Senate Caucus on International Narcotics Control

Hearing on
"Cannabidiol: Barriers to Scientific Research and Potential Medical Benefits"

June 24, 2015

Questions for the Record

Senator Dianne Feinstein

Questions for Dr. Nora Volkow, Director, National Institute on Drug Abuse

1. Based on your testimony, NIDA is currently funding the majority of the studies on marijuana. However, as you mentioned, those studies largely focus on the potential harms of marijuana, not its potential medical and therapeutic benefits, which would be researched by the respective Institute or Center related to the medical condition or illness.

    a. *Do NIDA and its components within the National Institutes of Health have adequate resources to support research on cannabidiol?*

Response: As mentioned in my testimony, NIDA's mission is to support research on drug use and addiction. As part of that mission we do support some research on the potential therapeutic value of cannabis and its components specifically for the treatment of substance use disorders and pain. However, research on potential therapeutic benefits of marijuana and its components for other health conditions would be supported by other NIH institutes as it aligns with their various missions. For example, epilepsy is studied by the National Institute of Neurological Disorders and Stroke (NINDS), cancer by the National Cancer Institute (NCI), etc.

Across NIH, research proposals that relate to marijuana and its components compete for limited resources with other proposed grants. There is no specific allocation for research on these compounds. Several NIH institutes, including NCI, NINDS, the National Institute on Aging (NIA), the National Center for Complementary and Integrative Health (NCCIH), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and the National Institute of Child Health and Human Development (NICHD) recently released a funding opportunity announcement encouraging research on the analgesic properties of cannabinoids. However, no funding was set aside for this specific funding announcement.

2. THC levels continue to increase in smoked marijuana and have tripled since the 1990s. It is my understanding that THC is the main psychoactive component of marijuana and that this component is what produces the "high."

    a. *How, if at all, do increasing levels of THC impact cannabidiol that is used as medicine?*

Response: Increasing levels of THC typically result in reduced levels of CBD due to the biochemistry of the cannabinoid synthesis pathway in marijuana. There has been a trend towards

increasing concentrations of THC with stable or decreasing concentrations of CBD in marijuana used recreationally, likely due to selective breeding to increase the euphoric effects. However, other strains of marijuana with higher concentrations of CBD and other cannabinoids are being cultivated by state medical marijuana dispensaries and under the University of Mississippi contract.

More research is needed to determine which cannabinoids may contribute to specific therapeutic effects and to test the efficacy of strains or extracts with varying concentrations of these compounds for specific health conditions.

b. Based on what is currently known, what health consequences are associated with increasing levels of THC? For instance, can higher THC levels lead to higher rates of addiction? Is additional research being conducted to better understand the impacts?

Response: We do not yet fully understand the health impact of the increase in THC levels.

While higher concentrations of THC are associated with increased euphoric effects, there is a point at which ingestion of high concentrations of THC becomes aversive, where people experience disorientation, vomiting, and report an unpleasant subjective experience.[i] Thus, for some users the very high potency forms of THC may discourage use. In addition, there is some evidence that regular marijuana users titrate their intake of marijuana to some degree based on the concentrations of THC, however this may not fully compensate for the higher levels of THC.[i,ii]

A study of drivers in Norway found that blood concentrations of THC have been rising at the same time that THC levels in marijuana have gone up,[iii] so people may be exposing their brains and bodies to greater amounts of THC than in the past. Higher concentrations of THC are also associated with motor impairment and may increase the risk for car accidents. It is also currently unknown how increased levels of THC will impact risk for mental health problems and other long term effects of marijuana.

Also, newly popular methods of smoking or eating THC-rich products including hash oil or wax extracted from the marijuana plant (a practice called "dabbing") may deliver very high levels of THC to the user. The average marijuana extract contains over 50 percent THC, with some samples exceeding 80 percent. In inexperienced users, these high THC levels can lead to adverse health effects, such as acute psychotic symptoms, cyclical vomiting syndrome, stroke, etc., that result in emergency-department visits.[iv]

Research is ongoing to understand the impact of changes in marijuana potencies on use patterns and related health outcomes.

Senator Jeff Sessions

1. On June 22, 2015, the *Journal of the American Medical Association* published a landmark study – the first comprehensive review of medical marijuana research – which found that medical marijuana has not been proven to work for many illnesses for which it has been legalized and that many studies found no conclusive evidence of any benefit. The review evaluated 79 studies involving 6,462 patients. Two Yale psychiatrists writing in the *Journal* observed:

> "Since medical marijuana is not a life-saving intervention, it may be prudent to wait before widely adopting its use until high-quality evidence is available to guide the development of a rational approval process. Perhaps it is time to place the horse back in front of the cart."

   a. Does this study support efforts to move marijuana from Schedule I to Schedule II?
   b. Does this research find any "accepted medical use" for marijuana as would be generally required for a Schedule II drug?
   c. In what other ways do you consider this study significant?

Response to a-c: The meta-analysis referenced[v] is helpful in providing a comprehensive overview of the current state of the research and highlighting gap areas where more research is needed. It found moderate quality evidence supporting the efficacy of cannabinoids in treatment of chronic pain and spasticity associated with multiple sclerosis. It also found some low-quality evidence of therapeutic benefit for marijuana-derived compounds in the treatment of nausea and vomiting due to chemotherapy, wasting due to HIV, sleep disorders, and Tourette syndrome. The question of whether these data are sufficient for drug approval – the standard for "accepted medical use" – is best addressed by FDA. We do note that many state medical-marijuana laws allow the use of cannabis for many other indications for which there is currently little or no clinical evidence.

Congressional efforts to move marijuana from schedule I to schedule II have focused on two separate issues. One is the approval of marijuana-based medications; the second is reducing barriers to research to encourage more clinical trials to address unanswered questions about the potential therapeutic value of marijuana and its components.

The article highlights the need for more research in this area. NIDA believes that streamlining the regulatory processes governing use of marijuana for research proposes could help to accelerate research in this area by reducing administrative and regulatory burden. However, the available evidence is unlikely to lead to rescheduling of the marijuana plant due to the variability in cannabinoid content and the difficulty in achieving reproducible dosing using a botanical product; one of the five criteria for "currently accepted medical use", used for making scheduling recommendations, is that "the drug's chemistry is known and reproducible".

2. At a meeting of the American Epilepsy Society in December 2014, Dr. Kevin Chapman, a neurologist at Children's Hospital Colorado, announced the results of his study, which involved a review of health records of 75 children who took CBD. While 33 percent had their seizures drop by more than half, 44 percent experienced adverse effects, including

increased seizures. Of the 30 patients whose records included the results of brain-wave tests, only three showed improvements. Dr. Chapman concluded: "We don't have enough data at this point to recommend marijuana products for families. It really wasn't the high numbers we were hoping for."

a. To your knowledge, how many peer-reviewed studies have there been showing that CBD is effective at treating seizures or similar ailments?

Response: As I described in my written testimony, there have been only a few small randomized clinical trials reported in the peer-reviewed literature examining the efficacy of CBD as a treatment for epilepsy; the total number of subjects enrolled in these studies was 48. Three of the four studies reported positive results, including decreased frequency of seizures. However, the studies suffered from significant design flaws, including failure to fully quantify baseline seizure frequency, inadequate statistical analysis, and a lack of sufficient detail to adequately evaluate and interpret the findings. Therefore, the currently available information is insufficient to draw firm conclusions regarding the efficacy of CBD as a treatment for epilepsy; a recent Cochrane review[1] concluded, there is a need for "a series of properly designed, high quality, and adequately powered trials." In addition to the human studies described above, there are at least 11 peer-reviewed studies in animals that have shown some level of efficacy when treating seizures with CBD.

Currently GW is conducting two large Phase III clinical trials for CBD in pediatric epilepsy that should provide additional data on the efficacy of CBD for this disorder.

b. Would you agree that early results from studies on CBD, such as the Children's Hospital Colorado study, show that while some children appeared to improve after taking CBD, others did not respond, or even worsened?

Response: Yes; however it is important to consider the caveats of this report. First, this was a parent-reported survey and the scientists who conducted this survey did not provide the CBD nor was the purity or dosing of the CBD verified and administered in a controlled setting. Second, this was not a randomized, placebo controlled study. This is important for two reasons: (1) the lack of randomization, blinding, and placebo control increases the potential for bias in reporting; and (2) it is possible that people with different types of epilepsy may respond differentially to CBD extracts, also potentially skewing some results. Collectively, the caveats of this study further emphasize the need for more scientifically rigorous studies on the safety and efficacy of CBD for the treatment of epilepsy.

c. Does the current evidence regarding CBD's effect on epileptic seizures support moving marijuana from Schedule I to Schedule II?

Response: The standard process for moving a substance from Schedule I to Schedule II is through FDA's drug-approval process. The currently-available evidence is promising but due to

[1] Gloss and Vickrey B. Cannabinoids for epilepsy. Cochrane Database Syst Rev. 3:CD009270. (2014).

the lack of large randomized controlled trials it is unlikely that the current evidence would be sufficient to draw firm conclusions regarding the efficacy of CBD as a treatment for epilepsy. The necessary larger scale randomized clinical trials are ongoing. However, Schedule I drugs are also defined as having high abuse potential. All of the available evidence suggests that CBD is not rewarding or intoxicating; however, the FDA may require additional studies before making a scheduling recommendation. It is important to note that if a specific formulation of CBD (e.g., epidiolex) received drug-approval from FDA, it would lead to a rescheduling of the specific product (epidiolex) to an appropriate level based on its abuse liability. It would not necessarily lead to a rescheduling of the marijuana plant itself or even the CBD molecule. Similarly, dronabinol, the synthetic form of THC was approved by FDA and placed in Schedule III; however other formulations of THC remain in Schedule I.

3. In your June 5, 2014, study published in the *New England Journal of Medicine*, you summarized the adverse health effects of marijuana use, emphasizing the risk of psychosis and the destructive effects on memory, cognition and learning. Please provide the Caucus with a brief summary of those findings for the record.

Response: The review article you reference[vi] highlights research related to the short- and long-term effects of marijuana use. Short-term effects include: (1) impairments in short-term memory, which can make it difficult to learn and to retain information; (2) impaired motor coordination, which can interfere with driving skills and increase risk for injuries; (3) altered judgment, which can lead to increased risk taking including engagement in risky sexual behaviors that facilitate transmission of sexually-transmitted diseases; and (4) paranoia and psychotic reactions that can result from high doses of THC in some individuals.

The long-term, heavy use of marijuana has been shown to be associated with adverse effects including: (1) addiction—approximately nine percent of individuals who use marijuana will develop abuse or dependence, a risk that increases to approximately 15 percent in those who begin in adolescence; (2) altered brain development in individuals who use heavily during adolescence; (3) poor educational outcomes; (4) cognitive impairments including loss of IQ among those who used heavily during adolescence; (5) reduced life satisfaction; (6) chronic bronchitis; and (7) increased risk of psychosis disorders (including schizophrenia) in persons with genetic risk factors.

4. A bill has been introduced in the Senate that would de-schedule CBD and define a "CBD-rich plant" as any part of a cannabis plant that contains less than 0.3 percent THC.

    a. At what concentration does THC cause psychoactive effects?

Response: We do not have sufficient data to establish a firm threshold at which THC causes psychoactive effects.

    b. Would that threshold be lower for children?

Response: We do not have sufficient research on the effects of marijuana with very low concentrations of THC on children to address this question.

c. Is it possible to cultivate a cannabis plant that has both high THC and low THC components, where the plant does not have a uniform concentration of THC?

Response: The marijuana plant does not have uniform concentrations of THC. The highest concentrations are found in the flowering tops, with lower concentrations in the leaves, stalks and seeds.

d. If so, isn't this definition over-inclusive and ineffective at limiting the development of high THC marijuana?

Response: The Administration has not fully evaluated this bill and cannot speak to the scope of its definitions at this time.

5. What is NIDA's role in regulating the cultivation of marijuana in the U.S., and how is that role impacted by the Single Convention on Narcotic Drugs – a treaty signed and ratified by the U.S. in 1961?

Response: Under the Single Convention, participating countries are required to restrict production, manufacture, possession and distribution of marijuana (referred to in the treaty as cannabis) except for medical and scientific purposes. Among other things, the Single Convention requires countries which allow the production of marijuana for research to establish a system of controls under which the national government licenses growers and directly controls the distribution of such marijuana. Historically, the United States has met this treaty obligation through two agencies: DEA and NIDA. DEA issues the licenses (DEA registrations) to growers and controls distribution through their schedule I registration process for researchers; and NIDA controls the distribution of marijuana to approved researchers through a contract with the University of Mississippi. Marijuana produced under this contract is made available to qualified researchers under NIDA's drug-supply program.[vii] There are additional measures of control required by the Single Convention, which the United States meets through implementation of various provisions of the CSA. For example, DEA determines the amount of marijuana that may be produced to meet U.S. research needs in a given year by establishing production quotas.

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[i] Murray and Bevins. Cannabinoid conditioned reward and aversion: behavioral and neural processes. ACS Chem Neurosci. 2010 Mar 10;1(4):265-278.

[ii] Freeman et al. Just say 'know': how do cannabinoid concentrations influence users' estimates of cannabis potency and the amount they roll in joints? Addiction. 2014 Oct;109(10):1686-94.

[iii] Vindenes et al. Has the intake of THC by cannabis users changed over the last decade? Evidence of increased exposure by analysis of blood THC concentrations in impaired drivers. Forensic Sci Int. 2013 Mar 10;226(1-3):197-201.

[iv] Bui et al. Psychiatric and medical management of marijuana intoxication in the emergency department. West J Emerg Med. 2015 May;16(3):414-7.

[v] Hill. Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review. JAMA. 2015;313(24):2474-2483.

[vi] Volkow et al. Adverse Health Effects of Marijuana Use (2014). N Engl J Med 2014; 370:2219-2227

[vii] See http://www.drugabuse.gov/drugs-abuse/marijuana/nidas-role-in-providing-marijuana-research.