smoked cannabis. GRADE (Grading of Recommendations Assessment, Development, and Evaluation) was used to rate the general quality of the evidence for publication bias, risk of bias, imprecision, inconsistency, indirectness, and magnitude of effect. Dr. Whiting and colleagues looked at effect by cannabinoid type and by treatment intent.

Most studies suggested that cannabinoids were associated with improvements in symptoms, but these associations did not reach statistical significance in all studies. Further, the analysis found moderate-quality evidence to support the use of cannabinoids for the treatment of chronic neuropathic or cancer pain (vaporized THC and nabiximols) and spasticity due to multiple sclerosis (nabiximols, nabilone, THC/CBD capsules, and dronabinol). However, the outcome being measured differed across trials. There was low-quality evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy (dronabinol and nabiximols), weight gain in HIV (dronabinol), sleep disorders (nabilone, nabiximols), and Tourette’s syndrome (THC capsules). There was insufficient evidence for all other conditions reviewed (depression, anxiety disorder, psychosis, and glaucoma).

² Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA*. 2015;313(24):2456-2473.

Cannabinoids were associated with an increased risk of short-term adverse events affecting the eyes, mouth, skin, heart, or muscles. However, there was no difference in the association for the type of cannabinoid, study design, indication, comparator, or duration of follow up. No evidence of long-term adverse events was found.

The results of the meta-analysis received widespread media attention and informed discussions at the policy and regulatory levels. Since its publication, numerous additional systematic reviews have been published reviewing the efficacy and safety of cannabinoids and cannabis for treating pain, epilepsy, movement disorders, fibromyalgia, symptoms of multiple sclerosis, and psychiatric indications. These reviews have produced similar findings of benefit in treating chronic neuropathic pain. In addition, benefits were shown for reducing seizure frequency in patients with epilepsy, an indication not included in the Whiting meta-analysis.

Therapeutic Cannabis Use in 2018: Where Do We Stand?

Kevin Hill, M.D., M.H.S., Harvard Medical School

As of November 2018, 33 states and the District of Columbia have initiated policies that allow the use of cannabis or cannabinoids for the treatment of specific medical conditions. In addition, 30 countries have initiated medical cannabis policies. Despite promising new research, the evidence base for the therapeutic use of cannabis has not grown as quickly as interest in the topic, and clinicians and patients are seeking guidance. With the recent FDA approval of Epidiolex, physicians now have three cannabinoids at their disposal that are approved for cancer-induced nausea and vomiting, appetite stimulation in wasting conditions such as HIV, and two forms of pediatric epilepsy (Dravet syndrome and Lennox-Gastaut syndrome [LGS]).

Beyond these conditions, the best high-quality evidence exists for chronic pain, neuropathic pain, and muscle spasticity associated with multiple sclerosis, according to a systematic review of medical marijuana for treatment of chronic pain and other medical conditions conducted by Dr. Hill and published in 2015.³ The 2017 NASEM report affirmed conclusive or substantial evidence of benefits of cannabis or cannabinoids for the treatment of chronic pain in adults (cannabis), as antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids), and for improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids).⁴

While many of the adverse effects of acute and chronic use are well described, there is a distinct need for longitudinal studies of the impact of cannabis and cannabinoids on physical and mental health. For example, the findings on cannabis for pain are mixed; thus, there is as yet no

³ Hill KP. Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: a clinical review. *JAMA*. 2015;313(24):2474-2483.

⁴ National Academies of Sciences, Engineering, and Medicine. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. Washington, DC: The National Academies Press; 2017.

consensus on recommended indications.^{5,6,7} Further, the NASEM report called for more evidence for specific cannabinoids or well-defined formulations versus the whole plant.

Despite a growing body of evidence for some conditions, people continue to use cannabis and cannabinoids in a multitude of ways that are as yet untested or unvalidated. Because most people are self-administering whole plant cannabis, there is a disconnect between the findings from randomized controlled studies and their translatability to common uses. Further, although laws in various states allow use of medical marijuana for an assortment of conditions, such as cancer, glaucoma, AIDS, hepatitis C, Crohn's disease, Parkinson's disease, and multiple sclerosis, there is a lack of conclusive evidence supporting such use for many of these conditions. Moreover, data suggest that a majority of people with medical cannabis cards do not actually have the conditions for which medical use is allowed, and many states have loopholes that allow physicians to certify use for any condition they think might be indicated.

The fact that policy has sometimes moved ahead of science can create risks associated with poorly prescribed or validated use—the risk of side effects without commensurate benefit, and the risk of forgoing other, proven therapies by choosing cannabis or cannabinoids. The adverse events on the brain are better defined than those on the physical domains. Acutely, users can experience learning, memory, attention, and motor coordination effects.⁸ Residual cognitive effects are still being debated.⁹ Others have reported chronic effects on increased risk of psychiatric illness, including addiction, anxiety, and psychotic disorders.^{10,11} Meier et al. reviewed the impact of chronic cannabis use on 12 physical domains and found only periodontal health to be adversely affected.¹² In sum, there are risks associated with use, but they are inadequately defined or understood, requiring more research.

The slow pace of research with cannabis has led to lack of uniformity in state policies governing indications for use, and providers and health care professionals are often operating without the benefit of best practices or even clarity about legal status. This is further complicated by the poor

⁵ Stockings E, Campbell G, Hall WD, et al. Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. *Pain*. 2018;159(10):1932-1954.

⁶ Hill KP, Palastro MD. Medical cannabis for the treatment of chronic pain and other disorders: misconceptions and facts. *Polish Archives of Internal Medicine*. 2017;127(11):785-789.

⁷ Hill KP, Palastro MD, Johnson B, et al. Cannabis and pain: a clinical review. *Cannabis and Cannabinoid Research*. 2017;2(1):96-104.

⁸ Volkow ND, Baler RD, Compton WM, et al. Adverse health effects of marijuana use. *New England Journal of Medicine*. 2014;370(23):2219-2227.

⁹ Scott JC, Slomiak ST, Jones JD, et al. Association of cannabis with cognitive functioning in adolescents and young adults. *JAMA Psychiatry*. 2018;75(6):585-595.

¹⁰ Halah MP, Zochniak MP, Barr MS, et al. Cannabis use and psychiatric disorders: implications for mental health and addiction treatment. *Current Addiction Reports*. 2016;3(4):451-462.

¹¹ Rabin RA, George TP. Understanding the link between cannabinoids and psychosis. *Clinical Pharmacology and Therapeutics*. 2017;101(2):197-199.

¹² Meier MH, Caspi A, Cerdá M, et al. Associations between cannabis use and physical health problems in early midlife: a longitudinal comparison of persistent cannabis vs tobacco users. *JAMA Psychiatry*. 2016;73(7):731-740.

quality of certification practices and care in some medical cannabis clinics. Insufficient understanding of CBD means that clinicians and patients are operating in an environment where very little is known about its risks and benefits and where inaccurate labeling is common.¹³ Risks increase when patients are self-administering and obtaining materials from sources that have few requirements for standardization or quality control, and off-label use is on the rise. This is particularly problematic with psychiatric conditions, where unsupervised use can cause lasting harms. During discussion it was noted that often people going to dispensaries are coming in precisely because of self-reported anxiety or depression.

Although international organizations such as the World Health Organization have made strides in promoting progress in research on cannabis and cannabinoids, much work remains for the United States to play a leading role in this area.

Session Discussion

In sum, this is a critical period for research on cannabis and cannabinoids. Discussants suggested that research funding should extend beyond NIH to states and companies already profiting from cannabis. Further, medical and scientific organizations should provide clear, evidence-based guidance as more research results become available and should offer independent continuing education efforts for clinicians. Finally, the research community needs to increase the rate and scale of effort to apply the same rigorous methods of investigation used for other compounds to both synthetic and whole plant formulations of cannabis. During the discussion it was also noted that studies are sorely needed to assess whether cannabis is safe and effective in the formulations that people are actually using.

Supporting Cannabinoid Research: Balancing the Need for Federal Regulations and Knowledge

The research foci and portfolios of the four NIH Institutes and Centers involved in cannabinoid and cannabis research were described, followed by presentations describing the Federal regulatory and legal environment for such research and the perspectives of investigators navigating the current environment.

The NIH Perspective

NIH is the leading funder of biomedical research in the United States. The role of NIH is to support meritorious scientific research on behalf of the American people. Four NIH Institutes and Centers described their interests in cannabinoid-related research and potential funding opportunities.

National Center for Complementary and Integrative Health (NCCIH)
Emmeline Edwards, Ph.D.

¹³ Bonn-Miller MO, Loflin MJE, Thomas BF, et al. Labeling accuracy of cannabidiol extracts sold online. *JAMA*. 2017;318(17):1708-1709.

NCCIH supports rigorous scientific investigation of natural products such as the cannabis plant and its components (e.g., cannabinoids and terpenes). The goals are to determine the usefulness and safety of complementary interventions and to investigate their roles in improving health and health care. As noted in NCCIH's Strategic Plan, a key focus of the Center's research efforts is pain management using complementary health approaches, such as mind and body practices and natural products. Many natural herbs are used for pain relief, including the cannabis plant. However, in the majority of cases, there is not sufficient scientific research to support their use.

Mouse models are beginning to provide clues to the relationships between stress-induced analgesia and cannabinoids, particularly with regard to CB1 receptors and antagonists. Cannabinoid receptor agonists have antinociceptive activity in animal models of tonic pain/hyperalgesia. They also have been found to have analgesic effects in inflammation and painful neuropathy. Cannabinoid receptors found in areas of the nervous system that are important for pain processing and cannabinoid receptors in immune cells appear to regulate inflammatory hyperalgesia. Thus, cannabis represents a potential option as part of a multimodal pain treatment plan, as several plant components have demonstrated analgesic properties. However, it is not known how individual cannabis constituents affect pain because very few of them have been extensively studied. The cannabis herb contains more than 430 constituents, with the most abundant being THC and CBD. However, there are 100 minor cannabinoids and 120 terpenes.

Terpenes comprise a smaller percentage of the phytochemicals in cannabis but give the plant its strain-specific properties such as aroma and taste. A number of therapeutic applications of terpenes have been identified, such as antibacterial, antimicrobial, antitumor, and anti-inflammatory activities. In addition, several mechanisms have been suggested for sedative and anxiolytic effects of terpenes. There is evidence to suggest that specific terpenes (e.g., myrcene, limonene) have analgesic properties. However, it is unknown how terpenes, either alone or in conjunction with minor cannabinoids, may modulate the biological and neural systems associated with pain perception and analgesia. Exploration of these issues is the focus of an NCCIH initiative. Similarly, the non-THC cannabinoids have been found to have neuroprotective, analgesic, and anti-inflammatory effects, but rigorous research is needed to identify the mechanism or combination of mechanisms underlying the analgesic properties of minor cannabinoids. NCCIH is also investing in such research.

NCCIH has identified research priorities, gaps, and opportunities in the following areas: pharmacology of terpenes and minor cannabinoids, potential effects on pain and underlying mechanisms, and special effects of terpenes and minor cannabinoids (e.g., interaction with the microbiome, opioid-sparing effects, and impact of sex, age, and ethnicity). The Center acknowledges the many legal and regulatory challenges in conducting cannabis research, such as its Schedule I status, the limited supply of legal cannabis for research purposes through the National Institute on Drug Abuse (NIDA) Drug Supply Program, the variety of products used by consumers, and the need to work with state and Federal agencies. Yet the need for research is critical. Marijuana and cannabinoids are being used for clinical conditions, and physicians and patients need to know the scientific rationale, strength of evidence, implications of medical marijuana laws, and health risks. Based on current evidence, cannabinoids may have benefit for a

limited number of conditions; first-line, FDA-approved medications could be considered for treatment. Finally, appropriateness of use must be based on risk-benefit analysis.

Moving forward, NCCIH encourages research on terpenes and minor cannabinoids as it relates to pain and comorbid conditions (anxiety, depression), nociception, and inflammation. A new initiative will support highly innovative basic and/or mechanistic studies in appropriate model organisms and/or human subjects aiming to identify, demonstrate, and predict if terpenes and minor cannabinoids can treat pain. Importantly, while adhering to DEA and FDA regulations, NCCIH encourages researchers to develop strategies to produce and make available a wider array of more clinically relevant cannabis products for research purposes. Programs will support pharmacokinetic and pharmacodynamic studies assessing the properties of cannabinoids, modes of delivery, different concentrations, and mixtures in various populations, including dose-response relationships.

National Institute on Drug Abuse (NIDA) Research Priorities: Cannabis, Cannabinoids, and the Endocannabinoid System

Susan R.B. Weiss, Ph.D.

NIDA has a substantial investment in cannabis research—more than \$88 million in 2017 covering a variety of topic areas, including: (1) epidemiology to track the prevalence, trends, and patterns of use; (2) prevention, focused especially on vulnerable populations such as youth, pregnant or breastfeeding women, and individuals with mental illness; (3) treatment development for cannabis use disorder; (4) potential therapeutic uses of cannabinoids for treating pain and substance use disorder; and (5) policy research to assess the impact of the changing legal environment on patterns of use and health consequences in the United States and globally.

NIDA also supports basic neuroscience research to understand the function of the brain's endocannabinoid system, including its role in pain, mental illness, neurodevelopment, and HIV, and to determine the impact of cannabis use and addiction on brain structure and function, cognition, motivation, affect, and adolescent and fetal development, among other functions. In 2017, NIDA spent approximately \$16 million on therapeutic cannabinoid research, mostly focused on pain, substance use disorder (e.g., CBD), and HIV. Most therapeutic studies use THC, CBD, their combination, or other chemical entities that modulate the activity of the endocannabinoid system rather than the cannabis plant itself. These are thought more likely than the plant or its crude extracts to result in an FDA-approved medication. NIDA is also interested in endogenous cannabinoid manipulation with inhibitors and modulators, or through receptor targets (CB1, CB2, TRPV1, and others).

NIDA recognizes the same challenges as NCCIH in conducting this research: the registration process for obtaining access to Schedule I drugs and the limits, to date, of a single public source of research-grade marijuana. Although the NIDA supply has diversified, it is costly and time-consuming to grow new products; thus, the research supply does not represent the diversity of products and formulations currently available, presenting an opportunity for further development. The Schedule I status of nonintoxicating components of cannabis (e.g., CBD) must be recognized, despite Epidiolex's Schedule V status. The inherent complexity of the plant and its many components also poses challenges and opportunities. The more than 100 cannabinoids

and other chemical entities that exist in different ratios confound understanding of the effects of each and whether there may be an “entourage effect.” The multiple routes of administration create additional research challenges in making comparisons and assigning effects. These challenges call for properly controlled trials of sufficient study duration. Finally, there is a need to study products that people are using in the marketplace to understand the full range of health consequences.

The National Institute of Mental Health (NIMH)

Mi Hillefors, M.D., Ph.D.

NIMH supports a small but important portfolio of research on cannabinoids, with approximately 12 active research project grants funded in 2018, primarily in the basic neuroscience and developmental translational portfolios. The major research areas of these efforts include: (1) furthering understanding of mechanisms and underlying pathophysiology of endocannabinoids and cannabinoid receptors, metabolism, and modulation; (2) mechanisms of synaptic plasticity and stress synaptic function; (3) modulation of adolescent maturation of the brain; (4) network connectivity and neural circuits associated with endocannabinoid signaling and cannabinoid neurotransmission; and (5) behavior (cognition, memory, anhedonia). Clinical areas of NIMH interest may include risk for psychotic disorders and cannabis, neuroinflammation and cannabinoid use, and mental health disorders such as depression, posttraumatic stress disorder (PTSD), and anxiety.

NIMH also focuses on a lifespan perspective. For example, exposure to cannabinoids may have different effects on signaling pathways in different periods of development. There are also possible linkages between cannabis use and psychosis: that is, adolescent exposure to cannabis may increase risk for schizophrenia. Brain imaging suggests there might be differentiable phenotypes in late-life depression (e.g., a phenotype marked especially by symptoms of anhedonia). Finally, if cannabis and cannabinoids are used long-term, how should side effects be measured and monitored?

For research on developing cannabis as a novel treatment, NIMH requires an experimental medicine approach that focuses on demonstrating that the drug engages the target as assessed with, for example, positron emission tomography or magnetic resonance imaging, that it changes brain function (e.g., brain waves), and that such target engagement and functional brain changes are linked to improvement in clinical outcome. This suggests that it might be more feasible to conduct research on one of the components of cannabis rather than the entire plant.

The National Institute of Neurological Disorders and Stroke (NINDS)

Mohamed Hachicha, Ph.D.

The accumulating pharmacologic evidence on phytocannabinoids in a variety of therapeutic indications suggests that increased translational studies are required to establish proof-of-concept in humans for various therapeutic indications. To expedite translation from basic science to the clinic, the NINDS Division of Translational Research (DTR) and Division of Clinical Research (DCR) offer different funding mechanisms such as Innovation Grants to Nurture Initial Translational Efforts (IGNITE), the Blueprint Neurotherapeutics Network (BPN), and the

Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT) programs to advance small molecules, biologics, devices, and natural products into the clinic.

The IGNITE program offers grants for assay development and therapeutic agent identification and characterization and *in vivo* efficacy studies. The goals are to develop assays and conduct screening to identify and characterize potential novel therapeutic agents for neurological disorders that will support future therapeutic development and lead to significant improvements over existing technologies/therapeutics.

The BPN involves 11 research institutions collaborating through grants and contracts to support pharmacologic studies, medicinal chemistry, pharmacokinetic and toxicology studies, data management, drug substance and drug product manufacturing, and Phase I clinical trials. This program includes contract resources that are tailor-made to support translational projects into the clinic.

NeuroNEXT was created to conduct studies of treatments for neurological diseases through partnerships with academia, private foundations, and industry. The program coordinates clinical sites testing promising new agents in Phase II clinical trials. It has an established clinical trials network with a central Institutional Review Board (IRB) and master clinical trial agreements, and it promotes optimal use of common data elements.

The NINDS mission includes several central nervous system disorders where phytocannabinoids may play a therapeutic role as witnessed by the therapeutic effect of CBD in Dravet syndrome (a rare form of intractable epilepsy that begins in infancy); consequently, the cannabinoids and natural products field in general is of interest to NINDS.

Regulatory and Law Enforcement Perspectives

Investigational drugs made from cannabis are controlled under the Controlled Substances Act (CSA) in Schedule I, which is the category of drugs with a high potential for abuse and no currently accepted medical use. Separately, tetrahydrocannabinols are also listed in Schedule I. Further, some cannabis low in THC and referred to as “hemp” is still cannabis, and remains Schedule I as of December 2018, including hemp oils and extracts, but not hemp seed or hemp seed oil (where negligible cannabinoids are present).

Representatives of the FDA and the DEA described their roles and responsibilities under the Federal Food, Drug, and Cosmetic Act and CSA as they relate to cannabis and cannabinoid drug development. The FDA representative laid out the process as it relates to human studies, and the DEA representative described the registration process needed to conduct research with a Schedule I substance.

FDA Regulatory Roles Concerning Cannabis and New Drug Research

Dominic Chaipperino, Ph.D.

Center for Drug Evaluation and Research, FDA

The FDA provides scientific and regulatory support for research on potential therapeutic uses of cannabis, regulates drug development from cannabis (under Investigational New Drug applications, or INDs), and takes enforcement actions against products made from cannabis or related compounds that make unapproved drug claims in labeling. The FDA also assists the DEA on the protocol registration process for Schedule I drug research and conducts scientific and medical analysis (Eight Factor Analysis, or 8FA) to recommend appropriate controls under the CSA. The FDA has approved some cannabis-related drug products. These include two formulations of dronabinol, nabilone, and CBD. These have been rescheduled under the CSA. Rescheduling of drugs involves the FDA conducting a scientific and medical analysis to support scheduling or rescheduling recommendations, which are then transmitted from the Department of Health and Human Services (HHS) to the DEA for a scheduling decision and action, which is published by the DEA in the *Federal Register*.

In the context of drug development, the FDA advises sponsors on what data should be collected to support its scheduling recommendations. The FDA supports drug development of product formulations derived from the cannabis plant and has regulatory programs available to prioritize important drug development that may address an unmet medical need, which it has offered for some cannabis-derived formulations (e.g., Priority Review of New Drug Applications [NDAs], Fast Track Designation, Breakthrough Therapy Designation). The FDA's website offers guidance for investigators researching cannabis and guidance on Botanical Drug Development. Industry (sponsors) and investigators can request a formal meeting with FDA offices to obtain advice either before submission of an IND application or during any subsequent phase of drug development, for example, with the Botanical Review Team to gain clarity on characterizing an investigational botanical drug to support a proposed clinical study or NDA submission, or with Controlled Substance Staff to gain clarity about abuse potential assessment requirements to support an NDA submission.

The FDA's primary regulatory role in investigational drug research is to ensure the reasonable safety of human subjects in research conducted under an IND application. The FDA also provides advice to sponsors as questions come up during their drug development under an IND. The FDA requires a 30-Day IND Safety Evaluation in which each protocol is evaluated for safety in relation to the intended dosing and patient population. Adequate safety qualification of each component of the drug product formulation must be provided, which may require nonclinical, animal studies to support human dosing. An adequate chemistry, manufacturing, and controls (CMC) data package must be submitted to ensure reasonable quality and safety for proposed clinical use. These requirements must be met for cannabis, which has been used for many years.

The source of the cannabis-derived drug products for use in clinical research dictates the regulatory requirements. For bulk cannabis, cannabis preparations, or pure cannabinoids, as available from the NIDA Drug Supply Program, in lieu of submitting CMC data investigators may gain right of reference to NIDA's Drug Master Files (DMFs) submitted to the FDA. For other sources that are DEA registrants, available CMC data or reference to a DMF is required. The DEA's 2016 *Federal Register* notice about expanding DEA-registered sources of cannabis for research lays out a process to become a registrant. To date, this has not yielded new registrants.

Investigators may also discuss with the DEA whether they can manufacture a cannabis-derived product formulation from NIDA or another lawful source of bulk cannabis; however, CMC data or reference to a DMF is required. Further, investigators must be compliant with the DEA registration framework for manufacturing. Another option is DEA-authorized importation of a study drug formulation, with CMC data or reference to a DMF required.

Drug products with abuse potential generally contain substances that have central nervous system (CNS) activity and produce euphoria (or other changes in mood), hallucinations, and effects consistent with CNS depressants or stimulants.¹⁴ Thus, if a drug substance is CNS-active, the new drug product containing that substance will likely need to undergo a thorough assessment of its abuse potential and may be subject to control under the CSA. The NDA for Epidiolex included an abuse potential assessment data package to support an 8FA, and Epidiolex was approved as a Schedule V drug. The DEA's placement of CBD in Schedule V was specifically for FDA-approved formulations of CBD with a THC impurity of no more than 0.1 percent. The DEA has asserted that CBD outside this definition remains controlled in Schedule I.

Future cannabis-related drugs in development may or may not need a new drug scheduling action upon FDA approval. If the drug meets the definition of an existing controlled drug class, consistent with accepted medical use and with the drug's relative abuse potential, it may by default be controlled in that schedule immediately upon approval. However, an abuse potential assessment, resulting data, and a proposal for scheduling are still required elements of the NDA submission. The submitted data must allow for FDA preparation of an 8FA to support a new drug scheduling action or support the control of the drug in an appropriate existing controlled drug class under the CSA.

Components of an abuse potential assessment in drug development, including cannabinoids, include data on receptor binding; pharmacokinetic data and brain penetration, if available; animal behavioral studies (to include general behavior, tetrad test, drug discrimination, self-administration, and physical dependence); clinical studies (assessment of adverse events, human abuse potential when recommended, evaluation of dependence), and post marketing or epidemiology data, if available. The FDA recommends use of positive controls in human abuse potential studies.

The FDA's review of an NDA is concurrent with the preparation of an 8FA. The Controlled Substance Staff reviews all abuse-related data submitted in the NDA. If an 8FA is needed to support a new drug scheduling action, it is prepared by Controlled Substance Staff for clearance through NIDA, the FDA, and the HHS, and ultimately transmitted from the Assistant Secretary for Health to the DEA Administrator. Transmission to the DEA can occur prior to or following an NDA approval action by the FDA. The DEA will only act once it has received both the HHS scheduling recommendation and a notification from the FDA that the NDA was approved. Based on 2015 legislation, the DEA should issue an interim final rule to schedule a drug within 90 days after both of these events have occurred.

¹⁴ See the FDA guidance for industry, Assessment of Abuse Potential of Drugs (2017). Available at <https://www.fda.gov/downloads/drugs/guidances/ucm198650.pdf>.

For all research with Schedule I drugs, the DEA's protocol registration requirements for both nonclinical and clinical studies involve a review by the FDA, separate from IND review. This involves DEA referral of protocols to the FDA for review of investigator qualifications and the scientific soundness of the proposed protocol, and particularly the requested study drug amount consistent with the proposed research protocol. The FDA has a fixed time period after receiving protocols from the DEA to respond with recommendations to the DEA (21 days for nonclinical protocols and 30 days for clinical protocols). For clinical studies, an IND authorized by the FDA as safe to proceed is a precursor requirement for DEA registration. Finally, there are DEA security requirements for all licensed study sites, as well as DEA registration of the principal investigator at each site implementing a given protocol.

In summary, the FDA has well-defined roles to play in the regulation and development of drug products containing or made from cannabis. The agency continues to focus on supporting scientific and rigorous testing to support approval of drugs derived from cannabis, and has made known its recommendations for adequate, well-controlled trials and appropriate formulations and routes of drug delivery for medicinal use. The FDA will continue to act on behalf of the HHS for delegated roles of the Secretary under the CSA provisions.

Marijuana, Research, and the Drug Enforcement Administration

James Arnold

Diversion Control Division, DEA

The CSA was enacted in 1970 to create a system of controls for the manufacture, distribution, import, export, dispensing, and prescribing of controlled substances. The DEA was established to oversee and enforce these efforts. The goals of the law were to protect public health and safety, curtail illegal use, and provide access to these substances for legitimate scientific, medical, and commercial purposes. To accomplish this task, the CSA established a system of registration for anyone handling a controlled substance, as well as multiple accounting requirements to protect against abuse and prevent diversion to illegitimate sources. As of December 2018, there were nearly 1.8 million DEA registrants including importers, manufacturers, exporters, pharmacies, practitioners, hospitals, researchers, patients, and narcotic treatment programs. Of these registrants, 8,771 were using Schedule I-V controlled substances in research, of which 535 were registered to conduct research involving use of marijuana, marijuana extracts, or THC.

The DEA has worked to improve the registration process. Since 2013 the DEA has reduced the approval time for new applications from 161 days to 105 days. The average days to approval of a new application once the DEA has received a complete protocol is 95. The DEA remains fully committed to assist an individual or educational, institutional, or any other organization with obtaining a registration to conduct legitimate research. On January 17, 2018, the DEA implemented an online automated application process for new and existing Schedule I researchers that improves efficiency and security (for more information go to www.deadiversion.usdoj.gov). It allows researchers to apply and update registration information and upload supporting documents, including state licenses as required. The website includes a Schedule I Researcher Preapplication Checklist to help guide researchers before they start the process.

As a final reminder for researchers interested in obtaining a Schedule I registration, all Schedule I controlled substances must be obtained from Federally identified legal sources (DEA registrants). Compliance with individual state requirements is also required prior to issuing a DEA registration to a researcher. State requirements for researchers vary from state to state.

Scientific Researchers' Perspective

Three researchers shared how they navigated the regulatory landscape to conduct scientific research with cannabis. Discussions focused on the steps taken to establish a research program, including innovative approaches to doing so, with the goal of informing the field of key considerations in undertaking such research.

Insights on Establishing New Cannabis Research Programs

Emily Lindley, Ph.D., University of Colorado, Anschutz Medical Campus

In 2014, the Colorado Department of Public Health and Environment issued a Request for Applications for studies on the medical efficacy of cannabis. Dr. Lindley received an award to study the acute (short-term) effects of study drug administration (i.e., vaporized cannabis, vaporized placebo cannabis, oxycodone hydrochloride, and placebo oxycodone) on chronic and experimentally induced pain and on cognitive performance. However, the University of Colorado Anschutz Medical Campus at that time did not have an established cannabis research program. Dr. Lindley described her experience initiating this study, which took roughly 2.5 years. That time was needed to meet the legal and regulatory requirements of the University of Colorado, NIDA, and the FDA; obtain local IRB and scientific advisory approvals; and complete DEA Schedule I and II (due to oxycodone) registration.

At the university level, several procedural hurdles had to be addressed. Because cannabis is illegal at the Federal level, the university wanted to be cautious about moving forward. In addition, a site had to be found where the research could be conducted on a smoke-free campus, and renovations needed to occur to allow for both the administration of vaporized cannabis and the Schedule I high-security storage requirements. The university and Dr. Lindley worked to determine who could hold the DEA Schedule I and II registrations (Ph.D. vs. Pharm.D. vs. M.D.) and who could handle/prepare cannabis and dispense it to subjects. The protocol and budget could not be finalized without these issues resolved, which took approximately 18 months. Ultimately, an exam room in the Clinical and Translational Research Center (CTRC) was renovated with a \$40,000 high-efficiency exhaust system to disperse vaporized cannabis outside the building in under 2 minutes. A drug storage room was updated to meet Schedule I and II security requirements (\$15,000). Dr. Lindley recommends that new entrants to this field of research consult with institutional officials early on to assess unanticipated requirements and costs associated with infrastructure renovations.

The DEA registration process took 6 months from the time of application submission because of multiple hurdles that delayed the registration process. The first hurdle was determining where the study drugs could be stored and who would manage and dispense the cannabis product. According to the Colorado Board of Pharmacy, no state licensed pharmacy or pharmacist can

manage Schedule I products. This meant that the University Hospital's research pharmacy could not manage the drugs for Dr. Lindley's study. A drug storage room was created (described above) and a Pharm.D. was included in the study to overcome this hurdle. The second hurdle was determining the DEA registrant. Because Dr. Lindley has a Ph.D., she initially submitted the DEA application with a Pharm.D. coinvestigator as the DEA registrant. The DEA processed the application and conducted a local site inspection and investigator interview. However, the DEA later advised Dr. Lindley that the DEA registrant for her study needed to hold an M.D. Per Dr. Lindley's understanding, this is because only an M.D. can prescribe scheduled drugs in Colorado. Pharmacy capabilities for managing cannabis-based products and rules regarding who can store and distribute scheduled drugs can vary by state, so Dr. Lindley recommended that investigators assess the landscape when considering a protocol.

The FDA IND process for the protocol was concluded in roughly 30 days. The whole plant cannabis is obtained from NIDA, which provided access to their drug master file (DMF) for the material (CMC: Chemistry, Manufacturing, Controls section). However, Dr. Lindley noted that one drawback of this arrangement is that the researcher never sees details on harvesting, processing, and storage. She also noted that if the researcher manipulates the NIDA product, it must be retested for cannabinoid identity and stability by a DEA Schedule I laboratory, and the researcher is responsible for the cost of testing. Delivery devices (e.g., Volcano vaporizer, vape pen) may require additional information (e.g., pharmacokinetic testing, analysis of vapor content). Further, IRBs require a Certificate of Confidentiality from NIH to protect research subjects' privacy.

NIDA has an approval process that requires protocol review and justification for the amounts of cannabis requested. Dr. Lindley cautioned that batches of available NIDA cannabis can change after the IND has been reviewed and authorized by the FDA to proceed, requiring the IND to be amended to reflect a new batch number and cannabinoid concentration. In her case, NIDA also retested her newly selected cannabis batch, which came back with a higher THC content than had been submitted on the IND, requiring another amendment. Dr. Lindley recommends that investigators refer to a general dose (e.g., "medium" dose) with a wide range in cannabinoid content (e.g. "approximately 4-7 percent THC") in anticipation of such variations in tested cannabis content. NIDA also requires an Indemnification Agreement, which is rarely authorized by state institutions and can take lengthy periods of time to resolve. Dr. Lindley recommends that investigators talk with their research administration and legal counsel early on and let them know of this requirement.

Novel Approaches to Research on Cannabis Products Available in State-Regulated Markets
Kent Hutchison, Ph.D., University of Colorado, Boulder

Despite the rapidly changing cultural, political, and legal landscape for cannabis in the United States and around the globe, the scientific literature is inadequate and mostly uninformative with respect to public policy, public health, and personal decisions regarding the potential benefits and harms of cannabis use. Many people obtain information from the Internet or by asking primary care providers, who often have no reliable evidence on which to base recommendations. People need information on the risks and benefits of cannabis use, and the scientific community

needs new approaches to study cannabis products commonly available in state-regulated markets.

To address this gap, Dr. Hutchison and colleagues launched several NIH-funded observational studies. An observational study is a type of research where the effect of something (e.g., cannabis) is observed without directing or influencing the use of it. Dr. Hutchison and colleagues' observational studies involve collecting blood, conducting subjective assessments of key outcomes such as mood and pain, conducting cognitive assessments, and identifying inflammatory biomarkers before and after the use of widely available cannabis products. Because the university had concerns about conducting the research on campus, the investigators created a mobile cannabis pharmacology laboratory to visit subjects at their homes, where cannabis use occurred inside their homes and then blood draws and assessments occurred in the mobile laboratory.

In a little over 1 year, the team collected data on more than 300 participants (both recreational and medical users) and gained some insight into the effects of high-potency flower, concentrates, and infused products. They found that THC concentrations in products people were using ranged from 16 to 90 percent. Plasma THC concentrations increased with increased THC levels in products, with some users of the highly concentrated products showing immediate post use plasma concentrations above 2,000 ng/mL. Unexpectedly, subjective effects of "feeling high" are not greater with the more concentrated products; in fact, it is the reverse, suggesting that users of highly concentrated products have a very high level of tolerance, with implications for their ability to cease use.

Another study focused on the effects of THC and CBD, specifically how CBD alters the use and effects of cannabis. Dr. Hutchison compared flower strains with high THC concentrations, THC plus CBD, and highly concentrated CBD. Plasma THC concentrations were highest in the high THC product and lowest in the high-CBD product. On measures of subjective intoxication, users of the high THC product and THC/CBD product reported feeling high at roughly the same levels and with nearly twice the effect of those who used the high-CBD product.

Typically, assessments of clinical benefits from a product are based on data obtained in Phase III randomized controlled trials, which precede marketing and approval. However, more than 30 states have approved cannabis for treating many medical conditions, without evidence; this suggests the need to use research designs to test real-world clinical effects, that is, observational prospective cohort designs.

An NCCIH-funded study, "Pain Research: Innovative Strategies With Marijuana," will assess use of edible cannabis for chronic low-back pain. At present, 76 million Americans suffer from chronic pain and nearly 95 percent of medical cannabis users report using it to treat pain. The study will recruit new chronic low-back pain patients who want to start using cannabis to treat their pain. The primary outcomes are pain and interference, inflammation, and cognition. Secondary outcomes include mental health, sleep, muscular control, and other medication use. Participants will acquire and consume edibles from a local dispensary that are THC-dominant, CBD-dominant, or a combination of THC and CBD. This type of observational study will

provide insights into current use of cannabis products, providing much-needed data on risks and benefits of products available in state-regulated markets.

The Challenge of Conducting Clinical Trials of Cannabis and Cannabinoids in the Treatment of Human Conditions

Thomas D. Marcotte, Ph.D., University of California, San Diego

The University of California's Center for Medicinal Cannabis Research (CMCR) was created in 2000, funded via the state's 1999 Medical Marijuana Research Act. The Research Act was, in part, a follow up to California's 1996 Compassionate Use Act, which allowed patients to use cannabis for medical reasons. The mission of the CMCR is to conduct high-quality scientific studies to ascertain the safety and efficacy of cannabis and cannabinoid products, including effects on cognition.

CMCR's earliest clinical studies were treatment trials assessing the effects of cannabis on diabetic neuropathy, HIV neuropathy, and multiple sclerosis spasticity, as well as studies of induced pain and cannabis pharmacokinetics. Those studies used NIDA-supplied cannabis and found significant treatment effects across all diseases studied, at different (and generally low) THC concentrations and modes of delivery (smoked, vaporized).

CMCR's current active studies focus on autism, neuropathic back pain, early psychosis, essential tremor, bipolar disorder, HIV neuropathy, anorexia nervosa, and migraine, as well as the impact of cannabis use on driving safety. Although the time required for a study to pass through all regulatory stages has decreased since the initial studies, the regulatory approval process for such research still routinely takes approximately 1 year.

Dr. Marcotte reported that there remain a number of misperceptions regarding cannabis research. For example, although early on THC levels in the NIDA cannabis were not reflective of current use, THC concentrations in NIDA's products have increased over time and more closely reflect the average of confiscated cannabis from a few years ago, although they are still below current levels reported in cannabis dispensaries. In addition, the regulatory agencies (e.g., the DEA) allow "take home" cannabis studies, if the protocol is approved by the FDA. CMCR currently has such a study, counter to misperceptions that they are not allowed (at least at the Federal level).

NIDA is currently the only Federally approved source for cannabis plant material. However, plant-derived formulations, as well as pure, synthetic THC and CBD are available from a limited number of Federally approved sources. In addition to NIDA products, the Center is using pure, synthetic CBD products for some of their studies. A major goal of the CMCR is to facilitate high-quality cannabis research, and as such the Center has established an infrastructure that can provide regulatory and clinical research expertise to investigators (aiming for standardization across studies); data management and information systems and data aggregation where feasible; standardized specimen collection, processing, and storage; toxicology services (controlling for site and batch differences); and facilities and equipment (e.g., negative pressure rooms, driving, simulation rooms, clinical exam rooms, and cognitive testing equipment).

Despite the progress made, Dr. Marcotte listed remaining challenges. First, there is still limited availability of products for Federally funded research (single source). There is a need for greater diversity with respect to cannabinoids and terpenes and for increased availability of other products (e.g., edibles, concentrates) for clinical trials, as well as for public safety research (such as impaired driving studies). The public has widespread access to products that currently cannot be legally accessed by researchers, and this needs to be remedied to facilitate clinical and safety studies. Other legal issues remain, such as interstate travel for subjects in longer term clinical trials, who would need to carry cannabis products into states where they are illegal. Another challenge concerns the ethical and clinical issues surrounding enrolling individuals who may already use cannabis to treat a condition and requiring them to stop using it in some cases. Finally, there is need for larger scale, longer term clinical trials assessing benefits and possible toxicities, including studies conducted in diverse or vulnerable populations (e.g., older age, patients with co-occurring conditions).

Balancing Federal Regulations and Knowledge: A Story of Success

GW Pharmaceuticals was founded in 1998 by Drs. Geoffrey Guy and Brian Whittle, specialists in development of plant-based pharmaceuticals, controlled substances, and drug delivery systems. Their goal was to develop a range of prescription medications derived from the cannabis plant or its individual components and to develop them under conventional regulatory standards for pharmaceutical products.

GW Pharmaceuticals developed an oral formulation of purified CBD, approved as Epidiolex in the United States for the treatment of Dravet syndrome and LGS. This is the first cannabis plant-derived medicine approved by the FDA, and it has been rescheduled by the DEA to Schedule V status. A Marketing Authorization Application (MAA) has been submitted to the European Medicines Agency (EMA) with an expected decision date in early 2019.

How Cannabis-Derived Medications Go Through the FDA Approval Process

Alice Mead, J.D., Greenwich Biosciences (U.S. subsidiary of GW Pharmaceuticals)

There remains a significant unmet need in epilepsy. There are 3.4 million U.S. patients with the disease, including roughly 470,000 children. One third of patients are pharmacoresistant, with seizures persisting despite multiple antiepileptic drugs (AEDs). Childhood-onset epilepsy involves multiple distinct orphan syndromes, almost none with a specific indicated therapy. Dravet syndrome and LGS represent two of the most difficult-to-treat epilepsy syndromes involving multiple seizure types, developmental delay, and high risk of Sudden Unexplained Death in Epilepsy (SUDEP).

GW Pharmaceuticals initiated its CBD research based on pressure and interest from the patient community, following the results of preclinical research in animal models. Families were seeking access to highly concentrated CBD for use in their children with these epilepsies and sought GW's help to gain access to standardized products. One child traveled to the United Kingdom to access the product, with a positive result, and on return his doctor applied for and received a single-patient IND under the FDA's expanded access program (EAP). This ultimately became the largest physician-sponsored EAP in the FDA's history, involving children and young adults

with multiple types of treatment-resistant epilepsies. The program involves 40 physician site EAPs and 6 U.S. state-sponsored EAP programs. To date, more than 1,000 patients have been approved by the FDA for treatment.

GW's first product outside of the United States was the first prescription medicine derived from the cannabis plant, called Sativex®, a complex extract (Δ^9 -THC and CBD in the European Union; nabiximols in the United States) that is now approved in more than 25 countries outside the United States for the treatment of spasticity in multiple sclerosis. It is a 1:1 CBD to THC oromucosal spray absorbed by the mouth. Because this is a complex product, it can be adjusted for different uses. For example, because chronic exposure to THC is harmful to a child's developing brain, the THC can be removed from the product for use in children.

GW's plants are highly standardized and controlled, so quality is built into the product from the start. Plants are grown in computer-controlled greenhouses where temperature, humidity, and lighting are controlled. A natural, proprietary growth medium devoid of heavy metals is used. No pesticides are used, and propagation is by clones; there are no genetically modified plants.

Securing approval from the FDA is difficult for any investigational medication, but the challenges are even greater for products derived from botanical materials. There are additional hurdles and requirements for products containing substances that may affect the CNS. Multiple quality control steps, specifications (agreed to by the FDA), and batch-to-batch consistency are required at each point along the way as the botanical raw material moves through various stages into a finished drug product. Stability studies are required to cover the expiration date, and a Quality Management System ensures all manufacturing steps follow current Good Manufacturing Practices (cGMP). Extractable and leachable studies are required because cannabinoids leach into certain containers and pull molecules out of others. The FDA inspects all manufacturing sites and manufacturing processes and documentation. GW's Clinical Operations manages documentation collected from monitoring of clinical trial sites and selected clinical research sites to ensure Good Clinical Practices.

Epidiolex requires a 45-acre glasshouse growing CBD-rich chemovars for efficient production. This is necessary because traditional hemp is an inefficient source of CBD—large volumes are required, the strains typically have low concentrations of CBD, and hemp is a bioaccumulator (phytoremediator) that absorbs heavy metals and other chemical waste from the soil.

Because cannabinoids have a specific therapeutic window, the goal of any formulation is to provide and maintain predictable and therapeutic blood and tissue levels of key cannabinoid components without incurring unacceptable side effects. There are numerous challenges in this regard, including inter subject pharmacokinetic variability; the rapid rate of rise of THC in plasma levels (e.g., inhalation), which can cause intoxication and affect blinding; poor solubility in water; the nature of the oral route and first pass; degradation with heat and light, especially in acid form; the need for decarboxylation; and bioavailability. Thus, developing precise, stable, and reproducible dosage forms to meet FDA standards can be challenging. In addition to human safety data, including drug/drug interaction studies, food/drug interaction studies, and studies in subjects with kidney or liver impairment, the FDA also mandates a series of toxicology tests in animals.

Since cannabis is classified in Schedule I of the Controlled Substances Act, special Federal and state license and security requirements apply. Because cannabinoids have CNS activity, a full battery of abuse potential studies must be conducted. Upon FDA approval, a new cannabinoid product must be rescheduled under both state and Federal law before it can be dispensed by pharmacies.

Session Discussion

The following issues were raised during discussion:

- Further research is needed on population differences in response to cannabis and cannabinoids. There is some evidence that in controlled conditions women are more sensitive to the rewarding/reinforcing effects of cannabis than the analgesic effects. In addition, the largest growing population of users is older individuals, which also raises the need to study the effects of use of concomitant medications, which is more likely in that population.
- Through observational controlled studies, there is growing evidence of safety and efficacy of use in some areas, such as treatment of chronic pain. The challenge is moving this knowledge through the regulatory environment, where the standards are the same as for other products; that is, products are characterized, dosing is established, and formulations are well characterized and quality controlled. These requirements stand in contrast to what is happening in the community, where there is unproven medical use through uncharacterized formulations. Taking a product into development requires financial investment and standardization of the product. Small observational studies can de-risk the drug development process by providing signals of effect. Questions were raised about whether cannabis and cannabinoids are changing the drug development process, and it was noted that the NIDA drug supply is not set up to respond to the entire regulatory and manufacturing infrastructure. Epidiolex provides a model approach to developing first-generation products that meet FDA standards, are lawful, and expand the supply beyond the NIDA cannabis resource, although it was produced abroad and imported.
- New products require adequate CMC data, and discussants said more guidance is needed on how to transition from bulk cannabis to formulations. However, the field is rapidly evolving. Synthetic cannabinoids will constitute second-generation drugs, and third-generation products will likely be biosynthetic cannabinoids. Fourth-generation products will eliminate cannabinoids altogether as small molecules that bind to the receptor; thus, the plant is not needed. As such, sourcing cannabinoids from cannabis, which might not be sustainable for the future, would no longer be necessary.

Working Within the System: Advances in Cannabis-Related Production and Distribution

Presenters focused on sources of cannabis and cannabinoids, both existing and emerging. While NIDA continues to provide research-grade product, research and development efforts in the private sector offer the promise of new products that can not only provide new opportunities for research and drug development but also potentially avoid some of the regulatory and legal challenges of using the whole plant and its products.

The NIDA Drug Supply Program and Analytical Services

Robert Walsh, NIDA

NIDA's mission is to support and conduct research across a broad range of scientific disciplines to bring the power of science to bear on substance use disorders. To facilitate research in basic and clinical science, NIDA established the Drug Supply and Analytical Services Program. This program provides the research community with a reliable source of authentic and quality-assured drugs, compounds, and services to meet emerging and evolving needs in the field. The drugs and compounds provided for research are DEA controlled, commercially unavailable, uncommon, and/or expensive. The analytical service is a chemistry support group for investigators providing analysis of experimental samples and determinations of the structure of chemical compounds.

The program researches, identifies, and selects new compounds; adds new compounds and updates the drug supply inventory; evaluates requests and reviews protocols; assesses analytical needs and develops methods for analysis; approves supplies and services; and interacts with the DEA, the FDA, the Office of National Drug Control Policy, and other agencies.

The drugs and compounds in the drug supply program include nonpeptides and peptides, both synthetic and natural, that include stimulants, sedatives/hypnotics, hallucinogens, cannabinoids, phencyclidines, narcotics, and designer drugs. Researchers requesting a drug or support must submit a letter of request, a research protocol, a curriculum vitae with publications, a DEA Form 222 for controlled substances, a Nuclear Regulatory Commission license if applicable, and an IND number (for clinical studies). Requirements are largely the same for foreign investigators with relevant import permits.

Currently, NIDA is the only source in the United States authorized to distribute marijuana for research purposes. NIDA has provided marijuana for research purposes since 1968, with the University of Mississippi as the contractor. To be more responsive to the needs of the cannabis research community, NIDA has requested information from the field to ascertain what additional varieties of marijuana and marijuana products are desired for research. Responses included requests for more diverse chemotypes, especially of higher THC content, to better match products currently available from dispensaries in states with regulated medical and recreational marijuana programs. In response, NIDA is working to produce an array of marijuana chemotypes with a large range of THC and CBD content, as well as several extracts and purified marijuana components for research purposes. There are also plans to provide additional chemotypes and products to further expand what is available from the NIDA Drug Supply Program. Currently, NIDA provides marijuana products in the form of buds, extracts, and crystalline CBD. There are also efforts under way to develop a better placebo for controlled studies.

A Cannabinoid Prodrug Approach to Treating Glaucoma

Brian Murphy, M.D., M.P.H., Nemus Bioscience, Inc.

Nemus Bioscience Inc. is a life-science, biopharmaceutical company focused on discovering, developing, and commercializing cannabinoid-based therapeutics. Nemus is developing novel and proprietary classes of pharmaceuticals with enhanced chemical engineering for optimized efficacy and safety. One area of interest for Nemus is glaucoma.

Glaucoma is one of the leading causes of irreversible vision loss globally. Therapies have focused on lowering intraocular pressure (IOP) to mitigate the loss of retinal ganglion cells (RGCs) secondary to the crush injury and hypoxia associated with elevated IOP. Cannabinoids have exhibited neuroprotective qualities *in vitro* and *in vivo* (multiple animal species) related to preservation of the optic nerve. Tissues in the eye regulating IOP have a significant density of cannabinoid receptors. Delivering a cannabinoid receptor agonist directly to the eye could be a viable method to preserve vision by lowering IOP and via direct neuroprotection of the optic nerve by cannabinoids. Further, human studies using routes of cannabinoid administration that included inhalational, oral, and intravenous access showed IOP reductions in normal controls and as high as a 65 percent decline in patients with glaucoma, but the time of activity was brief, often only 90 to 120 minutes, and there was a risk of systemic hypotension that could compromise blood flow to the retina. For these reasons, the American Academy of Ophthalmology has cautioned against extraocular delivery of cannabinoids for the management of glaucoma.^{15,16,17,18}

However, new classes of agents that can reduce IOP over time as well as prevent or decrease the loss of RGCs are urgently needed. Because glaucoma is a chronic disease, noninvasive topical application would be the most preferable means of drug delivery in an effort to avoid adverse events associated with broader systemic delivery. Nemus is developing an optimized cannabinoid technology that enhances bioavailability of THC and offers more predictable pharmacokinetics.¹⁹

To overcome the disadvantages observed with THC formulations and the solubility limitations of prodrugs, a new amino acid–dicarboxylic acid prodrug, which has not displayed active binding activity, THC-Val-HS (THCVHS, or NB1111), was designed. Experiments have shown that NB1111 does not substantively bind CB receptors; thus, the physiological effect comes from THC derived from the prodrug. NB1111 exhibited greater permeability into the eye versus THC, which helps explain its superior IOP-lowering effect. Further, NB1111 achieves tissue penetration in organs regulating IOP in a glaucoma model. The preformulation characteristics

¹⁵ Hepler RS, Frank IR. Marijuana smoking and intraocular pressure. *JAMA*. 1971;217(10):1392.

¹⁶ Cooler P, Gregg JM. Effect of delta-9-tetrahydrocannabinol on intraocular pressure in humans. *Southern Medical Journal*. 1977;70(8):951-954.

¹⁷ Green K, Kim K. Acute dose response of intraocular pressure to topical and oral cannabinoids. *Proceedings of the Society for Experimental Biology and Medicine*. 1977;154(2):228-231.

¹⁸ Goldberg I, Kass MA, Becker B. Marijuana as a treatment for glaucoma. *Australian Journal of Ophthalmology*. 1979;7(2):151-157.

¹⁹ Adelli GR, Bhagav P, Tasker P, et al. Development of a delta-9-tetrahydrocannabinol amino acid-dicarboxylate prodrug with improved ocular bioavailability. *Investigational Ophthalmology & Visual Science*. 2017;58(4):2167-2179.

and ocular bioavailability as well as the IOP-lowering activity of the compound were tested in an induced rabbit glaucoma model. When compared to pilocarpine and timolol, NB1111 achieved a 45 percent reduction in IOP and showed a significant decline in IOP using SLN (solid lipid nanoparticle) technology.

Cannabinoids have been shown to be neuroprotective in multiple animal models. Cannabinoid agonists have shown both clear hypotensive and neuroprotective effects on RGCs. Moreover, CB1 receptors to a greater extent than CB2 receptors have been implicated in mediating cannabinoid-induced neuroprotection. Therefore, cannabinoids can affect not only IOP but also RGC survival.

Nemus is looking to move into clinical studies in Australia conducting Phase 1b/2a clinical studies in patients to generate safety, efficacy, and pharmacokinetic data. The company has identified a synthesis partner with expertise in cannabinoid manufacturing, scaleup capability, and a global footprint as well as a formulation partner with specific expertise in developing modes of delivery directly into the eye.

Pharmaceutical Technological Approaches for NIH Collaboration, Product Development, & Commercialization

Santos Murty, Ph.D., Murty Pharmaceuticals, Inc. (MPI)

MPI is a practical industrial-based research, development, and manufacturing organization. The company focuses on drug substance and drug product dossier activities in an FDA-approved facility with DEA Schedule I–V registrations for research, analytical, and manufacturing activities. The company is an FDA-approved manufacturer for commercial and clinical trial material dosage forms. MPI technical capabilities include synthetic Active Pharmaceutical Ingredient (API) characterization, botanical extraction processes, preformulation, formulation development, analytical development, cGMP dosage form scaleup studies, and commercial-scale manufacturing.

For one project, MPI was able to engineer an approach to overcome poor water solubility and subsequently poor human bioavailability of cannabinoids (oral formulations). MPI now possesses numerous intellectual property assignments in over a dozen countries worldwide for therapeutically delivering poorly water-soluble drugs (PWSDs). Future organizational objectives include fostering collaborations for rapid development and commercialization of cannabinoid-based and other PWSD agents. With the United States currently lagging in cannabinoid product development, it is hoped a collaborative research, development, and manufacturing network could be established within the existing NIH scientific network.

Emerging Technologies: Using Yeast to Synthesize Cannabinoids

Anthony Farina, Ph.D., Librede, Inc.

Librede, Inc. is a synthetic biology company focused on unlocking the therapeutically relevant natural products from cannabis. Cannabinoids are no different than any other natural product that has found its way to therapeutic value. However, to control supply reproducibility there has to be a reliable means of production. Considering the trend toward producing pharmaceuticals in

unicellular organisms, the company believes biosynthetic production is the most cost-effective and efficient way of achieving this goal. As such, Librede primarily focuses on developing a yeast-based biosynthetic production platform for CBD/cannabidiolic acid (CBDA) and eliminating dependency on cannabis agriculture. However, the cannabis plant has potentially many more compounds that could become pharmaceutically relevant, thus creating a need to sustainably and economically produce them.

Cannabis produces many compounds, yet we have only scratched the surface of its chemistry. Considering its domestication by humans for millennia, only a small subset of the potential chemistry of this plant is understood. Further, engineering plants can take up to 10 years while engineering yeast strains takes days to weeks. Yeast is a model organism that is easily genetically modified and amenable to high-throughput engineering and screening. The acceleration of strain generation has come from researchers sharing and depositing genomic information. Understanding of the biosynthesis of cannabinoids comes from being able to test large sets of these genomic elements in a simplified yeast system.

Recently, Librede was granted a new patent for the production of CBDA in microorganisms. CBDA is a naturally occurring cannabinoid found in hemp and cannabis that is used to produce CBD. Librede's fermentation-based cannabinoid production platform has demonstrated that natural CBDA can be produced outside of the cannabis plant using yeast, in a process that is similar to brewing beer. The company combines targeted genetic optimization with a screened library approach to select yeast strains with improved CBD yield. It then optimizes growth and extraction conditions using commercial bioreactors to improve yield and develop methods compatible with high-volume commercial production. The goal is a fully developed process for producing and purifying CBD at large scale and low cost.

Fermentation for the production of high-value complex natural products offers a preferred route to synthesis at an industrial scale. Librede's biosynthetic approach has several potential advantages over agriculture-based methods including protection from supply volatility, improved consistency, reduced cost, and lower environmental impact. In addition to active pharmaceutical ingredient manufacturing, Librede's yeast platform enables unique insights into cannabis natural product chemistry, new molecular entities (whole cell mutagenesis or enzyme library variants), and control over formulation of phytocannabinoids to better understand endocannabinoid signaling.

Session Discussion

Discussion focused on how new methods for producing cannabinoid products can eliminate some of the challenges of working with the bulk plant or relying solely on NIDA for the supply. However, different manufacturing processes will yield different purity profiles, which have to be described for the FDA's purposes. On the other hand, one of the benefits of biosynthetic drug products is fewer isomers than with other manufacturing approaches. Discussion also centered on the challenges of going to scale for multisite clinical trials and whether scaling up can consistently recapitulate every pathway in the plant. Biosynthetic approaches can produce a high enough quantity of a compound of interest to facilitate studies of its mechanisms of action and

pharmacokinetics. These opportunities call for more open space and collaboration between basic researchers and commercial interests.

How to Move Cannabis-Related Research Forward: Workshop Overview

Perspective from the Workshop Discussant

Margaret Haney, Ph.D., Columbia University

Dr. Haney provided her assessment on the workshop discussions from the perspective of a NIDA-funded researcher of more than 20 years. She has conducted placebo-controlled human laboratory studies primarily focusing on cannabis use disorder but also on potential therapeutic uses. NIDA has supplied her laboratory with large volumes of cannabis as her research has focused on very high-volume users. Although it is an exciting time to be studying cannabis, and there have been enormous advances in endocannabinoid research in the past 20 years, Dr. Haney said human research on cannabis has actually become more challenging as societal use has become more prevalent. As states have made it easier for adults to legally possess relatively sizable quantities of cannabis, concentrate, and plants, scientists obtaining cannabis from NIDA (DEA-approved) still need to meet very high standards when using cannabis for research purposes.

Dr. Haney noted that cannabis has morphed into a large-scale, for-profit industry fraught with public health concerns, as discussed by workshop participants. Advertisements and labeling contain unsubstantiated health claims intended to increase consumption. There are insufficient data on pharmacokinetics/pharmacodynamics according to dose, route of administration, and relative cannabinoid ratios. In addition, quality control is lacking; there are no standards for cultivating, processing, testing, or labeling cannabis products. Against this backdrop, the FDA, the DEA, and scientific researchers have shared goals, which are to improve public health and safety, mitigate risk of abuse and diversion, and reduce problematic cannabis use.

As discussed in the workshop, meta-analyses and reviews have shown moderate effects on pain (primarily neuropathic pain), spasticity, and nausea/vomiting, but clinicians still have little to go on in terms of which cannabinoids to prescribe for which indication, and through what route of administration. Although medical cannabis has been voted in for more than 50 indications in states where it is allowed, there remains little evidence of effectiveness, and it is often used in lieu of FDA-approved medications. Further, only 31 percent of CBD on the market is accurately labeled. While no evidence of therapeutic effect does not necessarily mean cannabinoids do not work, we have to be cautious until randomized controlled clinical trials provide the data needed to keep pace with public use.

NCCIH's priorities are investigating the pharmacokinetics/pharmacodynamics of minor cannabinoids and terpenes, and implications for pain management and comorbid conditions. NIDA supports the majority of NIH funding in cannabinoid-related research and is focused on epidemiology, prevention, neuroscience, treatment of substance use disorders, therapeutics, and policy. In addition, NIDA's Drug Supply and Analytical Services Program provides quality-assured drugs and compounds and is striving to make higher CBD and THC products available as well as an improved placebo. NIMH's small cannabinoid portfolio is primarily focused on

basic neuroscience and developmental translational research, and centers on mechanisms, circuitry, and behavior. NINDS supports a range of translational studies. These and other NIH Institutes and Centers are ensuring that necessary and important research in this area proceeds.

The workshop also highlighted the collaborative roles of the FDA and the DEA in regulating new drugs and law enforcement. In sum, the 1970 CSA was enacted to prevent diversion of controlled substances while allowing research use. It covers all parts of the cannabis plant including hemp. The FDA assists the DEA on protocol registration for Schedule I drug research. Rescheduling drugs under the CSA involves FDA rescheduling recommendations based on scientific analysis. An IND may be authorized by the FDA to proceed, but then each investigator of a multisite study has to go through the DEA registration process.

Presentations by investigators provided useful advice for navigating regulatory, institutional, and legal hurdles when conducting cannabis and cannabinoid research as well as innovative approaches to administering cannabis to subjects on- and offsite. This is particularly useful information as the research field continues to study use of products in the marketplace, where there are no data on tolerance and withdrawal, especially with highly potent concentrates.

Presentations by industry representatives developing products emphasized the need to ensure batch-to-batch consistency and stable and reproducible forms of administration. Commercial activities are also improving the prospects of future generations of products, for example, a THC prodrug to avoid first-pass metabolism, CBD capsules with optimized bioavailability, and yeast-based biosynthetic production of cannabinoids.

Finally, there is increasing public interest in the therapeutic potential of cannabis, which requires that the research community explain the science and emphasizes the pressing need to conduct controlled studies to assess effectiveness, efficacy, and safety. This workshop provided a valuable description of the current scientific and regulatory environment on which to base future research priorities and actions.

Session Discussion

The following issues were discussed in the concluding session:

- NIH, the FDA, and the DEA are trying to facilitate this area of research, despite some systemic obstacles. Improved communication with investigators and institutions would clarify requirements and expectations and mitigate some misperceptions. Information resources and guidance on the infrastructure required and regulatory requirements would be helpful.
- The patchwork of state regulations and laws regarding medical and recreational use of cannabis and cannabinoids contrast with Federal law, which considers any use not research-related to be illegal. This can create complexities in terms of funding, use of facilities, and distribution of funds, which can be identified and negotiated in advance.

- FDA drug approval standards are the same as for other drugs. The FDA cannot set drug quality standards generally for regulating a substance that is illegal by Federal statute.
- Increasingly, there are pharmaceutical alternatives to the NIDA supply, but challenges in using them remain that can dissuade investigators from pursuing them, even for preclinical animal studies. For example, the grower/manufacturer and the investigator both have to be DEA registrants, and the costs of obtaining these alternative products can be prohibitive. Researchers in this field need additional sources of cannabis and cannabinoids.
- Since the NIDA supply is not intended to move into a commercial product, there is some risk in relying on it as material for an FDA-approved product; therefore, other manufacturers are needed for that intent, in particular for Phase III studies.

Conclusion

There is substantial interest in using cannabis to treat medical conditions. However, the scientific evidence base does not have information to support or refute specific medical uses of cannabis. There is a need for more rigorous scientific inquiry to evaluate the therapeutic potential of cannabis. While many states have legalized marijuana for medical or recreational purposes, it remains Federally illegal in the United States. This dual legality status complicates scientific investigation but does not prevent it. This workshop demonstrated how cannabinoid research can be conducted within the current regulatory framework. NIH, the FDA, and the DEA support this type of research; however, laws exist that must be observed. In addition to Federal regulations, each state, locality, and university has laws or regulations governing the handling of controlled substances. While this might seem daunting, it can be done, and the research is needed.