

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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The State of the Science on the Therapeutic Potential of Marijuana and Cannabinoids

Testimony before the Senate Judiciary Committee, Subcommittee on Crime and Terrorism

“Researching the Potential Medical Benefits and Risks of Marijuana”

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Chairman Graham, Ranking Member Whitehouse, and Members of the Senate Judiciary Subcommittee on Crime and Terrorism, thank you for inviting the National Institute on Drug Abuse (NIDA), a component of the National Institutes of Health (NIH), to participate in this hearing to review the state of the science on the therapeutic potential of marijuana and its constituent compounds and to discuss ways of facilitating more research in this area.

Background

While marijuana use remains illegal at the federal level, to date 25 States and Washington, D.C. have passed laws allowing marijuana to be used for a variety of medical conditions. An additional 16 States have passed laws that specifically permit the medical use of cannabidiol (CBD), one of approximately 100 cannabinoid chemicals found in the marijuana plant. There is a growing body of research suggesting the potential therapeutic value of cannabinoids in numerous health conditions including pain, nausea, epilepsy, obesity, wasting disease, addiction, autoimmune disorders, and other conditions. However, in general, adequate and well-controlled studies are lacking, which means that patients across the country are using marijuana strains and extracts that have not undergone rigorous clinical trials, are not regulated for consistency or quality, and are used for medical conditions with an insufficient evidence base supporting their effectiveness.

NIH believes that FDA's drug review and approval process represents the best way to ensure that new medicines, including those derived from marijuana, are appropriately evaluated for safety and effectiveness. The Food and Drug Administration (FDA) has approved three medications, Marinol (dronabinol), Cesamet (nabilone), and Syndros (oral drabinol solution), for severe nausea and wasting in patients with HIV and cancer. These medications contain synthetically-derived cannabinoids. Dronabinol is identical in chemical structure to delta-9-tetrahydrocannabinol (THC), the main active ingredient found in the marijuana plant; nabilone is similar in structure to THC.

With Americans across the country consuming marijuana for health related conditions, there is a pressing need for more research in this area. The progress of therapeutics development and clinical trials has been slow, in part due to the increased time, costs, and administrative efforts associated with the regulatory framework for conducting research on these and other Schedule I compounds. NIH is committed to working with Congress and our federal partners to facilitate more research on the therapeutic potential of marijuana and cannabinoids and to reduce barriers to research.

Therapeutic Potential of Marijuana and Constituent Cannabinoids

Cannabinoids exert their effect mainly by interacting with two types of receptors: CB1 and CB2 receptors. CB1 receptors are located mainly on neurons and glial cells in the brain and in several other organs in the body. CB2 receptors are found mainly on immune cells, and are less common in the brain than CB1 receptors.¹ The majority of the research on the therapeutic potential of marijuana has focused on two cannabinoids: THC and CBD. The euphoric effects of marijuana are caused by THC through activation of CB1 receptors. CBD has a very low affinity for these receptors (100-fold less than THC), and when it binds it produces little to no effect. Consequently CBD does not appear to produce euphoria or intoxication. CBD acts on other brain signaling systems (e.g., serotonin receptors), and it is these actions that are thought to be important to its therapeutic effects.²

Beyond the two THC-based medications already approved by the FDA, at least 79 clinical trials have been published exploring the therapeutic effects of marijuana or its constituent cannabinoids.³ These studies have suggested potentially valuable therapeutic effects of marijuana or its components in several areas.

Pain/Spasticity: Nabiximols (trade name Sativex), which contains THC and CBD in equal proportions, has been approved throughout most of Europe and in a number of other countries for the treatment of spasticity and pain associated with multiple sclerosis (MS). Multiple recent studies have confirmed that nabiximols (Sativex) reduced the severity of spasticity in MS patients,⁴ including two studies recently presented at the European Committee for Treatment and Research in Multiple Sclerosis annual meeting.⁵ Sativex has not been approved in the United States, where it is being developed for the treatment of refractory pain in cancer patients; two recent Phase 3 clinical trials did not achieve the expected clinical endpoint.⁶

Two recent reviews, one in the Journal of the American Medical Association³ and another by the American Academy of Neurology⁷ concluded that there is moderate evidence to suggest that some cannabinoids, including nabiximols, may be beneficial for the treatment of chronic neuropathic or cancer pain and spasticity due to MS, and strong evidence for the efficacy of oral cannabis extract for spasticity and pain associated with MS.^{4,8} In contrast, they also concluded that there was insufficient evidence for the use of cannabinoids in the treatment of involuntary movement disorders such as Huntington's disease or Tourette's syndrome.

Pediatric Epilepsy: A number of case studies and anecdotal reports, as well as a few small randomized clinical trials (RCTs), have also suggested that CBD may reduce seizures in children with treatment-resistant epilepsy. GW Pharmaceuticals is currently conducting two placebo-controlled, multicenter Phase III studies examining Epidiolex, a formulation of CBD, for both Dravet syndrome and Lennox-Gastaut syndrome, severe forms of pediatric epilepsy. According to company press releases in March and June 2016, initial results from the first Phase 3 trials of Epidiolex were positive. The first trial showed a median reduction in monthly convulsive seizures of 39 percent among patients with Dravet syndrome who took Epidiolex compared with 13 percent for placebo.⁹ The second trial showed a median reduction in monthly drop seizures of 44 percent among patients with Lennox-Gastaut syndrome who took Epidiolex compared with 22 percent for placebo.⁹ Insys Therapeutics has developed synthetic CBD and Phase 2/3 studies are underway.¹⁰ In May 2016, they reported successful completion of a Phase 1/2 safety and pharmacokinetic (PK) study in pediatric subjects with treatment-resistant epilepsy.¹¹

Post-traumatic Stress Disorder: Human laboratory studies have also suggested that THC administration may help facilitate fear extinction in healthy subjects which could have implications for treating patients with post-traumatic stress disorder (PTSD).¹² RCTs are currently ongoing that will examine the therapeutic value of smoked cannabis and dronabinol for patients with PTSD.

Other Potential Indications (Pending Future Research): There is some preliminary evidence from human trials for a potential therapeutic benefits of cannabinoids for the conditions listed below. Rigorous RCTs are needed because initial promising results are often not confirmed by subsequent more rigorous testing:

- THC for tics in Tourette syndrome¹³
- THC or THC/CBD for sleep disorders¹⁴
- Both CBD and THC in the treatment of substance use disorders including nicotine, cannabis, and opioid addiction^{15,16}
- CBD for anxiety in individuals with social phobia¹⁷
- CBD for psychosis in patients with schizophrenia¹⁸

Beyond these indications, pre-clinical research (including cell culture and animal models) has suggested that marijuana, THC, and/or CBD may have a range of therapeutically useful effects including analgesic, anti-seizure, antioxidant, neuroprotective, anti-inflammatory, anti-tumor, anti-psychotic, and anti-anxiety properties.¹ More research is needed to follow up on these findings to determine if they will translate to therapeutic benefits for human health.

Current NIH Research on Marijuana and Cannabinoids

NIH supports a broad portfolio of research on cannabinoids and the endocannabinoid system. This research portfolio includes some studies utilizing the whole marijuana plant, however most studies focus on individual cannabinoid compounds or other strategies to manipulate the function of the endogenous cannabinoid system. The marijuana plant itself is not considered an ideal medication candidate because:

- It is an unpurified plant containing numerous chemicals that have not been fully characterized;
- The variability of active components makes it difficult to reproduce a consistent dose;
- It is often consumed by smoking, potentially contributing to adverse effects on lung health;
- Its cognitive- and motor-impairing effects may limit its utility.

In FY 2015, NIH supported 281 projects totaling over \$111 million on cannabinoid research. Within this investment, 49 projects (\$21 million) examined the therapeutic properties of cannabinoids, including 15 projects (\$9 million) focused on CBD. Cannabinoid research is supported broadly across 17 NIH Institutes and Centers (ICs), with each IC supporting research specifically focused on the impact of cannabinoids on health conditions within their scientific mission.

Since 2011, there have been 139 clinical trials listed on clinicaltrials.gov studying the therapeutic potential of marijuana, CBD, and/or THC for a range of conditions including 10 NIH-supported trials for:

- Cannabis use disorder;
- Pain;
- Sickle cell anemia;
- Spinal cord injury;
- HIV related symptoms;
- Irritable bowel syndrome.

In March 2016, NIH convened a meeting entitled “Marijuana and Cannabinoids: A Neuroscience Research Summit” which focused on the neurological and psychiatric effects of marijuana, other cannabinoids, and the endocannabinoid system. The goal of the Summit was to ensure evidence-based information is available to inform practice and policy, particularly important at this time given the rapidly shifting landscape regarding the recreational and medicinal use of marijuana. More than 2,000

researchers, policy makers, clinicians, and members of the public attended the Summit, either in person or through the videocast. A summary of the summit can be found at

<http://apps1.seiservices.com/nih/mj/2016/Documents/BriefMJSummitMeetingSummary.pdf>

Facilitating Research on Marijuana and Cannabinoids

The current state of the research on marijuana and its constituent cannabinoids suggests the potential for therapeutic value for a number of conditions; however, more evidence is needed before marijuana or cannabinoid products (beyond those already FDA-approved) are ready for medical use. Promising preclinical findings do not always prove to be clinically relevant, and even fewer lead to new treatments.¹⁹ Moreover, clinical studies of sufficient quality to meet FDA standards for drug approval are currently lacking for most conditions. Among the factors that impact this research are the specific statutory requirements and treaty obligations that govern research on marijuana. NIH is working closely with the Office of National Drug Control Policy (ONDCP), the Drug Enforcement Administration (DEA), and FDA to explore ways to streamline these processes to facilitate research. Outlined below are some of the barriers or perceived barriers that we are attempting to overcome in this regard.

Under the Single Convention on Narcotic Drugs (1961), the United States is subject to several obligations related to the regulation of marijuana cultivation for research.²⁰ In addition, under the Controlled Substances Act (CSA), marijuana and its constituent compounds are classified as Schedule I controlled substances – defined as having high potential for abuse and no currently accepted medical use, and no accepted safety for use under medical supervision.²¹ As a result of these treaty obligations and marijuana’s status under the CSA, (DEA) with input from the Department of Health and Human Services regulates marijuana research and the cultivation of marijuana for research purposes through licensing requirements and by establishing annual aggregate production quotas. While research on marijuana and its constituent compounds is possible, there remains a number of barriers, described below, for doing this research²².

The registration process: Researchers have indicated that this process creates administrative burdens that can act as disincentives to conducting research. To help ease this burden NIDA and the DEA have been communicating directly, with the specific aim of reducing the time to it takes for researchers to get their Schedule I registration.

The Evaluation of constituent compounds: Per the CSA, all of the cannabinoids in marijuana are considered Schedule I compounds. Currently, evidence suggests that CBD does not have abuse liability. FDA has indicated that a human abuse liability study will be necessary to make a final determination on the abuse liability of CBD, which would be factored into the scheduling recommendation. NIH and FDA have committed to conducting this study and are working out the final details now.

Further, starting on December 16, 2015, the DEA Deputy Assistant Administrator, Office of Diversion Control mailed waiver letters to advise clinical researchers handling CBD under a FDA-approved investigational new drug application (IND) that DEA will accept applications from researchers who are currently registered to conduct clinical research with material that contains CBD, within the ranges specified (contain at least 98% of CBD), for a waiver of certain regulatory requirements that apply when the registrant seeks to make certain modifications to the research protocol. Our DEA colleagues tell us that as of July 12, 2016, DEA has received and granted all requested (42) waivers to researchers. DEA has taken approximately 11 days to grant these requests once received.

Single source of marijuana for research purposes: Currently, there is one registration for marijuana cultivation in the US, the University of Mississippi, which, through a contract with NIDA, supports the cultivation and distribution of research grade marijuana for the country. While the NIDA supply of marijuana has diversified to include different strains with varying concentrations of CBD and other cannabinoids of interest to researchers, it is both costly and time consuming to grow, isolate, and/or refine new products that scientists would like to study. NIDA on July 7, 2016 [issued](#) a request for information that is seeking feedback on which specific strains and products are currently of greatest interest to researchers.

Path from use of NIDA-supplied marijuana to market: The University of Mississippi, under the contract with NIDA, currently produces a limited number of marijuana extracts for researchers to use in drug development. Drug developers would need to transition from using NIDA-supplied marijuana products to other sources before FDA approval and market. It may be challenging for a pharmaceutical company to demonstrate equivalency between the marijuana used in the clinical trials and the drug product that will be marketed. While FDA has provided guidance on how this should occur²⁷, the process requires additional time and resources of the developer.

The DEA has been working with NIDA, ONDCP, and the FDA to identify strategies to make marijuana available from other sources, which could both speed the pace of research and afford individual

developers and researchers more options in formulating a marijuana-derived investigational products for eventual marketing.

Addressing these barriers: Multiple agencies (NIH, ONDCP, DEA, and FDA) are working together to find ways to streamline the process to facilitate research while meeting international and legislative obligations under the Single Convention on Narcotic Drugs and the Controlled Substances Act. In addition to actions taken by the Department of Health and Human Services to eliminate the Public Health Services (PHS) committee review for non-federally funded marijuana research,²³ the DEA recently streamlined the administrative process for CBD research to allow researchers to obtain a waiver of the requirement for review of changes to an approved protocol in their DEA research registrations,²⁴ and is attempting to address the marijuana diversity and product development concern by licensing additional manufacturers.

Conclusion

We appreciate the concerns of the Committee and share a mutual interest in supporting the development of safe and effective treatments to improve the health of our citizens while maintaining a commitment to rigorous clinical research. Rigorously conducted randomized trials are needed to confirm preliminary evidence suggesting the potential therapeutic value of cannabinoids for a variety of conditions and symptoms. Additional clinical and basic research is needed to support the development of new medications. NIH will continue to support research towards this end.

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