National Center for Complementary and Integrative Health (NCCIH)
Annual Principal Investigators' Meeting 2020
Exploring the Mechanisms Underlying Analgesic Properties of Minor Cannabinoids and Terpenes
Friday, October 23, 2020
Meeting Summary

Welcome From the National Center for Complementary and Integrative Health (NCCIH)

NCCIH Deputy Director Dr. David Shurtleff welcomed the meeting participants, including the large number viewing the meeting on videocast. He explained that much of the meeting will consist of presentations by NCCIH-supported researchers who received their awards a year ago or more recently. In addition, representatives from other parts of the National Institutes of Health (NIH) and other Federal agencies will share information on their involvement in cannabinoid research or regulation.

NCCIH is interested in cannabis and other natural products as they relate to pain. Much research has focused on tetrahydrocannabinol (THC), which has left a gap in the understanding of other cannabinoids and terpenes found in the cannabis plant, some of which are known or expected to have analgesic properties. NCCIH is working to fill this gap.

Meeting Overview and Goals

Dr. Emmeline Edwards, Director of NCCIH's Division of Extramural Research, explained that today's meeting and future annual meetings are designed to develop the community of researchers studying cannabinoids and pain and to foster collaborations. Enhancing pain management through the use of complementary health approaches, including natural products such as cannabinoids, is a key focus of NCCIH's research program.

NCCIH is actively involved in trans-NIH and interagency pain research programs, as well as NIH's ongoing research program on cannabinoids. In December 2018, NCCIH sponsored a workshop on the therapeutic potential of cannabinoids and how to conduct research on them within the current regulatory framework. Much attention is being paid to cannabinoids because of tantalizing leads suggesting that medical cannabis use by pain patients may be associated with a reduction of opioid use; however, more evidence is needed before conclusions can be reached. NCCIH is focused on three priority research areas: the pharmacology of terpenes and minor cannabinoids, potential effects on pain and underlying mechanisms, and special effects of terpenes and minor cannabinoids (such as potential opioid sparing and interactions with the microbiome). NCCIH has reissued its funding opportunity announcement on the analgesic properties of minor cannabinoids and terpenes, which is active until 2022.

Data Blitz Presentations on the Nonclinical Studies Funded by NCCIH Cannabinoids and Pain Funding Opportunity Announcements

Analgesic Efficacy of Single and Combined Minor Cannabinoids and Terpenes
Dr. Sara Jane Ward, Temple University

Dr. Ward explained that previous work in her laboratory showed that THC and cannabidiol (CBD) act synergistically to prevent chemotherapy-induced neuropathic pain in a mouse model. Her current project involves testing other phytocannabinoids and terpenes to determine their interactive effects in

this and other pain models. Preliminary data show that CBD and β-caryophyllene interact additively and, when administered together, can reduce microglial activation. These compounds have effects on microglial morphology at the same doses that provide protective effects in a behavioral assay. Dr. Ward and her colleagues have begun examining the effects of CBD and β-caryophyllene on acute nociception; effects can be detected, but they are very modest in comparison with those of morphine.

Identifying the Mechanisms of Action for CBD on Chronic Arthritis Pain
Dr. Yu-Shin Ding, New York University School of Medicine

Dr. Ding and her colleagues are working to determine the key targets of CBD related to its mechanisms of action on pain treatment in osteoarthritis in preparation for future clinical trials. Their imaging studies in mice are focusing first on 5-HT_{1A} and TVPV1/TSPO as targets. Early experiments have shown that CBD binds to 5-HT_{1A} *in vivo*, both in the brain and in the affected knees of animals with experimentally induced knee osteoarthritis. Decreased 5-HT_{1A} binding was observed after the induction of knee osteoarthritis. This finding is consistent with the idea that 5-HT_{1A} plays a role in the modulation of pain. Preliminary results from behavioral tests suggest gender differences in pain sensitivity and responses.

Synthetic Biology for the Chemogenetic Manipulation of Pain Pathways
Dr. Andrew Ellington, University of Texas at Austin

Dr. Ellington explained that he and his colleagues are working to dissect the molecular biology and biochemistry of potential interactions between cannabinoids and pain pathways using yeast as a model system. They hope to transplant the G-protein coupled receptors (GPCRs) that may be responsible for initiating these signaling pathways in humans into yeast, providing a convenient model system for screening of drugs and alleles. Dr. Ellington and his colleagues have attempted to do this with the cannabinoid receptors CB_1 and CB_2, which could allow for a high-throughput screen for evaluating compounds in yeast and potentially provide a way for yeast to produce compounds including cannabinoids. Attempts to engineer the yeast to be more sensitive to minor cannabinoids have not been successful, so the group is now working to improve the screening system. Dr. Ellington hopes to identify the portions of the receptors that are most active with different compounds and potentially evolve those receptors for new functions.

Mechanistic Studies on Analgesic Effects of Terpene-Enriched Extracts From Hops
Dr. Cassandra Quave, Emory University

Dr. Quave and her co-principal investigator (co-PI), Dr. Isaac Chiu of Harvard Medical School, are studying terpene-enriched extracts from hops *(Humulus lupulus)* rather than cannabis. Dr. Quave explained that hops and cannabis are closely related species with very similar terpene profiles, but hops is not subject to the complex laws that govern cannabis. Several hops varieties have been obtained, and gas chromatography–mass spectrometry has been used to select appropriate varieties for further investigation. The extracts have been formulated as topical preparations for testing in pain models. Dr. Chiu explained that *in vitro* testing is under way to assess whether primary dorsal root ganglion neurons respond to hops extracts, and the topical formulations are being tested in *in vivo* models of inflammatory and neuropathic pain. If signals are seen with specific extracts, efforts will then be made to identify the analgesic components.

Systematic Investigation of Rare Cannabinoids With Pain Receptors
Dr. David Sarlah, University of Illinois

Dr. Sarlah and his colleagues are using synthetic chemistry to make minor cannabinoids, including rare cannabinoids that are not commercially available, and testing them in experimental models of pain and inflammation. Most of these compounds are difficult to isolate from the cannabis plant, but identical molecules, as well as metabolites and analogs, can be created through synthetic chemistry. Dr. Sarlah has begun to test the synthesized minor cannabinoids for anti-inflammatory activity in microglia (the resident immune cells of the central nervous system, which play key roles in acute and chronic neuroinflammation). Preliminary data on 12 compounds show a variety of responses, with one compound greatly outperforming CBD as an anti-inflammatory agent.

Minor Cannabinoids and Terpenes: Preclinical Evaluation as Analgesics
Dr. Jenny Wiley, RTI International

Dr. Wiley explained that her project focuses on screening and evaluating minor cannabinoids and terpenes from the cannabis plant for *in vitro* binding and functional activity, THC-like subjective effects, and analgesic efficacy in rodent models of neuropathic, visceral, and inflammatory pain. The results of *in vitro* binding assays indicate that some structural changes in cannabinoids affect binding to the cannabinoid receptors (CB_1 and CB_2). Shortening the C-3 side chain from five to three carbons did not greatly affect affinity, but receptor-dependent alterations in efficacy were observed. Carboxylic acid forms of cannabinoids showed minimal if any CB_1 or CB_2 affinity and activity.

Mechanism and Optimization of CBD-Mediated Analgesic Effects
Dr. Zhigang He, Boston Children's Hospital/Harvard Medical School

The objective of Dr. He's project is to identify neural mechanisms involved in the *in vivo* actions of minor cannabinoids to optimize their analgesic effects. Dr. He and his colleagues are working to define the cortical and spinal circuit mechanisms underlying CBD's analgesic effects and to determine whether these effects, as seen in a mouse model of neuropathic pain, may be modulated by neural inhibitory changes induced by the neuron-specific chloride extruder KCC2. To date, they have optimized conditions to observe the analgesic effect of CBD and assessed the effects of treatment with CBD and KCC2. The KCC2 activator CLP290 has been shown to enhance the analgesic effects of CBD in the neuropathic pain model. The next steps in the research will involve determining where and how KCC2 and CBD interact.

Q&A:

NCCIH program director Dr. Inna Belfer moderated a Q&A session on the nonclinical studies.

- In response to a question about measurement of hyperalgesia, Dr. Ward explained that the primary behavioral measure she has been using is mechanical sensitivity using Von Frey filaments, in which responses involving movements of the animal's paw are assessed. However, it is important to make sure that responses are not caused by effects on the animal's ability to move the paw. Therefore, other assays are also used. Dr. Ward is also using spontaneous pain measures, including the mouse grimace scale.
- Dr. Sarlah was asked about the additive effects of combined cannabinoids. He said that he had not yet looked at the effects of combinations but will investigate them in the future.

- In response to a question on how the receptor binding studies were performed, Dr. Wiley said that displacement of CP-55940 was examined in isolated human CB_1 and CB_2 receptors.
- In response to a question about sex differences, Dr. Ding said that females appear to be less sensitive to pain at baseline but more sensitive after osteoarthritis induction. Dr. Ward added that some sex differences have been reported in humans in the potency of cannabinoids. Microglia may play a stronger role in immune signaling in male rodents, and T lymphocytes may play a stronger role in females; cannabinoids interact with both.
- Dr. Ellington was asked about CBD receptor genetic variants. He replied that currently he is working with wild type receptors and optimizing their performance for signaling in yeast. Future research may include specific human allelic variants.
- Dr. Quave was asked about the rationale for selecting the terpenes from hops. She explained that at least 10 anti-inflammatory terpenes are shared between cannabis and hops. She is examining how the relative ratios of terpenes in different formulations affect pain in experimental models.
- In response to a question about microglia, Dr. Ward said that most of the available data are from *in vitro* research, and most results indicate that both THC and CBD can reduce microglial activation. However, a few studies indicate that depending on the condition of the microglia, CBD might have complex effects. Her group is looking at microglial morphology as well as activation to try to better understand these effects. The only terpene Dr. Ward has examined to date is β-caryophyllene.
- In response to a question about differences among terpenes, Dr. Quave said that it is too early to say. She hopes to have more data next year.
- In response to a question about the quality of the cannabis extracts tested in these studies, Dr. Craig Hopp, Deputy Director of the NCCIH Division of Extramural Research, said that different investigators are using slightly different products, but all have provided detailed data to characterize the products they are studying. NCCIH has a product integrity policy to ensure that all natural products used in NCCIH-funded studies are well understood. This policy is essential to allow studies to be properly interpreted, compared, and reproduced.
- In response to a question about the training dose for drug discrimination, Dr. Wiley said that the dose is one that has been used in drug discrimination tests for years. The antinociceptive effect of compounds typically occurs at doses higher than those that produce the discriminative stimulus effect. THC is being used as the training drug. The goal is to identify compounds that have analgesic effects without THC-like properties.
- Dr. Ward was asked about interaction studies with THC. She explained that they are not included in her current project, but her group is interested in the topic.
- In response to a question about β-caryophyllene dosage, Dr. Wiley explained that with β-caryophyllene alone, the dose-response curve shows an inverted U shape. Some behavioral responses that may reflect an anxiolytic effect are seen at higher doses of β-caryophyllene.

Data Blitz Presentations on the Clinical Studies Funded by NCCIH Cannabinoids and Pain Funding Opportunity Announcements

Effect of Cannabidiol on Microglial Activation and Central Pain-Sensitization
Dr. Rajiv Radhakrishnan, Yale School of Medicine

Dr. Radhakrishnan is examining the effect of CBD on *in vivo* brain microglial activation (a biological mechanism of chronic pain) and central pain-sensitization (a physiological mechanism of chronic pain) in humans using intradermal capsaicin. CBD may have a role in preventing the transition of acute to chronic pain in humans by reducing central pain sensitization. The primary outcome measures, which have also been used in previous studies of THC or lipopolysaccharides, are the change in [^{11}C]PBR28 V_T in the thalamus and the area of capsaicin-induced hyperalgesia. Data collection is in progress but has been slowed by the COVID-19 pandemic.

Exploring the Mechanisms Underlying the Analgesic Effect of Cannabidiol Using Proton Magnetic Resonance Spectroscopy
Dr. Deborah Yurgelin-Todd, University of Utah

This study was presented by the co-PI, Dr. Perry Renshaw of the University of Utah. The overall aim of the study is to examine the mechanisms by which a CBD-enriched extract impacts brain chemistry in chronic pain by measuring *in vivo* brain metabolites using proton magnetic resonance spectroscopy (^{1}H-MRS). ^{1}H-MRS measures of glutamate, glutamine, and gamma-aminobutyric acid (GABA) are of particular interest because they have been shown to be altered in chronic pain. The study participants, all of whom are chronic pain patients, will receive a CBD-enriched extract for 5 days, with scans performed and blood samples collected at baseline and on day 5. Pain intensity and quality will be assessed prior to and 30 minutes after drug administration. Enrollment was delayed by the pandemic, but restrictions have now been lifted, and the researchers have begun work with study participants. Data should be available next year.

Neuroimmune Mechanisms of Minor Cannabinoids in Inflammatory and Neuropathic Pain
Dr. Judith Hellman, University of California, San Francisco

Dr. Hellman's study is testing the hypothesis that minor cannabinoids modulate inflammation and pain via neuroimmune mechanisms. Effects on activation of neurons, leukocytes, and endothelial cells and dependence on transient receptor potential vanilloid 1 ($TRPV_1$), which is involved in thermal sensation and pain, and cannabinoid receptor 1 (CB_1) are being examined. $TRPV_1$ is activated by various lipids, including some endocannabinoids, and by plant-derived substances such as capsaicin and some minor cannabinoids. The researchers will define the roles of the anti-inflammatory cytokine interleukin 10 (IL-10), $TRPV_1$, and CB_1 in the pain-modulating effects of minor cannabinoids in inflammatory and neuropathic pain models in mice. These studies should deepen the understanding of how minor cannabinoids impact pain and immunity, provide insights into the interactions between the nervous and immune systems, and contribute to the future development of pain therapies based on the minor cannabinoids.

Analgesic and Subjective Effects of Terpenes Administered Alone and in Combination With THC: Potential THC- and Opioid-Sparing Effects of Myrcene and β-Caryophyllene
Dr. Ziva Cooper, University of California, Los Angeles

Dr. Cooper explained that she received her grant just before the COVID-19 pandemic began, and therefore her research has been delayed. There is evidence that β-caryophyllene and myrcene have analgesic effects in mice, and that doses that produce pain relief don't induce cannabis-like behavioral effects. This study will focus on understanding the dose-dependent and THC-sparing effects of these terpenes in healthy participants. The pain-relieving effects of doses of these terpenes found in cannabis

will be examined alone and in combination with THC. Physiological effects and pharmacokinetic interactions will also be examined. The goal is to establish the potential of the terpenes in the treatment of pain.

Cannabinoid Interactions With Central and Peripheral Pain Mechanisms in Osteoarthritis of the Knee
Dr. Richard Harris, University of Michigan

Dr. Harris received his grant in August, so no data from his study are available yet. The goal of the study is to try to perform precision analgesia with cannabinoids by matching patient pathology with the mechanism of action of a specific cannabinoid. Knee osteoarthritis patients have a mixture of pathologies, some involving knee inflammation only and some involving central sensitization or both mechanisms. CBD may target inflammation, while THC may target central sensitization. The study will be a double-blind, randomized clinical trial comparing 14 weeks of treatment with CBD alone, THC alone, CBD and THC together, or a placebo. The primary outcomes are default mode network-to-insula connectivity, a cytokine marker of inflammation, glutamate and GABA in the brain, and changes in pain and physical function. Dr. Harris hopes to launch the study in February 2021.

Q&A:

Dr. Angela Arensdorf, a health science policy analyst at NCCIH, moderated a Q&A session on the clinical studies.

- In response to a question about the MRS profile in pain patients, Dr. Renshaw said that there are quite consistent patterns for people using even minor doses of cannabinoids.
- In response to a question about how terpenes might decrease the abuse liability of THC, Dr. Cooper said that there could be a mechanistic interaction. Also, by administering terpenes in combination with THC, it may be possible to decrease the THC dose to a level too low for abuse while maintaining an analgesic effect.
- Dr. Hellman and Dr. Radhakrishnan were asked about the similarities and differences in their research. Dr. Radhakrishnan said that his group is trying to do translational research, following up on work done in basic science labs and applying mouse data to humans. Dr. Hellman said that her studies are also translational and are complementary to clinical work. Her group is using primary human cells to bring findings from mouse models to humans.
- In response to a question about routes of administration of cannabinoids, Dr. Renshaw said that chocolate pudding has been used to hide the unpleasant taste of CBD extract. Dr. Cooper said that not much is known about the differences in pharmacology between oral and inhaled CBD or minor cannabinoids. Dr. Steven Harte of the University of Michigan (co-PI of Dr. Harris's study) said that vaporized cannabinoids work faster but oral products are easier to standardize.
- In response to a question about the dosing regimen of his study, Dr. Harris said that THC will be given at 5 mg for a week, with an increase to 10 mg if tolerated. CBD will be given at a dose of 75 mg, with an increase to 150 mg if tolerated. The same doses will be used in the group receiving THC and CBD together.
- Dr. Cooper was asked how terpenes may be synergistic with THC. She explained that the effects of terpenes may be decreased by opioid antagonists, but the terpenes don't cause behavioral impairments. Her group will look at opioid modulation and administer naltrexone to investigate the mechanism of the terpenes.

- Several investigators responded to a question about issues involved in obtaining U.S. Food and Drug Administration (FDA) approval of an Investigational New Drug (IND) application. Dr. Cooper explained that the terpenes she is studying have not been investigated in humans before, but commercially available cannabis is known to contain these terpenes. She specified in her IND that she would recruit study participants who had been exposed to the terpenes through prior use of cannabis by inhalation. Dr. Radhakrishnan said that his study of CBD needed an IND, but his study participants did not have prior exposure to cannabinoids. Dr. Renshaw said that obtaining a Schedule I license in a new state proved to be time consuming. Dr. Harris said that in his study, they specifically chose FDA-approved prescription drugs because extensive data on them are available, which might make it easier to obtain an IND. Most study participants were cannabis naïve. Dr. Harte, the co-PI on this study, added that one of the complications in obtaining an IND was making sure the placebo was matched properly to the active drug. Dr. Renshaw said that he was pleased to have been able to obtain approval even though his study involved smoked THC.

Keynote Presentation: Cannabis Research in Canada: Opportunities, Risks, and Lessons Learned
Dr. Mark Ware, Canopy Growth Corporation

Dr. Shurtleff introduced the keynote speaker, Dr. Ware. He explained that Dr. Ware began to evaluate the role of cannabis in pain management in 1999, while on the faculty at McGill University. In his current role as chief medical officer at Canopy Growth, Dr. Ware advises on scientific and ethical aspects of the company's research efforts and is responsible for the company's product safety and pharmacovigilance program, encompassing all research and development and commercial activities.

In his talk, Dr. Ware likened opinions on cannabis to the parable about six blind men examining different parts of an elephant and reaching different conclusions about its true nature. Many different perspectives on cannabis exist. People take strong positions, which lead to heated discussions. In his role as vice chair of the task force on legalization of cannabis in Canada, Dr. Ware reviewed hundreds of submissions that made it evident that cannabis policy affects a remarkable number of stakeholders and that science plays a key role in understanding the different impacts of cannabis.

The Canadian Institutes of Health Research, which is equivalent to the U.S. National Institutes of Health, put together an integrated cannabis research strategy, starting with small, focused opportunities for small-scale studies to stimulate research. The next step was team grants to bring people together to examine different aspects of cannabis, followed by partnership grants in late 2019 to bring in additional stakeholders. Building infrastructure, capacity, and experience working with cannabis is a priority. The research that has been funded includes 34 clinical studies, 7 of which are clinical trials. Many partnerships and collaborations have been established. Studies have just begun, and results are not yet available.

The establishment of focused cannabis research centers at Canadian universities has brought together different aspects of cannabis science. In the United States, some universities are evolving similar pathways and networks.

Health Canada has recognized that sourcing products for cannabis research is a challenge and clarified the requirements. Studies for therapeutic indications are subject to standard drug development

requirements. Nontherapeutic studies and observational studies are subject to different requirements. Useful data can come from many sources, including observational studies of real-world use.

Canada made a specific effort to begin evaluating the impacts of its policy change by collecting baseline data. A national cannabis survey was conducted in 2018 before the law changed, and annual surveys have been conducted since then. The surveys provide an opportunity to track the impacts of cannabis policy change over time on economic outcomes and health. Another opportunity presented by the Canadian framework is the ability to monitor safety. Cannabis producers are required to report adverse events, which provides an additional source of data.

Work is in progress on the possible creation of a category of nonprescription cannabis health products that can make authorized claims to treat minor ailments based on evidence. This would be a third category that is neither a prescription drug nor a food/beverage product. Work is needed to determine the level of evidence that would be required.

Cannabis is an enormous topic of interest around the world, Dr. Ware said. The sharing of information among different groups of stakeholders and different countries will benefit everyone.

Q&A:

Dr. Edwards moderated a Q&A session on the keynote presentation. She began by asking about functional food status for cannabis products. Dr. Ware said that the concept of a functional food implies some type of structure/function claim, and that speaks to the third regulatory pathway that Canada is exploring. If a category of this type is approved, it's likely to be based around CBD products rather than THC, for which greater oversight may be needed.

In response to a question on cannabinoids for pain management, Dr. Ware explained that University of Toronto researchers are looking at the types of products patients are using and characterizing the products in detail to see whether different pain types may respond to different cannabinoid/terpene profiles. In response to a question on field sobriety tests, Dr. Ware said that this is outside his area of expertise, but Canada has had problems with tests that don't work well in below-freezing temperatures. In response to a question about limited pharmacokinetic and pharmacodynamic data on CBD, Dr. Ware said that studies on these aspects of the drug are needed before Phase 1 trials in the drug development pathway can begin. Some work in this area is in progress. Regarding standardization, Dr. Ware said that he is not aware of any effort to standardize cannabis education in the medical school curriculum. Regarding regulation of marketing, Dr. Ware explained that the Canadian framework is quite restrictive in terms of what companies may say or claim in advertising, promotion, and sponsorship.

Dr. Shurtleff asked about challenges in developing cannabis-based drugs in Canada. Dr. Ware explained that some classical drug development work is taking place, but there is also academic interest in doing small studies in different therapeutic areas that will probably never lead to drug development. These studies currently require products that meet drug development requirements. How to navigate this situation is a work in progress.

Dr. Wendy Weber, Chief of the Clinical Research Branch in the NCCIH Division of Extramural Research, asked whether work on Canadian products available in the community is generalizable to the United States. Dr. Ware said that if the science is good, the results should be meaningful in all jurisdictions if the products are available in the same form in another market.

In response to a question on chronobiology research, Dr. Ware said he was not aware of any work on this topic, but it's an important area to investigate because sleep is one of the areas where consumers say cannabis products are helpful. In response to a final question on how he would advise medical graduates interested in cannabis research, Dr. Ware said that the field draws people in very quickly. It's a fascinating area, and there are many unanswered questions.

Panel Discussion on Gaps and Future Directions

In this session, representatives of various NIH components and other Federal agencies briefly summarized their organizations' roles in cannabinoid research or regulation.

Dr. Inna Belfer of NCCIH explained that pain management using complementary health approaches is a key focus of NCCIH's research efforts. Many natural herbs, including the cannabis plant, have been used for pain relief without substantial scientific evidence. NCCIH participates in NIH's ongoing program of cannabinoid research and has initiated its own research program on cannabinoids and pain, which supports research on underlying mechanisms and therapeutic targets for minor cannabinoids and terpenes to advance novel nonaddictive approaches for pain relief. NCCIH's research priorities include studying novel minor cannabinoids and terpenes, targeting novel mechanisms of their analgesic effects, investigating special effects such as interactions with the microbiome and potential opioid-sparing effects, and studying the mechanisms by which cannabinoids and terpenes may impact chronic pain through effects on sleep and circadian regulation. Funding opportunities for research on cannabinoids and pain are currently available.

Dr. Roger Little of the National Institute on Drug Abuse (NIDA) explained that NIDA is interested in supporting cannabinoid research that fits in with the institute's priorities. Work supported by NIDA led to publication of the structures for both the CB1 and CB2 receptors. Research gaps include lipid signaling, for which new tools and methods are needed; interactions of host and microbial metabolites with the endocannabinoid system; and robust platforms to share data and enable interoperability of different data types. NIDA funds a wide range of research on cannabis, THC, and chemicals related to THC. Topics include brain changes associated with cannabis use across the lifespan; routes of exposure; social, behavioral, public health, and safety impacts of policy; and medications for treating people with marijuana use disorders. Many funding opportunities are available.

Dr. Jeffrey White of the National Cancer Institute (NCI) said that NCI's grant portfolio on cannabis and cannabinoids is relatively small and focuses primarily on the epidemiology of cannabis smoking but has included occasional projects on cancer-related pain. A cannabis and cancer research interest group within NCI has been created to identify areas of scientific opportunity and hindrances to progress in various areas of cannabis- and cannabinoid-related cancer research and propose initiatives to address them. One current initiative involves funding 12 NCI-designated cancer centers to survey cancer patient populations about their cannabis use, including therapeutic use. The next step will be a virtual symposium to bring together researchers in the areas of cannabis, cannabinoids, and cancer research in December 2020. NCI hopes to use the information presented to develop a strategic plan for research in this area.

Dr. Qi-Ying Liu of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) explained that NIAAA is interested in cannabinoids as they may relate to alcohol use disorder and to the hyperalgesia and neuropathic pain that may occur during alcohol withdrawal. The effects of alcohol and CBD may be synergistic, and transdermal delivery of CBD may attenuate binge alcohol-induced neurodegeneration. CBD may help reduce several symptoms of alcohol addiction and withdrawal and may help prevent relapse. Research on cannabinoids may fit in with NIAAA's interest in the relationship of pain to alcohol use disorder. NIAAA is also interested in studies of coexposure to alcohol and cannabinoids and the use of cannabinoids to treat alcohol withdrawal or alcohol use disorder.

Dr. Smriti Iyengar of the National Institute of Neurological Disorders and Stroke (NINDS) explained that NINDS provides opportunities for pain therapeutics development through its Early Phase Pain Investigation Clinical Network (EPPIC-NET) and Preclinical Screening Platform for Pain (PSPP). Both programs involve NINDS-directed studies conducted at no cost to participating researchers. In addition, through the NIH HEAL (Helping to End Addiction Long-term^{SM}) Initiative, NINDS supports the development of novel nonopioid, nonaddictive analgesics through grant mechanisms.

Dr. Mi Hillefors of the National Institute of Mental Health (NIMH) said that NIMH has a small cannabinoid research program, with grants in the institute's basic neuroscience and developmental translational portfolios, plus research training and career development awards. At the clinical level, NIMH is interested in research on treating post-traumatic stress disorder and mood disorders, effects of cannabinoids over the lifespan, and long-term side effects of cannabinoid use. NIMH takes an experimental therapeutics approach to clinical trials; rigorous evaluations of an intervention's effect on a hypothesized target are performed first, followed by trials to determine whether the changes produced in the target affect clinical symptoms.

Dr. Dominic Chiapperino of the FDA explained that his agency's policy interest is in protecting the public from harmful products, protecting the public from fraudulent products with unproven disease claims, incentivizing rigorous scientific research to support beneficial therapies, protecting research subjects, and protecting the integrity of the food supply and dietary supplements. In general, cannabis research in human subjects requires an IND. Manufacturers or investigators can make use of Drug Master Files to submit or reference proprietary information. The FDA has botanical drug development guidance, which focuses on quality controls and botanical raw material growing conditions. Although hemp (cannabis low in THC) has been removed from the definition of marijuana in the Controlled Substances Act (CSA), research on hemp is still subject to FDA regulation. New draft drug development guidance specific to cannabis and cannabis-derived compounds was published in July; it focuses on quality considerations for clinical research. Currently, the NIDA Drug Supply Program is the only domestic federally legal source of cannabis with THC content that exceeds the legal limit for hemp. Regardless of the source of cannabis or other botanical products under study, sponsors must meet all FDA requirements to conduct human trials. Many resources for investigators are available on the FDA website.

Dr. Terrence Boos of the Drug Enforcement Administration (DEA) explained that his agency wants to make it possible for researchers to identify early whether they are working with materials regulated under the CSA. The DEA has resources available for researchers who need to become registered as handlers of controlled substances. Email inquiries (to DPE@usdoj.gov) are welcome. The DEA also has staff (reachable at DPEScheduleIResearch@usdoj.gov) who can provide scientific support for researchers.

Mr. Robert Walsh of NIDA discussed the NIDA Drug Supply Program. He explained that NIDA contracts with the University of Mississippi, which grows marijuana for research purposes, and with RTI International, which acts as the distributor. The program can provide marijuana, standardized marijuana cigarettes, and a variety of cannabinoids of different classes. Some, but not all, products are suitable for human use. Requesting materials is more complicated than usual right now because the program cannot accept courier packages due to COVID-19 restrictions. The program does not carry terpenes, but some are available from commercial sources.

Q&A

Dr. Shurtleff moderated the Q&A session for the panelists.

- In response to a question about whether there are any approved sources of hemp other than the NIDA Drug Supply Program, Dr. Chiapperino explained that other sources exist. The FDA cannot promote specific companies. The investigator must locate the source.
- In response to a question about the quality of minor cannabinoids available from the NIDA Drug Supply Program, Mr. Walsh explained that the program currently does not have minor cannabinoids suitable for human use but is looking into how to make such products available.
- Dr. Little was asked whether approving studies of therapeutic use goes against NIDA's mandate to identify harms. He explained that NIDA's primary focus is on understanding the negative aspects of cannabis to be able to treat people with cannabis use disorders, but NIDA would fund research on cannabinoids if there was reason to think they are beneficial for substance use disorders. Many NIH institutes have other interests, including the effects of cannabinoids on pain.
- In response to a question about long-term clinical outcomes in people with cancer, Dr. White explained that NCI is interested in this topic as part of its general research program, and any research that is funded is likely to include mechanistic aspects. When NCI completes its cannabis strategic plan, more specific funding opportunities may become available.
- In response to a question about appropriate resources for clinicians to share with patients, Dr. Belfer suggested that developing such materials may be of interest to NCCIH.
- In response to a question on cannabis/kratom combinations and their possible effect on opioid addiction, Dr. Little said not much is known about kratom. His institute is interested in understanding both the positive and negative effects of its constituents. It is too early to say whether the two substances in combination might have a benefit for any indication related to addiction.
- Dr. Boos was asked to clarify the Schedule I status of minor cannabinoids that have been synthesized. He explained that the DEA intends to provide clarification in the Federal Register as a follow-up to a final rule on hemp. Dr. Boos suggested writing to the DEA with specific questions.
- In response to a question about the balance of research funding between harms and therapeutic use, Dr. Shurtleff said that the path forward involves doing rigorous research to further elucidate the safety and efficacy of cannabinoids for therapeutic use, such as the work supported by NCCIH and other NIH institutes and centers. Dr. Hillefors added that cannabis is of interest from many perspectives and noted that changes in the legal status of cannabis at the

state level have affected recruitment for clinical trials, particularly trials that need to recruit patients who have no prior experience with cannabis.

- In response to a question on whether NIMH is interested in studying the effects of CBD on autism, Dr. Hillefors said yes, and if the mechanisms could be better understood, there might be potential for its use as an intervention.
- In response to a question about edibles, Mr. Walsh said that the NIDA Drug Supply Program does not have them available. Dr. Chiapperino explained that a product for therapeutic use would be regulated as a drug even if it is in the form of a food product. From the points of view of stability, potency, dosing, and consistency, formulating a drug as a food product is difficult, and there would need to be good reasons to go down that path.
- In response to a question about how to find out what products are available from the NIDA Drug Supply Program, Mr. Walsh said to go online to the program's webpage; one link is to the catalog of products.

Ms. Catherine Law, Director of the NCCIH Office of Communications and Public Liaison, and Dr. Belfer adjourned the meeting and thanked the speakers and participants. They urged attendees to contact NIH with specific questions.