

**MARIJUANA AND AMERICA'S HEALTH: QUESTIONS
AND ISSUES FOR POLICY MAKERS**

HEARING

BEFORE THE

**SENATE CAUCUS ON INTERNATIONAL
NARCOTICS CONTROL**

UNITED STATES SENATE

ONE HUNDRED SIXTEENTH CONGRESS

FIRST SESSION

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SENATE CAUCUS ON INTERNATIONAL NARCOTICS CONTROL

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MARIJUANA AND AMERICA'S HEALTH: QUESTIONS AND ISSUES FOR POLICY MAKERS
CAUCUS ON INTERNATIONAL NARCOTICS CONTROL

WEDNESDAY, OCTOBER 23, 2019

U.S. SENATE,
Washington, DC.

The hearing was convened, pursuant to notice, at 3:22 p.m., in 215 Dirksen Senate Office Building. Senator John Cornyn, Chairman, presiding.

Members Present: Senator Dianne Feinstein, Co-Chairman and Senator Jacky Rosen.

The CHAIRMAN. Good afternoon. I would first like to begin this hearing by thanking our witnesses, and thanks to my Co-Chair, Senator Feinstein. We have been looking for a forum to have a hearing like this. As in so many areas, it seems like we are putting the cart ahead of the horse, and we would now really like to hear from the experts about what they can tell us about the public health consequences of marijuana use in the country.

So far this year we have centered our efforts on prevention of addictive substances from entering the country and infiltrating our communities, but now we want to talk about something a little different.

As you know, a 2018 Report by the Substance Abuse and Mental Health Services Administration found that an estimated 43.5 million Americans used marijuana in the last year. The percentage of the population 12 years of age and older currently using marijuana has increased in recent years from under 7 percent in 2010 to more than 10 percent in 2018.

And while marijuana is still a prohibited drug under federal law, more than 90 percent of the states allow for some medical use of marijuana in some capacity, and 10 states and the District of Columbia now allow for the recreational use of marijuana.

Despite growing acceptance and accessibility of this drug and its derivatives, I believe we lack definitive evidence on the short- and long-term health implications of marijuana use. That is especially true for vulnerable populations like adolescents, pregnant women, and people suffering from mental health issues.

Earlier this year, our Surgeon General, one of our witnesses here today, issued an Advisory that highlighted the risks of marijuana use for pregnant and nursing women and adolescents.

I remain concerned about the lack of evidence regarding health risks of these groups, as well as the general population. And it may be helpful at some point for the witnesses to discuss what type of evidence that the medical community considers conclusive, or at

least solid enough to make a policy determination on. Because there seems to be a lot of folk myths and other idiosyncratic ideas that really have not gone through the sort of peer review and published requirements that most scientific evidence has to go through in order to be accepted by policymakers.

In 2017, the National Academy of Sciences, Engineering, and Medicine published one of the most comprehensive studies on the research of the health effects of recreational and therapeutic use of marijuana and cannabis-derived products.

It included nearly a hundred conclusions. They found conclusive or substantial evidence that cannabis or cannaboids, but not necessarily marijuana or marijuana-derived cannaboids, are an effective treatment for chronic pain, chemotherapy-induced nausea and vomiting. However, they found insufficient or no evidence regarding potential therapeutic effects of cannabis or cannaboids for a variety of health conditions considered.

Additionally, they found substantial evidence that marijuana use had increased the risk of motor vehicle crashes, the development of schizophrenia, and other psychoses, and complications in pregnancy like lower birth weight.

It is critical for people like Senator Feinstein and I and other policymakers to understand the public safety implications of increased marijuana use before we dive into the admittedly complex and difficult job of changing federal policy.

In 2018, the Food and Drug Administration approved the first drug with an active ingredient derived from marijuana to treat rare, severe forms of epilepsy. It was only after rigorous studies and a thorough review by the FDA that physicians can have confidence in the safety, efficacy, and consistency of that drug. All this is to say that there are so many questions that still need to be answered.

Surgeon General, Dr. Volkow, and the experts on our second panel will help shed light on what science tells us about the public health risks of marijuana and what we still need to learn.

I look forward to hearing the testimony and discussing how we can work to prevent youth access to marijuana, and properly evaluate the safety and efficacy of any therapies that may utilize marijuana and cannabinoids.

Let me now turn the floor over to my Co-Chairman, Senator Feinstein, for any opening remarks she would care to make.

Co-Chairman FEINSTEIN. Thanks very much, Mr. Chairman. As you know, I enjoy very much working with you, so this is a pleasure.

The point of today's hearing is to better understand marijuana's impact on public health, and so I thank you very much for holding it.

One thing I have learned is that marijuana is much more complex than I thought. It apparently contains hundreds of different compounds, all of which produce different effects. I am told that much of what we know about marijuana is anecdotal, which of course is problematic for us in terms of making policy. It is problematic for medical professionals in knowing how to treat it. And it is problematic for consumers when they use it.

I am told this is due in part to the fact that marijuana's status as a Schedule One Drug makes it difficult to research. It is my belief that science should inform our policy, and that is why I, along with Senator Grassley and others, introduced the Cannabidiol and Marijuana Research Expansion Act which would remove barriers to research.

The NIH recently increased the number of grants awarded to study marijuana, and I hope it will continue to do so. This will enable marijuana's potential therapeutic benefits really to be more understood as they are explored.

It is important that we learn more about appropriate dosing and delivery mechanisms. It is important that we learn how marijuana components interact with other medications, how long-term use impacts the body. It is my understanding that the limited existing research has found varying degrees of evidence that components of marijuana may effectively treat conditions like intractable epilepsy, chemotherapy-induced nausea. I know that for a fact from family issues. And, vomiting. Muscle spasticity, chronic pain, and short-term sleep disturbances.

The Food and Drug Administration has approved four marijuana-derived drugs to treat many of these illnesses. Despite the potential benefits, it is equally important to understand its adverse effects.

For instance, studies show that marijuana can have a negative impact on the developing brain—this is one thing I hope to hear a little more about—including decreased cognitive abilities, loss of IQ, and increased risk of psychosis.

I am going to end here, Mr. Chairman, in the interests of seeing—of listening to our panel, and I will put my remarks in the record. Thank you.

The CHAIRMAN. Thank you, Senator.

Our first witness is Vice Admiral Jerome Adams who serves as the 20th Surgeon General of the United States. During his tenure as Surgeon General, Dr. Adams has created several initiatives to tackle our Nation's most pressing health issues, including the opioid epidemic, oral health and the links between community health and both economic prosperity and national security.

The Surgeon General issued an Advisory in August of this year on the potential health effects of marijuana use for adolescent brain development and use by pregnant mothers.

Our second witness on the first panel is Dr. Nora Volkow, who has served as Director of the National Institute of Drug Abuse, or NIDA, since May 2003. That is quite a run. As a research psychiatrist and scientist, Dr. Volkow pioneered the use of brain imaging to investigate the toxic effects and addictive properties of abusable drugs.

If I could ask each of you to limit your opening statement to about five minutes, and then we will make your complete statement part of the record, and then we can engage in some questions and answers, that would be great.

So let me turn to you, Dr. Adams, to start, please.

**STATEMENT OF JEROME ADAMS, M.D., SURGEON GENERAL OF
THE UNITED STATES**

Dr. ADAMS. Thank you very much, Chairman Cornyn, Co-Chairwoman Feinstein, and members of the Caucus. I appreciate the opportunity to share my recent marijuana advisory with you and to join national experts to discuss a complex issue that I feel demands our attention and our action.

As you mentioned, in August 2019 I issued a Surgeon General's Advisory on Marijuana Use in the Developing Brain, emphasizing the importance of protecting our Nation from the health risks of marijuana use in adolescence and during pregnancy.

I did this in response to alarming rates of marijuana use among pregnant women and young people, widespread and growing access to increasingly potent marijuana through legalization at the state level, and mounting evidence that marijuana use poses a risk to healthy brain development and to public health.

As Surgeon General I have visited with communities and clinicians in places like California and Colorado, Georgia and Texas, Nevada and Oklahoma. And as a former state health commissioner myself, I have spoken with health department leaders across the country, my friends, many of them reluctant overseers of an enormous and poorly informed national public health experiment.

Over and over I hear great and escalating concern about the rapid normalization of marijuana use, and the impact that a false perception of its safety is having on our communities, and specifically our young people and our moms-to-be.

As you mentioned, sir, as of today 33 states and the District of Columbia have legalized marijuana in some way. I will say it again: We are conducting a massive public health experiment on our citizenry. And with greater legalization, young people are reporting a decline in perceived harmfulness of the drug. In 2018, only a third of adolescents said they thought weekly marijuana use was harmful.

Marijuana is now the third most commonly used illicit substance in adolescents, behind alcohol and e-cigarettes. Last year, over 9 million 12- to 25-year-olds reported marijuana use, and each day 3,700 adolescents become new marijuana users.

Unfortunately, the scary truth is that while the perceived harm of marijuana is decreasing, the potential for harm is actually increasing due to widespread access, increased potency, and multiple forms.

Marijuana is now everywhere, especially in states that have legalized. And it can be smoked, drunk, eaten, and baked. As I like to say, this ain't your mama's marijuana. Not enough people know that today's marijuana is far more potent than in days passed. The amount of THC has increased three-fold in commonly cultivated plants over the last few decades, and dispensary products are often much stronger. Edible oils and waxes can deliver unpredictable concentrations of THC often of 70 percent or more. This is important because the higher the THC concentration, the higher the risk to our young people.

Across the country we have seen increased emergency department visits for psychosis and for nonfatal overdose. The earlier and

more often a person uses marijuana, especially at these higher THC levels, the greater the peril.

Nearly one in five people who begin marijuana usage during adolescence will become addicted. Yes, you can become addicted to marijuana.

Science tells us frequent marijuana usage during adolescence can impair a child's attention, memory, and decisionmaking, and young people who regularly use marijuana are more likely to show a decline in IQ in school performance, are more likely to drop out, and are even more likely to attempt suicide.

In pregnant women, marijuana is actually the most commonly used illicit substance. Between 2002 and 2017, marijuana use among pregnant women doubled. Marijuana usage during pregnancy can not only affect the baby's brain, but also can result in lower birth weight, a marker for early death and disability. And that is why that is so important.

The Colorado PRAM study revealed a 50 percent increase in low birth weight in marijuana-using moms. THC is transmitted via breast milk, meaning the risk continues even after delivery.

And finally, marijuana and tobacco smoke share some of the same harmful components, so no one should smoke either product around the baby.

We already know a lot about the harms and potential harms of marijuana use on the developing brain, but I will be the first to admit we need to know more. We need to better understand the long-term health consequences of prenatal and youth exposure to marijuana, as well as strategies to decrease harms.

But I want you to hear me say this: We know enough now to deliver sound guidance to protect the future of our Nation's youth. My Advisory includes resources to help parents, teachers, clinicians, and others safeguard our youth from harm, but it will take all of us using the best evidence and communicating it clearly to ensure a healthy future for our young people.

This Advisory was carefully written based on the best currently available science, with input from NIDA, SAMPHSA, CDC, FDA, ACOG, AAP, and others. So please go to surgeongeneral.gov and share it.

I will finish by saying my bottom line to you today is this: No amount of marijuana use during pregnancy or adolescence is known to be safe. Therefore, communities must consider and should not minimize the short- and long-term public health impacts of marijuana use.

Thank you again for the opportunity to share this important information, and for your support in promoting healthy fetal and adolescent development to protect the youth of America. And I look forward to your questions.

The CHAIRMAN. Thank you, Doctor. Dr. Volkow.

STATEMENT OF NORA VOLKOW, Ph.D., DIRECTOR, NATIONAL INSTITUTE OF DRUG ABUSE, NORTH BETHESDA, MARYLAND

Dr. VOLKOW. Good afternoon. Thanks very much for having me here, Chairman Cornyn and Co-Chairman Feinstein, and for holding this hearing on marijuana.

It is an opportunity for us to bring to you what we are funding at the National Institute on Drug Abuse and what type of research we are funding to try to clarify the effects of marijuana in the young brain.

As you mentioned, in 2018 there were 43.5 million people who reported use of marijuana in the past year, making it the most commonly used illicit drug in the United States, and its use is increasing.

Marijuana exerts its effects by activating cannabinoid receptors which are part of our endogenous cannabinoid system that modulates multiple physiological processes in our brains and bodies. This system emerges early in gestation when it plays a critical role in helping to orchestrate brain development, which is why exposure to marijuana during early development can impact the function of the brain later in life.

THC, the component of marijuana responsible for its intoxicating and addictive effects, freely crosses the placenta. Fetal exposure is associated with significant negative outcomes, including fetal growth restriction, lower birth weight, and preterm delivery.

Research is ongoing to clarify the mechanisms through which it contributes to these effects, and to investigate the effects of marijuana to the fetal brain when used by itself or when combined with teratogenic drugs such as alcohol and nicotine.

Adolescents, whose brains are also undergoing major developmental changes, are also particularly vulnerable to the negative effects of marijuana. Clinical studies of THC exposure during adolescence have shown greater sequence sensitivity to the rewarding effects of other drugs, which could be one reason why dosages of marijuana at a young age are more vulnerable to addiction later in life, not just to marijuana but to also to other drugs.

Epidemiological studies have found repeatedly that kids who regularly consume marijuana have lower academic achievements and a higher risk of dropping out school. Brain imaging studies have shown that frequent marijuana use during adolescents is associated with structural and functional changes in areas of the brain necessary for attention, memory, emotions, and motivation, which might account for the adverse cognitive and behavioral effects associated with youth marijuana use.

The association between marijuana use and mental illness is another area of major concern, particularly in light of the higher content of THC in today's marijuana. Serious mental illnesses and suicide are on the rise in our country. And while multiple factors are likely contributing to this rise, it is imperative to understand if exposure to high potency cannabis in adolescence is one of them.

High potency marijuana can trigger acute psychotic episodes, which is one of the main causes for emergency department visits associated with cannabis use, which are also rising.

While most of these episodes are short lasting, they can become chronic. Multiple studies, though not all, have associated adolescent marijuana use with an overall risk for the early onset of chronic psychosis such as schizophrenia.

Adolescent marijuana use is also associated with increased risk of suicidal behavior. Many of the studies done to assess the effects of adolescent marijuana use have been criticized because of certain

limitations. For example, some of them may have not controlled for other factors that affect adolescent brain development. Some may have had insufficient sample sizes. Most of them were conducted at the time when THC content in marijuana was much lower.

To address this shortcoming, NIDA is leading two major studies. Study one is the Adolescent Brain Cognitive Development, or ABCD study, which is the largest long-term study of brain development in child health in the United States. The study has recruited over 11,000 children, aged 9 to 10, who will be followed into early adulthood to investigate how the brain develops, and how its development is affected by substance use, including marijuana.

The other one, which complements the ABCD study, is A Healthy Brain Child Development, or HBCD study, which is part of the NIH initiative and is currently in its pilot phase. This study would establish a large cohort of pregnant women and their infants to assess the child's brain cognitive and emotional development longitudinally over the course of the first 10 years of their lives. Findings will help researchers develop standards for normal brain development in childhood and to characterize the long-term impact of prenatal and postnatal drug exposures.

Ensuring normal brain development is fundamental for achieving a person's full potential, which is why we owe it to the future generations to protect them from the potentially disruptive effects of cannabinoids to their brains and well being.

Thank you very much, and I look forward to your questions.

The CHAIRMAN. Thank you very much, both of you.

I am struck, Dr. Adams, by your description as a poorly informed national health experiment with regard to marijuana. And of course part of what we are trying to do today is have a better informed discussion about this national health experiment.

I see some parallels, perhaps—and I would be interested in your commentary on this—to what we learned about tobacco decades in the past. I even went back, with my staff's help, and found some advertisements by the tobacco industry where they would tout the health benefits of smoking. And not only were those not proven using the sort of peer-reviewed evidence, scholarship that we would expect, but there was not disclosure of the negative, the detriment to health—things like addiction to nicotine, lung cancer, cardiovascular disease, and the like.

And I feel like there are some parallels, perhaps, here in the way we are wading into this debate. Do you think that is analogous, Dr. Adams, and Dr. Volkow? Or is it different?

Dr. ADAMS. Well, sir, thank you for saying that. Because as the Surgeon General, I want every policy decision to have as much science infused into it as possible. And you are correct.

We have seen this play before. We have seen it with a number of substances. Once upon a time, cocaine was thought to be an effective medicine and harmless. Once upon a time, opioids were thought to be good for whatever ails you, and to not have any harmful effects and no higher dosage limit.

And not that I am in any way, shape, or form comparing marijuana to those substances, but from a policy point of view I think the lesson we should have learned was that we have to make sure the science is leading the policy, and that the tail is not wagging

the dog. And many of the indications that people are using marijuana for are unproven. We are overstating the benefits and, in my opinion, we are downplaying the risks. And that is why I put out my Advisory, because one risk we cannot afford to ignore is the risk to our pregnant women and our young people, our Nation's future.

The CHAIRMAN. Dr. Volkow.

Dr. VOLKOW. Yes, I will completely agree, and I do want to state also the other aspect that we are learning with the use of marijuana at very high content, is we are finding out medical negative effects that we did not know existed. For example, a perfect example is the iferamesic syndrome where people that take high content THC chronically develop a syndrome where they cannot stop vomiting, with very, very intense abdominal pain.

This was not described until 2006. And again, we have never seen it because we did not get exposed to this type of marijuana. So my concern relates to the fact that if we are not looking at something, particularly as we for example are discussing the use of marijuana in pregnancy, if we do not evaluate the outcome in these infants, we will not be able to understand what could be potentially very negative effects.

And that is illustrated also with tobacco. In nicotine we did not know that smoking during pregnancy could have such negative effects until we studied it.

Dr. ADAMS. And I am so glad you have someone on the second panel who is an expert on MVAs. There is this big misbelief out there that marijuana makes you a better driver, but the Colorado data shows us that MVAs went up, fatal MVAs went up in Colorado involving marijuana usage.

And again going back to young people, I have got a teenager who is about to drive. The chips are already stacked against him. And we know that, just statistically speaking. The last thing we want is for these young people to think that marijuana use is safe or, Heaven forbid, that it actually will make them a better and more relaxed driver and lose even more of our teenagers on the roads now than what we already are.

The CHAIRMAN. I know much of your testimony so far has focused on adolescents, pregnant women, and people with other conditions that would maybe make them more vulnerable, but are you suggesting, by inference, that marijuana consumption for a consenting adult who is otherwise healthy is harm-free?

Dr. ADAMS. Well, as Surgeon General of the United States, the first thing I would say is absolutely not. There are plenty of substances out there which adults can partake of that are not only not harm-free, but which my office has a long history of trying to rein the horse back in on.

You mentioned tobacco. Alcohol is one of the top killers of folks in our country. I think that again we need to learn from our mistakes and be careful about normalization of behavior.

One of the other dangers about marijuana usage is that we do not know what we do not know. And so we do not want to conduct this experiment on our citizenry. And that is adults and young people. But we know enough about young people to take action now,

and that is why I focused my efforts and my attention in that space at this point in time.

But again, sir, I do not want anyone to mistake what I am saying as implying that these products are considered safe for general adult usage.

The CHAIRMAN. Let me ask you about the research, because you have both referred to studies that have been done. Are there impediments, legal or otherwise, to the study of the health effects of marijuana in place?

Dr. ADAMS. I will start off just by saying that Secretary Azar, the President, and I, have all stated publicly we need to make it easier to do research.

The CHAIRMAN. What do we need to do to make that happen?

Dr. ADAMS. Well, HHS is partnering with DEA. We are going around the country and talking to folks to find out barriers that exist to research. One of the things that has been announced within the past month was DEA making more strains of marijuana available so that folks can test more than just the—from the one facility in Mississippi, where you could typically get strains from.

But Dr. Volkow is an expert in this area, and NIDA is intimately involved in the research process. So I would turn it over to her.

Dr. VOLKOW. Part of the problem relies on the fact that marijuana is a Schedule One. And if you want to do research on a Schedule One, you have to get a DEA registration that can take, if you are lucky, one year to obtain, and that delays the process enormously.

And every time that you make a change in your protocol, that also has to be submitted, and you have to wait for that to be approved. So it is a very lengthy, on the ability to get the research going. And then once you are going, right now the only source for marijuana that is available in our country is that that we provide through a contract to Missouri to a farm in Missouri.

So if you as a researcher are interested in a particular strain of marijuana, you come to us at NIDA, it is probably unlikely that we have it and we will have to cultivate it. So the process also is very slow there.

And finally, to the other component that makes it very difficult is that we are interested in understanding what people are taking out there. I mean, in the states they are legalizing marijuana and there are these dispensaries. And the varieties are very distinct.

And so we do not know the difference between this or that. This product is being sold telling that it has this characteristic. We cannot fund research that relates to products that are actually being bought through these dispensaries because it is illegal.

So we have been working for the past, I would say, several years with DEA to try to come up with an accommodation that would allow researchers to streamline the process so that they can work on an understanding both potentially negative but also potentially therapeutic effects of cannabinoids.

The CHAIRMAN. Well I know Senator Feinstein mentioned some legislation that she is working on with Senator Grassley on the impediments to research, but that is perhaps something that we could work on together.

Co-Chairman FEINSTEIN. Great. I would love it. Thank you.

Dr. ADAMS. Can I give a shout-out to Senator Feinstein? I am not allowed—

The CHAIRMAN. Absolutely.

Dr. ADAMS. I am not allowed to endorse or comment on pending legislation, but I was doing my homework. And you and Senator Grassley made a statement in the introduction of your legislation. You said medical treatment should be based on sound science, and for those who are sick that there are safe medications that have been proven effective.

I could not agree with that more. And I think it is very important that folks such as yourself are acknowledging that and spreading that word.

Co-Chairman FEINSTEIN. Thank you.

The CHAIRMAN. Senator Feinstein.

Co-Chairman FEINSTEIN. Thanks very much, Mr. Chairman.

And thank you—[coughing], excuse me, I have a little throat problem.

Dr. ADAMS. I am a doctor. I can help you with that. [Laughter.]

Co-Chairman FEINSTEIN. I may come to you.

As I understand, investigations are ongoing. To date, nearly 1,500 lung injuries have been associated with the use of e-cigarettes and vaping products, with 33 confirmed deaths.

THC has been present in most of the tested samples of these cases. Here is the question: Do we have enough research to understand the potential impacts of using e-cigarettes and vaping devices to consume marijuana products? What is the situation? And what happens to the lung when you use it?

Dr. ADAMS. Thank you for that question. This is something I am terribly concerned about, and that HHS is really mounting an all-hands-on-deck response to.

We have stood up our Emergency Operations Center at CDC. We are working with state and local health departments to get information in as quickly as possible. And you summarized it correctly, ma'am. A large number of these cases have been associated with vaping THC, particularly THC that has been obtained through the black market, if you will.

Co-Chairman FEINSTEIN. Explain what happens when you do this.

Dr. ADAMS. Ma'am, well as an anesthesiologist I can tell you, God did not mean for much of anything besides oxygen to go into your lungs. And when you aerosolize oil and then suck it into your lungs and let it re-accumulate on the lining of your lungs, it can cause all sorts of bad things to happen.

And I will also tell you, one of the big problems is we do not know what is in these pods. A lot of them are made on the black market, and the ones that are even made through, quote, "legitimate sources" we do not know all that is contained in them. And it is why last December I put out a Surgeon General's Advisory warning about the epidemic rise in vaping among young people, a 78 percent increase in vaping among students. And I pointed out at the time that a third of young people who were vaping had reported vaping marijuana.

So I would say to you, before I turn it over to Dr. Volkow that, number one, the FDA and the CDC advised against vaping products containing THC.

Number two, we advised not to modify or add any substances such as THC or other oils to products purchased in stores.

And finally, no amount of marijuana usage during pregnancy or adolescence, no matter how it enters the body, is known to be safe. And no pregnant woman or young person should be vaping.

Dr. Volkow?

Co-Chairman FEINSTEIN. Could I ask you a question? Have autopsies been done on the lungs of the 33 confirmed deaths? Do we know what happens to the lungs?

Dr. ADAMS. Ma'am, what I would say is that—and again, I used to run a state department of health in Indiana. And one of the challenges is that these investigations start at a local level, and a lot of times the decisions about which samples are going to be collected, and which autopsies are going to be done are made before the state department of health is even alerted.

And then the CDC finds out after that. So one of the big things that we are trying to help people understand is that we have to have a high index of suspicion. We have got to ask the right questions. And we should be doing an autopsy on all of these cases.

Co-Chairman FEINSTEIN. So autopsies have not been done?

Dr. ADAMS. On some of them, but not all of them, ma'am.

Co-Chairman FEINSTEIN. On some of them?

Dr. ADAMS. Yes.

Co-Chairman FEINSTEIN. Well what has been learned from the autopsies? What happens to the lungs?

Dr. ADAMS. We know that there is damage to the cells of the lungs, to the tissues of the lungs. There is a lot of misinformation out there. Some of these cases had been reported to be associated with Vitamin E, and that was the case for some but it actually looks—it is an inflammatory injury. It is almost—I am trying to think of a good comparison—but again, it is as if a cell—

Co-Chairman FEINSTEIN. Enough to cause death?

Dr. ADAMS. Oh, absolutely, ma'am. Lymphoid pneumonia has been found in some of these folks. But in other folks, it is as if the cells and the tissue were being eaten away. Again, you are putting toxic materials into the lungs that were never meant to be inhaled.

Dr. Volkow.

Dr. VOLKOW. Yeah, just basically in medical school they teach you that you should never, ever allow lipids to get into the lungs because they produce a very massive inflammatory reaction. So that's—and since you require the lungs to function properly for oxygen to be transferred, this is probably one of the reasons why it has had such negative effects.

But I think it is also highlighting how we are approving these technologies in ways without recognizing what their negative effects are. And you are highlighting the acute effects. But, for example, we do not know what may be the effects on the function of the lung long term in those cases that you do not see this acute presentation.

Co-Chairman FEINSTEIN. Well let me ask this question. Are vaping devices well enough known? Do they bring on death—

Dr. VOLKOW. Well, that—

Co-Chairman FEINSTEIN [continuing]. As it goes into the lungs? If you use—I do not know how to ask this question. If you use a vaping device, are you more apt to die?

Dr. VOLKOW. Not necessarily. You are using a device that has quality control. And, for example, one of the things that we have done at NIDA is to develop a standard electronic cigarette that can be used to determine whether, for people that cannot stop smoking, that use of these vaping devices can help them actually be able to protect them from the negative effects of combustible tobacco.

So provided that you have standards of quality control, both the device as well as the cartridges that you are using and the content of nicotine and the products, this device could be given as a therapeutic option for those that cannot stop smoking.

Dr. ADAMS. And can I answer that question in another way, ma'am?

Co-Chairman FEINSTEIN. Yes.

Dr. ADAMS. Even the people who are advocates for e-cigarettes and vaping devices describe them as “harm reduction.” Less harm does not mean harmless. No young person, no pregnant woman, no person who is not currently smoking, should even entertain using these devices. Because, again, you are taking substances that are in an unknown pod, and you are vaporizing them and taking them back into the lungs. And whether that is marijuana, or anything else out there, again we do not know what we do not know. But we know that those substances were never intended to go into your lungs, and they can be toxic.

Co-Chairman FEINSTEIN. Yes. I have particular concern about marijuana use by very young children. And the fact that—reports have shown that it results in a decline in IQ, in poor school performance, and higher rates of school absences.

How prevalent is this?

Dr. ADAMS. Let me take that at the 30,000-foot level, and then kick it to Dr. Volkow. It is important for us to understand, and a lot of folks say, well, I have smoked a joint, or I smoked marijuana back in the '80s, back in the '70s. The potency is much, much higher. A higher THC content equals more danger.

Number two, not everyone is going to have the same effect. Every person is different. And so some people—as we know, some people smoke for five years and get lung cancer, and some people smoke for 50 years and do not get lung cancer.

But if you are talking about a child, you want to give that child—I have three young kids—the best chance at life.

Co-Chairman FEINSTEIN. Yes.

Dr. ADAMS. And we know that on a population level that the cumulative effects of having an entire population, 9 million young people using marijuana products is going to be a net negative for our country.

But do you want to get into specifics, Dr. Volkow?

Dr. VOLKOW. Yeah, I will just point out, I mean it is not surprising in a way because this endogenous cannabinoid system, one of the things that it does, it modulates the activation of neuronal networks. So when you are hyper-stimulated, it brings it down. When you are hyper-inhibited, it brings it up to create that certain

window of optimal function. So if you are taking marijuana, in a way you are filtering many of those stimuli. And your development is dependent on those stimuli to actually create the final architecture.

Co-Chairman FEINSTEIN. How does marijuana impact school performance? What does it do to the brain?

Dr. VOLKOW. The simplest one, it interferes with memory and learning. Someone that is stoned cannot remember. And that is not just adolescents, that is any adult.

Co-Chairman FEINSTEIN. I did not know that.

Dr. VOLKOW. And as a result of that, if you are a student and your job is to learn, and marijuana stays in the body for a long time, you are going to have a long-lasting effect in your capacity to memorize and you will fail school.

And that is without addressing the possibility that—

Co-Chairman FEINSTEIN. Is the memory loss permanent?

Dr. VOLKOW. That is a question that there is controversy. There is some evidence that there is long-lasting impairment in memory and attention by some studies, and others show that after several months it recovers.

And we don't—that is one of the reasons why we are doing the ABCD study, to actually, unequivocally determine if long-term use of marijuana will produce a long-lasting or irreversible change in memory, attention, and other process of cognition.

Co-Chairman FEINSTEIN. Wow. Is it because marijuana today is stronger, the THC factor?

Dr. VOLKOW. That is not going to help at all. The content is much, much higher. And the higher the content—it is actually three-fold higher overall, and—

Co-Chairman FEINSTEIN. Wait, wait, wait. I am not trying to—three times higher than when?

Dr. VOLKOW. Than 2002.

Co-Chairman FEINSTEIN. Really?

Dr. VOLKOW. Yes.

Dr. ADAMS. Ma'am, there was a study that looked at marijuana from 1995 till 2014, and they saw that marijuana in 1995 the average strains were about 4.5 percent THC. The average strains in 2014 were about 12 percent. So that is where we get the three times number. But it is important to remember now that dispensaries have marijuana that is testing at about 20, 25 percent. So that would be five times stronger than 1995.

And then when you put it into oils and waxes, you can get 70, 80, 90 percent THC. So I hate comparisons, but something that I say to folks that tends to resonate is, that is like the difference between having a light beer in 1995 and drinking a pint of vodka today. It is literally that much of a difference in concentration.

Co-Chairman FEINSTEIN. I do not think people know that.

Dr. ADAMS. I do not think they do either, ma'am.

Co-Chairman FEINSTEIN. How do we get that out?

Dr. ADAMS. Well, again, the Surgeon General Advisory. We need you all to help share it at surgeongeneral.gov. Please let people know this ain't your mother's marijuana.

Dr. VOLKOW. And the other problem that is confounded is that when you go and buy a product, you do not actually know what the

content of 9 THC is. And this particularly becomes problematic when you get an edible. You get the chocolate and you do not know the content, and so you do not know how much to take of it.

And one of the reasons why people end up in emergency room admission with a psychotic episode is because the content is so high.

Co-Chairman FEINSTEIN. Well, now how big a problem is this?

Dr. VOLKOW. In terms of emergency department—

Co-Chairman FEINSTEIN. No, the high content of hallucinogenic quality in marijuana today versus 10—excuse me, 10, 15 years ago?

Dr. VOLKOW. It is very problematic. And studies have consistently shown, for example, that investigate the negative effects of marijuana that the higher the content of 9-THC the greater the likelihood that you will have a psychotic episode. The greater the likelihood, actually, the risks associated with schizophrenia—

Co-Chairman FEINSTEIN. Which changes the nature of beliefs about marijuana. Because most people that I know believe it is relatively harmless. And what you are saying is, it is not today; that it is much stronger, and that it is much more volatile.

Dr. ADAMS. Exactly. And Dr. Volkow is an expert and speaks on the effects on the individual, and she has, again, spoken of her wonderful brain imaging studies. I tend to look at the population level. And the metrics we look at are motor vehicle accidents going up. Emergency department admissions going up.

Co-Chairman FEINSTEIN. For marijuana use? You can prove that?

Dr. ADAMS. Yes, ma'am. The emergency department admissions have gone up for accidental ingestions and for people showing up with psychosis. We are seeing all sorts of untoward effects from marijuana usage, again particularly in young people. But real concerning population health trends related to marijuana usage.

Co-Chairman FEINSTEIN. Could you provide us with some information? We may want to put out a paper as a result of this, and that might be one of the things that we would discuss.

The CHAIRMAN. Well I know that has been one of the functions of this Caucus in the past, is to issue reports or papers on different topics, and certainly that is something we ought to consider doing.

Co-Chairman FEINSTEIN. Because I have young people in my family and, you know, you think it is all nothing. Hopefully they do not use it, but they sure can talk about it. So I think if I am understanding what you are saying, the potential danger of marijuana has gone up rather dramatically in the last 10, 15 years?

Dr. ADAMS. The potential danger has gone up, while the perceived harm of the product has gone down. And what I was quoting in my opening statement was NISDA data that looks at—that surveys young people from SAMPHSA. SAMPHSA data that surveys young people and asks them their perception of the dangers of marijuana. And their perceptions of danger are going down, particularly in states that have legalized, because they see it all around them. While the actual risk, both from a scientific point of view and on a population health level, is going up.

Co-Chairman FEINSTEIN. What has California done?

Dr. ADAMS. Well, you have got someone from the California Cannabis Research Commission who is going to be on the second panel.

Co-Chairman FEINSTEIN. Oh, good.

Dr. ADAMS. And I have been out there. I visited U.C. Davis. I have visited U.C.S.D. I have been to the L.A. County Health Department. I will tell you that all of the health officials I have spoken to are terribly concerned about the spike in pregnant women who are using.

We have seen a doubling in pregnant women who report using marijuana, and they are concerned about the number of young people. It is causing disciplinary problems in schools, and we do not know what the long-term health effects are going to be. So in your State, ma'am, we are very concerned.

Co-Chairman FEINSTEIN. So just quickly, how is it more concentrated, more volatile, than it used to be?

Dr. VOLKOW. The plant itself. I mean, like in biology you can determine the content of the active ingredients by breeding up varieties that have higher content. And that is how they have come up with plants that have higher and higher content, manipulating it.

And now, with the use of resins, you can extract the active ingredient and put it in a cartridge—

Co-Chairman FEINSTEIN. Oh, dear.

Dr. VOLKOW [continuing]. And that gives you even higher content. So this is just basically genetic, what the agricultural business has been doing to try to improve on the quality of the plants.

Co-Chairman FEINSTEIN. So we should not regard it as “harmless”?

Dr. VOLKOW. Oh, it is not harmless at all. And when you were asking about your own state, there were actually showing me that one of the emergency departments in one of the main hospitals in San Diego where they basically will have an eight-fold increase in emergency admissions from the cannabis over a period of eight years. Eight-fold. It is gigantic.

Co-Chairman FEINSTEIN. This is not just vaping—

Dr. VOLKOW. This is not just vaping—

Co-Chairman FEINSTEIN. Oh, I thought you said—

Dr. VOLKOW [continuing]. And smoking, and edibles, and every single way of administering cannabis.

Co-Chairman FEINSTEIN. So if a mother uses this strong stuff while she is pregnant, will that impact—

Dr. VOLKOW. She can become psychotic herself. High-content THC, what people do not realize is high-content marijuana with very high THC can trigger an acute psychotic episode. And that leads you to the emergency department. It is a horrible experience.

Co-Chairman FEINSTEIN. What if she is pregnant? What does it do to the unborn child?

Dr. VOLKOW. Well, you have there, on top of the negative effects to the mother, the fact that the marijuana will go into the fetus and affect the brain of the fetus. The fetus cannot complain, right?

Co-Chairman FEINSTEIN. Right.

Dr. VOLKOW. But it is going to very likely be interfering. Imagine that there is this very precise process by which your brain determines when this neuron migrates here, when this neuron divides, when this neuron interconnects with another, and that is modulated by your own endogenous cannabinoid system.

When you artificially stimulate that system, you are basically disrupting all of that perfect orchestration. That is why we have so

much concern about the use of marijuana among pregnant women, children, and adolescents.

Co-Chairman FEINSTEIN. Can a baby be born addicted to marijuana?

Dr. VOLKOW. I do not know of any description of a baby having been born addicted to marijuana. But what we do know is that babies can be born sedated because of the use of marijuana, particularly during the last trimester.

But the condition of a baby that is born addicted, that has not been something that has been documented.

Dr. ADAMS. And ma'am, something that again I was just in your state two weeks ago talking about were the infant mortality rates. We know one of the predictors of infant mortality is low birth weight. Well I was shocked when I saw the Colorado PRAMS data that showed that women who smoke marijuana have a 50 percent increased chance of having a baby born at low birth weight.

And so that is another thing that people do not think about when they are prescribing marijuana to women who are pregnant or could be becoming pregnant.

Co-Chairman FEINSTEIN. Thank you.

The CHAIRMAN. Well, unfortunately we are going to have to stop there with the first panel, because we obviously have a lot of questions and we want to continue the conversation, but we want to get to the second panel, too.

So thank you, Dr. Adams, Dr. Volkow, for your contribution. And, believe me, we want to continue the conversation. Because as you can see, Senator Feinstein and I, and I am sure our other colleagues who could not be here today, have a lot of questions. And I think the American people deserve the facts, which is what we are trying to get to here.

So thank you very much, and we will invite the second panel to come forward and get situated, and we will get started in just a second.

Dr. ADAMS. And, Senator, we are happy to submit any information you need about the harms of marijuana usage that we have collected. Please share my Advisory, surgeongeneral.gov. We need to get the word out to folks that this is not some harmless product out there.

The CHAIRMAN. We will do that, sir. Thank you.

Dr. VOLKOW. And thanks for doing the hearing.

The CHAIRMAN. Thank you.

(Pause.)

Well thank you very much. Our second panel includes experts who have conducted research on various aspects of public health and marijuana use.

First, Dr. Robert Fitzgerald, who currently serves as a Professor in the Department of Pathology at the University of California-San Diego, where he is also the Director of the Toxicology Laboratory, Director of the Toxicology Laboratory, and Associate Director of the Clinical Chemistry Laboratory. He is Board Certified in Toxicology and Clinical Chemistry by the American Board of Clinical Chemistry, and his research, Senator Feinstein, focuses on marijuana-impaired driving. I know you had questions about that.

Dr. Staci Gruber is Director of the Cognitive and Clinical Neural Imaging Core and the Marijuana Investigations for the Neuroscientific Discovery Program, otherwise called the MIND Program, both housed at the Harvard-affiliated Psychiatric Hospital in Belmont, Massachusetts' McLean Hospital. She is also an Associate Professor of Psychiatry at Harvard Medical School. Her research focuses on cognitive development and the effects of marijuana's major constituent compounds.

Dr. Sean Hennessy is Professor of Epidemiology in Bio Statistics at the University of Pennsylvania's Perelman School of Medicine. Dr. Hennessy conducts research in the field of pharmacoepidemiology. That is a mouthful. Which is the study of the health effects of drugs and other medical products in populations. Dr. Hennessy is the past Scientific Chair and past President of the International Society for Pharmacoepidemiology and has served as the FDA's Drug Safety and Risk Management Advisory—served on that committee, the Drug Safety and Risk Management Advisory Committee for the FDA. Dr. Hennessy contributed to the National Academies of Science's 2017 Study on Marijuana's Health Effects.

And finally, Dr. Madeline Meier is the Assistant Professor of Psychology at Arizona State University and Post-Doctoral Fellow, with support from the Duke University Trans Disciplinary Prevention Research Center. Her research interests involve adolescent marijuana use, as well as the health effects of marijuana concentrates.

So obviously there is a lot of interest in what you have to say. If I could first recognize Dr. Fitzgerald and ask each of you maybe to speak for about five minutes, and then maybe be open to some questions. Your written remarks will be made part of the record, without further ado.

So, Dr. Fitzgerald.

STATEMENT OF ROBERT FITZGERALD, Ph.D., PROFESSOR OF PATHOLOGY, UNIVERSITY OF CALIFORNIA-SAN DIEGO, CALIFORNIA

Dr. FITZGERALD. Thank you, Senator, Senator Feinstein. It is a pleasure to be here today to discuss issues related to marijuana and driving.

As a way of brief introduction, my first job out of graduate school was as a forensic toxicologist from the State of Virginia where I helped work with the medical examiner to determine the cause and manner of death in medical examiner's cases.

At the ME's office, I saw the devastating effects of driving under the influence on a routine basis. I also had the opportunity to work with both state and local law officers, along with prosecution and defense, to present scientific data in courts of law.

Currently I am a clinical toxicologist at UC-San Diego where my research focuses on developing analytical methods to measure concentrations of THC and metabolites following recent marijuana exposure.

I am part of a large team of investigators at the University of California-San Diego's Center for Medical Cannabis Research focused on understanding both beneficial and detrimental effects of cannabis on human health. We recently completed enrolling sub-

jects in one of the largest studies to date looking at the effect of smoked marijuana on driving performance, and are in the initial stages of analyzing this data.

The relationship between marijuana use and driving impairment is complex because of the unique pharmacokinetics—that is the time course in the body, and pharmacodynamics—that is its physiological effects—of THC.

With ethanol there is a clear relationship between amount consumed, blood concentrations, and effect on driving. With marijuana, these types of relationships are much more complex.

The relationship between blood THC concentrations and crash risk has not been established. But there is a clear understanding that THC impairs driving performance. The question that remains is how to best identify drivers who are impaired by marijuana. There are no perfect solutions, and legislative directives must balance keeping our roadways safe with due process.

The problems with determining the relationship between concentrations of THC and impairment is that levels of THC vary widely depending on the route of administration, the time of sampling after dosing, and the characteristics of the individual consuming.

Generally, smoked marijuana causes effects that start shortly after inhalation and last for about three hours. While subjects who eat marijuana start feeling effects about an hour later, and can have effects up to eight hours later.

Unlike alcohol, which is cleared within 24 hours of drinking, THC and several metabolites accumulate in the body with repeated dosing. So frequent users have baseline concentrations of THC that exceed the per se limits in many states.

After smoking, THC concentrations in blood change rapidly. And our studies have documented the poor relationship between concentrations of THC and measures of impairment. Studies like this led the National Safety Council to put out a Position Statement in 2017 that reads: “It is further concluded that, due to rapid changes in blood THC concentrations over time, there is no minimum safe threshold blood concentration below which a driver can be considered to have been unaffected while driving following recent marijuana use. Consequently, there is no scientific basis for the adoption of THC per se laws for driving.”

This statement was also supported by the International Association of Chiefs of Police. Despite these position statements, 18 states currently have some form of per se statutes.

How do we keep our roads safe? In California, prosecution of driving under the influence of drugs is currently based on officer observations combined with toxicology testing. This practice will likely continue for the foreseeable future.

Since there is no reasonable expectation that THC or a metabolite of THC will be useful for per se impairment, an alternative approach would be to develop methods that identify recent use. The biological specimens that could be used to determine if a driver has recently used marijuana are blood, breath, and oral fluid.

The primary advantage of breath and oral fluid over blood is that they can be collected at the roadside at the time of a traffic stop,

as opposed to blood which typically takes about 90 minutes to collect.

This is an important consideration because, unlike ethanol, concentrations of THC fall by more than 90 percent in that short time frame. There is a variety of ongoing efforts to identify recent-use markers.

In respect to my time limit, I would like to close my initial statement by mentioning two items that I think this Caucus needs to be aware of so they can help shape appropriate regulations.

Due to federal restrictions, investigators cannot study the cannabis products our population is exposed to. As Dr. Adams indicated, we have unleashed a massive experiment that is sort of uncontrolled in our population, and our most powerful resources, our research community, has limited ability to study that.

This is a critically important public health issue that needs to be changed. Currently there is no standardized data collection for driving under the influence of drugs. Without good data, it is difficult to develop good policy.

I hope my testimony was helpful and look forward to answering questions. Thank you.

The CHAIRMAN. Thank you very much. Dr. Gruber.

STATEMENT OF STACI GRUBER, Ph.D., PROFESSOR OF PSYCHIATRY, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS

Dr. GRUBER. Thank you, Senator Cornyn and Senator Feinstein, and members of the Caucus who may tune in later to see this—

Co-Chairman FEINSTEIN. Could you speak directly into the microphone?

Dr. GRUBER. Certainly. Is that better?

Co-Chairman Feinstein. Yes.

Dr. GRUBER. I should be better at this.

So as you have heard, and as we know, the Nation is in the midst of a green rush, and marijuana or cannabis headlines flood news outlets daily. Yet it is often difficult for people to read through study findings and make sense of what we know and what we do not.

Despite the fact that 33 states have fully legalized medical marijuana, and another 15 have limited medical marijuana laws, leaving only 2 states without access, nearly all of what we know about the impact of marijuana comes from studies of recreational marijuana users.

These studies typically focus on those with chronic, heavy marijuana use. Data across studies is somewhat inconsistent, but generally reflect differences between those who use marijuana and those who do not spanning a number of areas that we have heard allusions to already, including cognitive performance. Domains most commonly affected include memory and executive functioning. For example, the ability to inhibit inappropriate responses, or to use feedback to change one's behavior. These are reportedly impacted by marijuana use.

Earlier onset of marijuana use, as well as higher frequency and magnitude of use, are also associated with greater difficulty on these tasks. And studies of brain structure and function have also

reported deficits or differences between marijuana users and non-users, specifically as among early onset or adolescent users of marijuana.

This is not surprising. As you heard from Dr. Volkow, we know that during adolescence the brain is neuro-developmentally vulnerable. That is, it is under construction. It is sensitive not just to marijuana but to other substances—alcohol, illness, injury.

Another concern that we have heard a lot about today is the rising potency of marijuana products. Particularly problematic for youth, our most vulnerable consumer group, THC, the primary intoxicating compound of the plant has increased 300 percent, or more than three-fold, in flower products since 1995. And these novel concentrate products that we have also heard illusions to, Dabs, Shatter, Wax, you have heard these terms, THC levels of these products go at least up to and sometimes north of 90 percent.

Cannabidiol, or CBD, may mitigate some of the negative effects that we see from THC, but it is virtually undetectable in recreational products today. Thus far there have been no studies that have directly assessed the impact of potency or novel versus conventional products in either recreational consumers or medical patients.

It is also important to remember that not all marijuana use is the same. And our recreational marijuana consumers are not the same as our medical marijuana patients.

For example, their goal of use is wholly different. Our recreational marijuana consumers—I have spent nearly 30 years with these folks—their goal is to change their current state of being, or to get high. Our medical marijuana patients are not interested in getting high. They use to alleviate symptoms. They say things like I want to sleep through the night. I would like to be able to take a drive with my son. I want to go for a walk with my kids.

As a result, their product choices are often different. Recreational consumers often choose products very high in THC. Our medical patients choose products that may be high in THC but often contain other compounds, things like cannabidiol or other non-intoxicating compounds.

Cannabis and cannabinoids have demonstrated therapeutic potential for a number of indications. We heard reference to the 2017 National Academy's report noting conclusive or substantial evidence that cannabis or cannabinoids were effective for, quote, "the big three, chronic pain, nausea and vomiting as a function of chemotherapy, and muscle spasticity as a function of MS.

We also know that epiadiallexis or purified CBD extract was approved for pediatric onset intractable seizure disorders. But despite the fact that medical cannabis has been legal since 1996, data regarding the impact of medical marijuana treatment is severely limited. Preliminary evidence from the very first longitudinal studies of medical marijuana patients demonstrate improvements in some areas of cognitive performance, including areas noted to be impaired in those with recreational use.

We also see improvements in clinical state, better sleep, decreased pain, and notable reductions in the use of conventional medications including opioids, so important in the midst of this crisis.

When it comes to marijuana, one size does not fit all. We have a single term, marijuana, and we often hear it used to refer to anything like the whole plant or individual compounds from the plant, intoxicating or not, which mean very different things.

Current regulations around marijuana limit the type and scope of research projects we can do. And, contrary to popular belief, we cannot currently study the impact of products that patients and consumers are actually using via clinical trial models, significantly reducing external or ecologic validity.

Further, as Dr. Volkow testified, the Schedule One status of marijuana leads to a number of obstacles in conducting research. Policy at this point has clearly outpaced science. And as the Nation has warmed toward both the use of medical and recreational marijuana, the need for empirically sound data is critical in order to maximize benefit and reduce harm.

Regardless of how you feel about marijuana, science and not emotion or rhetoric must be our guide. We have a responsibility to provide the best and most accurate data to our medical marijuana patients, our recreational consumers, our health care providers, and the general public so they can make the best, most informed decisions about marijuana use.

At this point, I would thank you for your ongoing efforts and being willing to help move things forward. Thank you.

The CHAIRMAN. Thank you, Dr. Gruber. Dr. Hennessy.

STATEMENT OF SEAN HENNESSY, PHARM.D., Ph.D., PROFESSOR OF EPIDEMIOLOGY, UNIVERSITY OF PENNSYLVANIA PERELMAN SCHOOL OF MEDICINE, PHILADELPHIA, PENNSYLVANIA

Dr. HENNESSY: Good afternoon, Senators. My name is Sean Hennessy and I am a Pharmacist Epidemiologist at the University of Pennsylvania. I was a member of the 16-person committee that wrote this 468-page report entitled “The Health Effects of Cannabis and Cannabinoids” that the National Academics of Science, Engineering, and Medicine released in January 2017.

The report is a comprehensive review and synthesis of the then-existing literature about the potential health effects, both therapeutic and harmful, of cannabis and cannabis-derived products.

The report lists nearly 100 different conclusions about these effects. It also discusses four barriers to conducting research on cannabis and makes four recommendations on how to address research gaps.

I would like to summarize this report as 6–4–4. Six health effects with high-level evidence. Four challenges to conducting research. And four recommendations to moving forward. So among the highest levels of evidence about the health effects of cannabis we made the following conclusions.

One, cannabis use prior to driving appears to increase the risk of motor vehicle crashes, as we have heard about today.

Two, in states where cannabis is legal, there is an increased risk of unintentional cannabis overdose in children.

Three, pregnant women who smoke cannabis increase the risk that their baby will be born with lower birth weight.

Four, initiating cannabis use at a younger age is a risk factor for developing problematic cannabis use later in life.

Five, long-term cannabis smoking increases the risk of chronic breathing problems. And six, some people with chronic pain or muscle spasm from multiple sclerosis can obtain relief of their symptoms using cannabis-based products.

Most of the studies for these uses examined orally administered cannabis extracts, rather than smoked cannabis. The report also identified the following four challenges to conducting research on the health effects of cannabis.

One, there are specific regulatory barriers, including the classification of cannabis as a Schedule One substance that impede research.

Two, it is difficult for researchers to gain access to the quantity, quality, and type of cannabis product that they need to conduct research.

Three, it is difficult to obtain funding to support cannabis research. And four, improvement and standardization in research methods are needed.

Finally, the report makes the following four recommendations:

One, public health agencies and other groups should fund a national cannabis research agenda.

Two, agencies of the U.S. Department of Health and Human Services should convene a workshop to develop a set of federal standards and benchmarks to guide high-quality research on cannabis.

Three, federal, state, and local health authorities should fund improvements to the public health surveillance system.

And four, the CDC, NIH, FDA, and others should convene a committee to characterize regulatory barriers and propose strategies to develop the resources and infrastructure that are needed to conduct cannabis research.

I thank you for your attention and the opportunity to discuss these important issues, and look forward to answering your questions.

The CHAIRMAN. Thank you, Dr. Hennessy. Dr. Meier.

STATEMENT OF MADELINE MEIER, Ph.D., ASSISTANT PROFESSOR OF PSYCHOLOGY, ARIZONA STATE UNIVERSITY, TEMPE, ARIZONA

Dr. MEIER. Good afternoon, Mr. Chairman and Senator Feinstein.

Co-Chairman FEINSTEIN. Could you speak directly into the mike? It is hard to hear.

Dr. MEIER. Thank you for inviting me to contribute to my knowledge about cannabis effects on cognitive functioning.

The most comprehensive study of cannabis use in cognitive functioning was published by our group in 2012. Today I am going to describe that 2012 study and explain the findings, why they are important, and what additional research is needed.

We have studied the association between persistent cannabis use over time and change in IQ from childhood to adulthood. And we asked whether cannabis effects on IQ were concentrated among ad-

olescent onset cannabis users. That is, cannabis users who began using before age 18.

Data came from the Dunedin Study, which is a study of 1,000 children born in 1972 and '73 in Dunedin, New Zealand, and followed from birth to age 38, with 96 percent of the sample taking part in the study at age 38.

IQ was tested at age 13, before anybody in the cohort had started using cannabis, and again at age 38 after some members of the cohort had been using cannabis for years. We found that persistent cannabis use from ages 18 to 38 was associated with decline in IQ. And this decline in IQ was concentrated among adolescent onset persistent cannabis users. These are cannabis users who began using cannabis before age 18 and continued using for many years thereafter.

Specifically, individuals who began using cannabis in adolescence before age 18, and used it for years showed an average 8 point IQ decline from childhood to adulthood. However, individuals who used cannabis short-term in adolescence showed only weak evidence of IQ decline.

Further, individuals who began using cannabis in adulthood sometime after age 18 did not show decline in IQ even when they used persistently.

Quitting or reducing cannabis use did not fully restore intellectual functioning. Decline in IQ could not be explained by alcohol or other drug use, or by reduced years of education among cannabis users.

Decline in IQ could also not be explained by low childhood socioeconomic status or poor childhood self-regulation. Friends and relatives reported noticing more attention and memory problems in everyday life among the persistent cannabis users. These findings are important for a number of reasons.

First, an especially important feature of this study is that we had IQ test data from both before and after study members started using cannabis. This allowed us to rule out the possibility that IQ deficits in cannabis users predate the onset of cannabis use.

We showed that regardless of their IQ test performance in childhood, adolescent onset persistent cannabis users performed worse than nonusers, and worse than adult onset cannabis users on IQ tests in adulthood.

Second, the eight-point IQ decline we observed among cannabis users who began using cannabis in adolescence and continued using for many years is non-trivial. For example, an average person has an IQ of 100, placing them in the 50th percentile for intelligence, compared to same-age peers. If this average person loses 8 IQ points, they drop from the 50th to the 29th percentile for intelligence.

Third, IQ is a predictor of a person's access to a college education, their lifelong total income, their access to a good job, and their performance on the job. Individuals who lose 8 IQ points may be disadvantaged relative to their same-age peers in many important aspects of life. In fact, the adolescent onset persistent cannabis users from our 2012 study ended up in occupations that were less prestigious, less skilled, and less well paid than their parents' occupations.

Finally, only about 2 percent of the sample became those adolescent onset persistent cannabis users. Thus, any effect of cannabis on IQ is confined to a relatively small segment of the population. Nonetheless, findings are concerning given that fewer adolescents today believe that regular cannabis use presents a serious health risk.

Additional research is needed to answer the following questions:

One, what are the mechanisms underlying cannabis-related IQ decline?

Two, what are the parameters of cannabis use that determine the magnitude and persistence of cognitive deficits? These are things like frequency, duration, quantity of use, and potency.

Three, does cognitive functioning recover with abstinence?

Four, are there individual differences in susceptibility to cannabis-related cognitive deficits?

To answer these questions, we need large-scale longitudinal studies to follow use from before to well after cannabis initiation, and to combine cognitive testing with brain imaging to better understand the mechanisms that might underlie cannabis-related decline in IQ.

The Adolescent Brain and Cognitive Development Study was launched in part to meet this need. Thank you.

The CHAIRMAN. Thank you, Dr. Meier.

Welcome, Senator Rosen. Thank you for joining us. Let me start with a five-minute round of questioning.

Dr. Gruber, just a point of clarification. We heard from the previous panel that THC concentrations in recreational marijuana have at least tripled. But I see in your paper you say that you believe it has quadrupled from 1995 to 2017. Is that correct?

Dr. GRUBER. I think the prior panel referenced the paper that was published—

I think the prior panel referenced the paper that was—

Co-Chairman FEINSTEIN. Louder, please? I'm sorry.

Dr. GRUBER. Sure. Is that better? I think the prior panel referenced the publication from 2014—

The CHAIRMAN. Oh, okay.

Dr. GRUBER. At that time, the difference from '95 to 2014 was about three times.

The CHAIRMAN. Three times?

Dr. GRUBER. Right now, the average potency across the Nation from government-seized products is about 17 percent. That is contrasted to about just under 4 percent in 1995.

The Chairman. Okay, so that is significant. You think the best information is it has quadrupled in concentration?

Dr. GRUBER. I would say in terms of national averages for THC, that is right.

The CHAIRMAN. But—

Dr. GRUBER. Those were recreational products.

The CHAIRMAN. But you also point out—and this is really the point I wanted to get to—is that there are concentrates, other products that have been created. You mentioned things like Dabs, the colloquial name for concentrated oil, created by extracting THC from flower-based marijuana products, Shatter Wax, Butter, and others, that all have a significantly higher concentration potency

compared to conventional marijuana products as high as 80 percent more concentrated. Is that correct?

Dr. GRUBER. Or higher, absolutely right. This is the recreational market that is very focused on increased THC because if the goal of use is to become intoxicated, or to change your current state of being, you are looking for products that will deliver that bigger bang for the buck, if you will. So these products are very, very popular and becoming more popular across the Nation in the recreational market.

The CHAIRMAN. Well it strikes me as significant. If you smoke it, it is about four times more powerful than it was in 1995. But you can take it in a concentrated form that could be 80 percent of traditional marijuana product.

Dr. GRUBER. Exactly. THC is significantly higher, as we heard from our first panel, significantly higher these days than in prior years.

The CHAIRMAN. Well I can imagine just from a scientific standpoint trying to figure out what the dosing is, and what the effect of a dose is very difficult given the range of ways that people can get access to the active ingredient.

Dr. GRUBER. Mode of use is very important in terms of onset of effects and duration of effects. Absolutely true. Especially important for our medical cannabis patients.

The CHAIRMAN. Dr. Fitzgerald, you have done a lot of work, you said, in terms of its impact on impaired drivers. Would it be fair to say that the concentration of THC and whether it is consumed from recreational use of smoking marijuana compared to these concentrates? Does it have a— is there a correlation between the concentration of the product that you consume and the level of impairment for drivers?

Dr. FITZGERALD. So I think that is one of the issues that Dr. Adams brought up, as well, is that we have not even been able to study the Dabs and the concentrates. It is not possible to do those studies, currently.

The CHAIRMAN. But those are not standardized products? I mean, like you would be able—you cannot compare widgets to widgets, I guess.

Dr. FITZGERALD. Correct.

The CHAIRMAN. Because they are all sort of concocted by whoever makes them, according to their own recipe, and the like.

Dr. FITZGERALD. Several issues there. One, we do not know what is actually in those. They are labeled. California actually does have a reasonably good laboratory system for analyzing plant materials, as well as Dabs and things for pesticides and concentrations of THC. But that is only in the legal market. And the legal market, unfortunately, is a small share of the total market of recreational marijuana.

The CHAIRMAN. As we know, there has been an unfortunate increase in suicides in the country, a lot of concerns about our Veterans in particular, but not just Veterans. It is just young people and others who end up taking their life.

I wonder, do you find any correlation between self-medication of people with underlying mental health disorders that get exacer-

bated by the use of marijuana or some of these concentrated products?

I do not know who would be the most appropriate person to ask. If you have an opinion, please jump in.

Dr. GRUBER. I have an opinion, since I work in a psychiatric hospital and have been seeing the patients for about 30 years.

The CHAIRMAN. It sounds to me like you are qualified.

Dr. GRUBER. Maybe, I don't know. It's under debate. I can tell you that there are many, many patient populations that derive real benefit from using cannabis or cannabinoid-based products. And the potential risk for individuals with undiagnosed conditions or disorders—you know, where we hear about these individuals who are using and not necessarily disclosing, or they are self-medicating. One of the important things to be mindful of is that it is not necessarily the cannabis. But we have to be mindful of what is driving the cannabis use.

Individuals who have different types of conditions, as I mentioned, often get benefit from use. But it is very, very important to watch these people over time and to look at the impact versus, you know, sort of a cross-sectional assessment, in a longitudinal fashion.

No doubt some individuals with differing conditions have their conditions exacerbated by cannabis use. That is why it is so important to be able to identify the most likely compounds from the plant which may make things worse versus those which may make things better.

In fact there is evidence to suggest some compounds from the plant may actually really positively impact some of these conditions that we see. And this is why so many people are turning toward them. But without real empirically sound data to guide these types of studies, we have limited ability to give them information.

The CHAIRMAN. Well my understanding, my layman's understanding, is that there is some evidence that epilepsy can be treated using THC-related products.

Dr. GRUBER. Cannabidiol.

The CHAIRMAN. Okay. Is there any—what other benefits have you been able to identify based at least on anecdotal information, in the absence of these longitudinal studies? What other benefits do you suspect may be derived from use of marijuana?

Dr. GRUBER. So different compounds from the plant may very well have individualized benefits. We know about cannabidiol. I think this was mentioned in your bill. Cannabidiol has been shown to potentially be efficacious not just for epilepsy, which is now approved by the FDA, Epidioliol Schedule Five, but for other conditions. There have been some interesting studies, including pre-clinical work, in areas like anxiety. A number of different conditions may be positively impacted by cannabidiol. Other compounds may yield, again, therapeutic potential, but we do not have much in the way of long-term studies. And unfortunately, it is very difficult to study these compounds using clinical trial models, sort of the gold standard for deriving empirically sound data, given our current restrictions.

We have an ongoing—we just started a long-term clinical trial, open label to double-blind, of a whole plant full spectrum product

for patients with anxiety. This data will be very, very important since so many people turn to things like CBD and they say it is good for this, it is good for this, and it would be great to have empirically sound data to lean on to actually guide patients and care givers.

The CHAIRMAN. I even have a friend who said they put CBD product in their pet food—

Dr. GRUBER. Sure.

The CHAIRMAN [continuing]. So their pet—it relieves their pet of anxiety. So I guess it cures everything.

Dr. GRUBER. I do not know about everything, but there is some data from studies outside of this country, small studies, in terms of cannabidiols' impact on anxiety, some pre-clinical work, and finally some work here. So it certainly begs the question of how much more we need, which in my opinion is a lot more. But we are starting.

The CHAIRMAN. Thank you. Doctor—Doctor Feinstein? Senator Feinstein. [Laughter.]

Co-Chairman FEINSTEIN. Thank you. Thirty-three states and the District of Columbia have legalized marijuana in some form. And each state has its own laws and regulations.

Should we be concerned that the lack of uniformity across states in terms of testing, labeling, packaging, the strength of products that may be sold, how they may be advertised, and how they may be accessed, can lead to consumer confusion? And this could produce unintended acute public health effects, including increased emergency room visits.

In Colorado, for example, there was a three-fold increase in marijuana-related emergency room visits between 2012 and 2016. So here is the question:

Would uniform regulations across states be helpful to ensure consumer safety and reduce public health impacts such as emergency room visits associated with marijuana use? Who would like to go—why don't we just go right down the line. If you have a comment, make it. If you do not, you do not.

Dr. FITZGERALD. Yes, certainly I think California is a model there for the fact that all the state-approved marijuana has actually been through a very sophisticated testing scheme to show its purity, show that it does not have pesticides, show it does not have fungus, and those things. There is some question about the reliability of different laboratories, and it would be nice to have a reference laboratory that everyone else sort of standardizes against. That would be useful to have uniform labeling. And certainly the CDC can be helpful in that regard.

Co-Chairman FEINSTEIN. Thank you.

Dr. GRUBER. I think it is incredibly important to have uniformity.

Co-Chairman FEINSTEIN. I am having trouble hearing you.

Dr. GRUBER. I think it is incredibly important to have uniformity, and even more important to have full disclosure of “what's in your weed”? People have no idea very often what they are getting. So I think it is incredibly important, since states make their own, sort of their own rules and regulations about what is allowed.

In my State of Massachusetts—and I spend a lot of time in California as well—these things are clearly defined in terms of testing for aflatoxins, heavy metals, pesticides, contaminants, yeast, mold—

Co-Chairman FEINSTEIN. So a standard across the United States would be helpful?

Dr. GRUBER. I think having a reference standard would be incredibly important in making sure every state does thorough testing is critical.

Co-Chairman FEINSTEIN. Thank you.

Dr. HENNESSY. I agree. I do not have anything to add.

Co-Chairman FEINSTEIN. Thank you.

Dr. MEIER. I agree, as well, and do not have anything additional to add.

Co-Chairman FEINSTEIN. Okay. What is the most common form of marijuana concentrate being used by adolescents? And how much THC does it contain? Adolescent use is my big concern.

Dr. MEIER. My group just published I believe the first epidemiological study of that. And we found that you can talk about concentrates as a general class, but there are two really different types of concentrates—one that is extracted using a solvent like butane—and those tend to have generally higher concentrations than the other class of concentrates where the THC is extracted using ice, or just rubbing it. And that has still much higher THC content than, for example, marijuana which is the buds of the cannabis plant. And that adolescents are using all of that. But primarily they are using the solvent-extracted—

Co-Chairman FEINSTEIN. They are using the what?

Dr. MEIER. The solvent-extracted concentrates.

Co-Chairman FEINSTEIN. What is that?

Dr. MEIER. Which go by names, various names. Dabs is the generic name to refer to just taking a very small kind of waxy piece of the concentrate. But then there's Butane Hash Oil, or they call it BHO, and it is called that because you extract the concentrate with butane solvent.

It is also called "Honey Oil," "Crumble," lots of different names for it. And while those products look different, one can look like a waxy sticky substance, one can look like butter, they all contain similarly high levels of THC.

Co-Chairman FEINSTEIN. Ah-hah. So are they heavily used by adolescents?

Dr. MEIER. We know from the State of Arizona one in four adolescents have said they have tried concentrates.

Co-Chairman FEINSTEIN. So what would you suggest we do, if anything?

Dr. MEIER. I think we need—my primary concern is educating parents and people like you to recognize what a concentrate is. It does not look like marijuana. It looks very different, and recognizing that that contains very high levels of THC which could pose risks to health.

Co-Chairman FEINSTEIN. Well would you have a standard for this? Does that makes sense? Or should government get involved in this? I think, you know, when you talk about adolescents, you

do not want them to die and you do not want them to become addicted.

Dr. MEIER. Correct. We do not want them to become addicted. But we still need to do research on whether adolescents who use concentrates are more likely to become addicted than if they use the lower THC marijuana.

So I think we need more research, because some evidence suggests that it is possible that these concentrates will not have ill effects if adolescents are titrating their use, which means using less when the THC content is high.

Co-Chairman FEINSTEIN. Thank you. Thanks, Mr. Chairman.

The CHAIRMAN. Senator Rosen.

Senator ROSEN. Well thank you. I want to thank Chairman Cornyn, Ranking Member Feinstein, for holding this important hearing. I want to thank all of you for your years of school and research and dedication to this extremely important topic.

I want to talk a little bit about medical marijuana. Although marijuana is legal in Nevada for both medicine and recreational purposes, the research that you are doing is so important for my state's hospitals, providers, schools, parents, law enforcement agencies, anybody that is concerned with the public health impact. And there are approximately in Nevada about 17,000 medical marijuana patients.

So this research that you do really impacts their lives, their ability to seek treatment for their medical conditions. And so with that in mind, I really appreciate the bipartisan approach which has led to this hearing, and I hope the conversation will continue to be research and science based. It is so important that we have these longitudinal studies, epidemiological studies, so on and so forth. It makes a real difference as to how our communities can educate and legislate, if we need to, to do the right thing.

But I want to talk about the potential benefits of medical cannabis in treating our Nation's Veterans. We have over 220,000 Veterans in Nevada. And, let me tell you, I do not have to tell you how much they do struggle. They struggle with chronic pain. They struggle with depression, anxiety, post traumatic stress symptoms, and in too many cases they are becoming addicted to medications prescribed to them—opioids, other things like that.

Our Veterans have given so much to their country, they just want to come back. They want to claim their lives and continue to serve their communities in whatever way is good for them and their families.

And so VA providers are currently prohibited from recommending or prescribing cannabis use. The VA will not reimburse Veterans for medical marijuana prescriptions from any source.

Former VA Secretary David Shulkin, he stated last week he believes the VA should be involved in research and anything that could potentially help Veterans and their wellbeing.

So to Dr. Hennessy, and then anyone else after, you were a member of a committee that conducted rigorous overview of available research on the potential health benefits of cannabis, or therapeutic benefits. It also identifies barriers to research and you made recommendations.

So I would really appreciate your thoughts of how we might use cannabis to help our Veterans through anxiety and depression in those ways, and find alternatives to treat the issues that they are suffering from when they come home.

Dr. HENNESSY. So thank you for your question, Senator. So of the uses that you mentioned, there is randomized trial data supporting the use of cannabis products for chronic pain. And the cannabis products that were studied most often for chronic pain was an oral solution of one-to-one THC to CBD. It was not either smoked or vaped cannabis.

The other indications that you mentioned, anxiety, depression, PTSD, there are not good data from randomized trials that support the efficacy of either whole cannabis or cannabis-derived products for those indications.

Lack of evidence does not mean that the products are not—that none of the constituents of cannabis are not effective. In some cases it merely means that the studies have not been conducted, or not enough of them have been conducted to identify a beneficial effect, if there is one.

Senator ROSEN. But you would support us funding, or lifting the ban on some of the research to find out if we can use these products effectively, Dr. Gruber?

Dr. GRUBER. Yes. And thank you so much for focusing on this issue. We have a program through the MIND program called Serving Those Who Have Served. And it is dedicated to our Veterans. Because so many are already using cannabis or cannaboids for treatment, many are interested in using it. But we have no real data.

Senator ROSEN. Right.

Dr. GRUBER. So, you know, we come at this as a quasi clinical trial because we cannot administer products that are in the marketplace, given our current federal regulations and restrictions. So we do the best that we can.

But we followed these folks over time, longitudinally. And we need more data like that to be able to really understand the impact. As referred to by Dr. Hennessy, we do not have a ton of data. But certainly lifting anything that would allow greater research efforts to be made I would be in favor of.

Senator ROSEN. Well thank you. I want to—you spoke about chronic pain, and I was fortunate enough to be able to start the Comprehensive Care Caucus, which is focusing on palliative care, people living with a terminal illness or chronic disease, and they need palliative care, although they may not be getting curative care.

And so can you speak to the effects of how we could use cannabis in the palliative care spectrum for those, as I said, living with chronic disease, or living longer with terminal illness, to relieve some of the symptoms that they may be having as a result of their disease?

Dr. HENNESSY. Sure. So one of the symptoms that patients in palliative care experience is chronic pain. And as I mentioned, there are clinical trials showing that oral solutions of cannabis extract are effective for chronic pain.

In terms of other indications for use in the palliative care setting, I think more research is needed to be able to recommend them as effective therapies. We do not want to recommend therapies and offer false hope to people for therapies that end up not being effective. That, in addition, has side effects on their own.

Senator ROSEN. Right. Thank you.

Dr. GRUBER. I think it is also important, just to dovetail on what Dr. Hennessy is saying, to be able to assess the actual products that patients are using, as opposed to just sort of guessing. And the one-to-one ratios of oral solutions, things like Sativex, are not necessarily in the marketplace for our palliative care patients.

Our ongoing longitudinal study at the MIND program actually follows patients with chronic pain as a subgroup, and they demonstrated improvements over time using lots of different products. But this research is really in its infancy, and this is, as far as I know, the only longitudinal study like this in the country.

Senator ROSEN. Right.

Dr. GRUBER. We need a lot more.

Senator ROSEN. Well I applaud all of your work, and I do think that particularly in the medical space trying to find the ways that we can use marijuana, whether for chronic pain, anxiety, terminal disease, PTSD, depression, if we can find ways that make people—help them go better through their lives, then it is definitely worth researching. And I appreciate your hard work. Thank you.

The CHAIRMAN. Thank you, Senator Rosen.

Dr. Gruber, I think I understand what you were telling me earlier. Let me just confirm I got this right. There is a part of marijuana that will make you high. That is THC, right? The active ingredient?

Dr. GRUBER. That is the primary psychoactive compound in the plant, yes.

The CHAIRMAN. Okay, that is a more eloquent way of saying it than I did. And then there are other products from the marijuana plant, or that can be derived from that, like CBD that you think has some medicinal or beneficial effects? But that has little or no THC in it. Correct?

Dr. GRUBER. Correct. Just to clarify, really quick and dirty, cannabis sativa-L, the plant, is comprised of hundreds of compounds. The primary psychoactive compound is THC. That gets you high. The primary non-intoxicating constituent is cannabidiol, shown to have tremendous—at least thought to have tremendous therapeutic benefit.

There are many, many other cannabinoids—canabachromine, canabajeral, tetrahydro canabaren, as well as terpenoids, the essential oils that give cannabis its characteristic scent and flavor profile that have also been touted to have potential beneficial effects. Flavanoids. The plant is incredibly complex. It is not just THC and CBD, although I know that is where we start our discussions, but it is important to remember that alongside THC we have CBD and other players.

The CHAIRMAN. Would it be possible for Congress to de-schedule or to treat CBD and other non-THC products differently than it would THC or psychoactive components of the plant?

Dr. GRUBER. As I understand it, currently under the Controlled Substance Act anything that comes from the plant *cannabis sativa* with greater than .03 percent THC by weight falls under Schedule One. Anything that comes from industrial—so-called “industrial hemp” legalized in the 2018 Farm Bill, or Hemp Bill, CBD from that source is legal. So that is de-scheduled.

The CHAIRMAN. So Congress has already carved out an exception, basically, for hemp?

Dr. GRUBER. For industrial hemp-derived CBD, ostensibly the DEA will allow those types of research studies to move forward.

The CHAIRMAN. And what differentiates those two, is one has a negligible, if any, THC component.

Dr. GRUBER. That’s right.

The CHAIRMAN. And the other product that is a psychoactive one has the THC at a much more concentrated level.

Dr. GRUBER. Much more concentrated levels. Both plants have THC. Industrial hemp maxes out by definition as .03 percent THC by weight. *Cannabis sativa-L*, when we think of marijuana, we think of that plant that can be bred to have very, very high levels of THC, as well as levels of other cannaboids. There are differences in the two cultivars.

The CHAIRMAN. Well that is helpful. Thank you, very much.

Senator Rosen, do you have anything else you would like to ask?

[No response.]

The CHAIRMAN. Well, let me express my gratitude to each of you and our previous panel of witnesses. This is a conversation we should have started a long time ago, but I am glad at least we are starting it now.

And as you can tell, there is a lot we have to learn, Members of Congress, the policymakers, but I think the American people. I think the risks, the health risks of marijuana use have been undersold, and as we heard from the previous panel, but yet there are beneficial uses that do not involve the psychoactive component we have heard that could be enormously helpful.

So this has been very informative and so I thank you for it. Thank you for your participation. We are going to close the hearing now, but we will leave the record open for another week in case any member of the Caucus has written questions they would like to ask to follow on.

But taking Senator Feinstein up on her suggestion, it may be that the Caucus would decide to publish a white paper on what we have learned here, perhaps for the benefit of others, including policymakers like ourselves, and that is something we are going to look into as well.

So we look forward to continuing the conversation with you, and thank you very much for being here.

(Whereupon, at 5:01 p.m., Wednesday, October 23, 2019, the hearing in the above-entitled matter was adjourned.)

[Questions and answers and submissions for the record follow.]

**Senate Caucus on International Narcotics Control
Marijuana and American's Health October
23, 2019 Hearing**

Questions for the Record

Senator Cornyn:

Dr. Volkow –

Marijuana and Risk of Mental Illness

The Surgeon General's advisory noted the risk for early onset of psychotic disorders, such as schizophrenia that increases with a higher frequency of marijuana use, higher potency of marijuana products, and younger age of use.

- Could you discuss the studies NIDA has initiated or funded that are looking into this increased risk? Is this risk limited to certain psychotic disorders, or does it apply more broadly to mental illness?

Response:

Multiple NIH Institutes and Centers, as well as other federal and non-federal organizations, have supported research examining the link between marijuana and psychosis. Studies have found that having ever used marijuana, compared to never having used marijuana, is associated with double the risk of schizophrenia,¹ while frequent use or use of marijuana with high delta-9 tetrahydrocannabinol (THC) potency is associated with a six-fold increased risk compared to non-users.²³ Research also suggests that marijuana use has the potential to trigger the first symptoms or exacerbate the course of a lasting psychotic illness in some individuals (e.g., those with a genetic vulnerability).⁴ In one study of patients in Europe and Brazil who sought treatment for their first psychotic episode, daily marijuana users were at three times greater risk for a psychotic disorder than non-users. Daily users of *high-potency* marijuana were at nearly five times greater risk compared to non-users.⁵

While the research to date shows the strongest link between marijuana and psychosis, there is evidence for an association between marijuana use and other mental health conditions. A comprehensive review of all the data available in 2017 conducted by the National Academies of

¹ van Os J, Bak M, Hanssen M, Bijl RV, de Graaf R, Verdoux H. Cannabis use and psychosis: a longitudinal population based study. *Am J Epidemiol.* 2002;156(4):319-327

² Andréasson S, Allebeck P, Engström A, Rydberg U. Cannabis and schizophrenia: a longitudinal study of Swedish conscripts. *Lancet.* 2000;355(9237):1483-1486.

³ Caspi A, Moffitt TE, Cannon M, et al. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene × environment interaction. *Biol Psychiatry.* 2005;57(10):1117-1127.

⁴ Di Forti M, Quattrone D, Freeman TP, et al. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. *Lancet Psychiatry.* 2019;6(5):427-436.

Sciences, Engineering, and Medicine, concluded there is a moderate association between cannabis use and suicidal behavior; that among individuals diagnosed with bipolar disorders, near daily cannabis use may be linked to increased symptoms of mania compared to non-users; and that regular cannabis use is likely to increase the risk for developing social anxiety disorder.⁶ The report states that cannabis use does not appear to increase the likelihood of developing depression, anxiety disorder (except social anxiety disorder), or posttraumatic stress disorder.

Additional research is needed to delineate the complex relationships between marijuana use and the risk of mental health conditions. NIDA is leading two major studies with significant potential to advance knowledge in these areas. The Adolescent Brain Cognitive Development (ABCD) study is the largest long-term study of brain development and child health in the United States. Over 11,000 children ages 9-10 have been recruited and will be followed into early adulthood to determine how substance use—including marijuana use—and other childhood exposures affect brain and cognitive development and other childhood health outcomes. While a full picture will take years to emerge, this study has already begun to yield significant insights into the links between marijuana and psychosis. For example, earlier this year, ABCD researchers reported that prenatal marijuana exposure after, but not before, maternal knowledge of pregnancy may be associated with a small increase in risk of psychosis during middle childhood.⁷ Complementing ABCD is the HEALthy Brain and Child Development (HBCD) Study, which is supported in part by the NIH HEAL (Helping to End Addiction Long-term) InitiativeSM and is currently in its planning phase. HBCD would establish a large cohort of pregnant women and assess maternal and child outcomes over the course of at least 10 years. Findings will help researchers understand both normal childhood brain development as well as the long-term impact of prenatal and postnatal drug exposure. The National Institute on Mental Health (NIMH) also supports research on the association between marijuana use and mental health conditions. One NIMH study is examining preexisting differences in key components of the endogenous cannabinoid system as potential predictors of first episode psychosis patients.⁸

Are there studies looking into other health risks of these higher-potency products? Are you able to expand on those?

Response:

It is difficult to conduct research on high-potency products in the United States. Although the NIDA Drug Supply program offers higher potency marijuana for research, the potency of NIDA products does not match that available on the market. Moreover, federally-funded researchers are unable to access dispensary products, so research on those products is limited to observational studies. Those studies are in turn limited by researchers' inability to analyze the composition—

⁶ The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Board on Population Health and Public Health Practice, Health and Medicine Division. The National Academies Press. 2017

⁷ Fine JD, Moreau AL, Karcher NR, Agrawal A, Rogers CE, Barch DM, Bogdan R. Association of Prenatal Cannabis Exposure With Psychosis Proneness Among Children in the Adolescent Brain Cognitive Development (ABCD) Study. *JAMA Psychiatry*. 2019 Jul 1;76(7):762-764.

⁸ https://projectreporter.nih.gov/project_info_description.cfm?aid=9765411&icde=47747207

including THC potency—of the products that research participants are using or the dose at which they are using them.

Nevertheless, there have been some studies examining other health risks associated with higher-potency marijuana products. For example, some of the studies examining the impact of high potency products on psychosis mentioned above also examined effects on brain structure, cognition, and metabolism. One study found that frequent use of high-potency marijuana was associated with changes in brain structure that may underlie cognitive changes.⁹ Researchers are also studying whether known health effects associated with chronic marijuana use may be more severe in individuals using higher-potency marijuana. These effects include impairments in learning, memory, and attention,¹⁰ as well as effects on insulin sensitivity and metabolism.¹¹ In addition, through the NIH-supported ABCD study, researchers will be able to examine the effects of marijuana at various levels of potency on brain and cognitive development and a host of other child health outcomes.

Another important outcome of interest is the development of cannabis use disorder (CUD), which takes the form of addiction in severe cases. Recent data suggest that 30 percent of those who use marijuana may have some degree of CUD. The use of higher potency marijuana is associated with increased risk of developing CUD¹² and increased CUD severity.¹³ Researchers are also examining how the use of high potency marijuana concentrates, which have become increasingly popular, affect risk for substance use disorder more broadly. A recent study found that relative to adolescent marijuana users who had not used concentrates, those who had were more likely to use other substances and to experience more risk factors and fewer protective factors for substance use problems, raising concerns about high-risk adolescents' exposure to high-THC marijuana.¹⁴

Researchers are also interested in how the potency of marijuana products may relate to impaired driving. Marijuana significantly impairs judgment, motor coordination, and reaction time, and studies have found a direct relationship between blood THC concentration and impaired driving ability.^{15,16,17,18} However, the exact nature of the impairment remains unclear and is often complicated by individuals who have used both alcohol and marijuana. NIH is supporting a project that uses a driving simulator and various levels of THC and cannabidiol (CBD) potency to better characterize these effects and the relationship between potency, blood levels, and driving impairment.¹⁹

⁹ Rigucci S et al. Effect of high-potency cannabis on corpus callosum microstructure *Psychol. Med.*, 46 (2016), pp. 841-854

¹⁰ https://projectreporter.nih.gov/project_info_description.cfm?aid=9456715&icde=47797167

¹¹ https://projectreporter.nih.gov/project_info_description.cfm?aid=9740528&icde=47797188

¹² Arterberry BJ et al. Higher average potency across the United States is associated with progression to first cannabis use disorder symptom. *Drug and Alcohol Dependence*, Volume 195, 1 February 2019, Pages 186-192

¹³ Freeman TP, Winstock AR. Examining the profile of high-potency cannabis and its association with severity of cannabis dependence *Psychol. Med.*, 45 (2015), pp. 3181-3189

¹⁴ Meier MH et al. Cannabis Concentrate Use in Adolescents. *Pediatrics*. August 2019. e20190338; DOI: <https://doi.org/10.1542/peds.2019-0338>

¹⁵ Lenné MG et al. The effects of cannabis and alcohol on simulated arterial driving: Influences of driving experience and task demand. *Accid Anal Prev*. 2010;42(3):859-866. doi:10.1016/j.aap.2009.04.021

¹⁶ Hartman RL, Huestis MA. Cannabis effects on driving skills. *Clin Chem*. 2013;59(3):478-492. doi:10.1373/clinchem.2012.194381

¹⁷ Hartman RL, Brown TL, Milavetz G, et al. Cannabis effects on driving lateral control with and without alcohol. *Drug Alcohol Depend*. 2015;154:25-37. doi:10.1016/j.drugalcdep.2015.06.015

¹⁸ https://projectreporter.nih.gov/project_info_description.cfm?aid=9735170&icde=47797188

Dr. Volkow –

NIH Research into Medical Uses

NIH has supported research into the pharmacology of THC and other cannabinoids, and the National Academies report from 2017 found that orally administered THC is effective in treating some medical conditions.

- Do you think those studies are sufficient for patient use of those products? If not, what regulatory structure should be used to evaluate the safety and efficacy before they are prescribed?

Response:

While NIH supports research that generates evidence on the safety and efficacy of potential therapeutics, it is outside of NIH's purview to determine if there is sufficient evidence to support approval of such products for patient use. The U.S. Food and Drug Administration (FDA) is the Federal agency charged with determining whether medical products are safe and effective for their intended use, and the FDA has a rigorous evaluation process. To date, the FDA has not approved marijuana (the whole plant) for the treatment of any disease or condition. However, several synthetic or plant derived cannabinoid drugs have been approved. These include Marinol and Syndros for the treatment of anorexia associated with weight loss in AIDS patients and for nausea and vomiting associated with cancer treatment. Marinol and Syndros include the active ingredient dronabinol, a synthetic form of THC. The FDA also approved Cesamet, which contains the active ingredient nabilone, a synthetic chemical similar to THC. Cesamet is approved for nausea and vomiting related to cancer treatment. Epidiolex, which contains purified marijuana-derived cannabidiol, was approved for the treatment of seizures associated with Lennox-Gastaut and Dravet syndromes in patients two years of age and older.

- Do studies related to treating medical conditions typically utilize orally administered THC and cannabinoids?

Response:

Studies examining the therapeutic potential of cannabinoids use various routes of administration. Some studies use orally administered THC and/or cannabidiol, often as a capsule or a liquid extract, and others use vaporized or smoked forms. Observational studies examining the impact of marijuana use to self-treat health conditions include patients using marijuana in whatever form they choose. Most therapeutic studies (including those summarized in the NASEM report²⁰) do not use marijuana plant material. Various factors make smoked marijuana less therapeutically promising than purified cannabinoid medications delivered through alternative routes of administration. These include the potential harmful effects on the lungs and heightened risk for addiction. In addition, the marijuana plant contain numerous poorly understood chemicals in

²⁰ The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Board on Population Health and Public Health Practice, Health and Medicine Division. The National Academies Press, 2017

addition to THC and CBD, and it is difficult to standardize dosages of a smoked plant with highly variable cannabinoid concentrations. Moreover, researchers who want to study the therapeutic use of marijuana plant material are required to obtain their product from the NIDA Drug Supply Program. This might be a disincentive for developing the plant as a medication insofar as it is not clear how developers would demonstrate equivalency between the marijuana available through NIDA that they would have to use in their clinical trials and the drug product that would ultimately be approved by the FDA for eventual marketing and sale.

- Are there any known medicinal uses for smoked marijuana?

Response:

There are currently no FDA-approved medicinal uses for smoked marijuana.

Senator Feinstein:

Questions for Nora Volkow, MD, Director of the National Institute on Drug Abuse (NIDA)

1. Using Marijuana to Treat Chronic Pain and Post Traumatic Stress Syndrome (PTSD)

A 2014 study published in the *Journal of the American Medical Association* found an association between lower opioid overdose death rates and marijuana use. This study was based on data from 1999 to 2010.

A subsequent study, published in the *Proceedings of the National Academy of Sciences*, which examined data from 1999 to 2017, found that states with medical marijuana laws actually saw a 23 percent increase in opioid overdose deaths.

- a) *What should we make of these studies, which seem to be in conflict?*

Response:

The study published in 2014 in the *Journal of the American Medical Association (JAMA)*, which analyzed data through 2010, showed slower rates of increase in opioid analgesic overdose death rates in states with medical marijuana laws compared to states without such laws.²¹ The subsequent study published in the *Proceedings of the National Academy of Sciences* reexamined this relationship using data through 2017. Similar to the previous study, it found that opioid overdose mortality rates between 1999-2010 in states allowing medical marijuana use were 21 percent lower than expected. However, when the analysis was extended through 2017, it was found that the trend reversed, such that states with medical marijuana laws experienced an overdose death rate 23

²¹ Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010. *JAMA Intern Med.* 2014;174(10):1668-1673.

percent higher than expected.²² This discrepancy suggests that overdose death rates are changing due to factors that weren't accounted for in the model, which could include a large range of influences from cultural shifts to state opioid policies to changes in the drug supply.

Many similar studies have assessed the impact of medical marijuana laws on opioid outcomes. Overall, results are inconsistent. There is some evidence to suggest that legalization of marijuana for recreational purposes and ready availability of marijuana dispensary products are associated with decreases in rates of opioid overdose.^{23,24} There is also evidence that medical marijuana laws are associated with lower levels of opioid prescribing in Medicaid and Medicare Part D enrollees.^{25,26} On the other hand, one study of a nationally representative sample found that medical marijuana law enactment was not associated with a reduction in nonmedical use of prescription opioids.²⁷ It should be emphasized that ecological studies that look at population measures of opioid outcomes cannot prove causation. More prospective studies controlling for important individual and state-level covariates are needed. It should also be emphasized that marijuana use carries risks, and the FDA has not approved marijuana or any cannabinoid drug for the treatment of pain, opioid misuse, or opioid use disorder.

b) Does medical marijuana have the potential to be an effective substitute for opioids in treating pain?

Response:

Preclinical and clinical research suggest that cannabinoids (chemicals found in marijuana) may have a role in treating pain, especially neuropathic pain; indeed, treatment of chronic pain is the most frequently cited reason for medical marijuana use.²⁸ In theory, marijuana could reduce or replace opioid use for pain, and this idea has significant anecdotal support. Survey data have shown that patients report substituting marijuana for opioids and benzodiazepines, and that patients replacing prescription opioids with marijuana have a preference for the pain relief to side-effect profile of marijuana.²⁹ However, a prospective study in Australia failed to confirm an opioid-sparing effect of marijuana over a four-year period.³⁰ Patients who used marijuana had more severe pain; continued to use opioids; had lower confidence in their ability to function while in pain; and had greater anxiety. It should be noted that this study was observational rather than a randomized clinical trial and is not conclusive.

²² Shover CL, Davis CS, Gordon SC, Humphreys K. Association between medical cannabis laws and opioid overdose mortality has reversed over time. *Proc Natl Acad Sci U S A*. 2019 Jun 25;116(26):12624-12626.

²³ Livingston MD, Barnett TE, Delcher C, Wagenaar AC. Recreational Cannabis Legalization and Opioid-Related Deaths in Colorado, 2000-2015. *Am J Public Health*. 2017 Nov;107(11):1827-1829.

²⁴ Chihuri S, Li G. State marijuana laws and opioid overdose mortality. *Inj Epidemiol*. 2019 Sep 2;6:38.

²⁵ Wen H, Hockenberry JM. Association of Medical and Adult-Use Marijuana Laws With Opioid Prescribing for Medicaid Enrollees. *JAMA Intern Med*. 2018 May 1;178(5):673-679.

²⁶ Bradford AC, Bradford WD, Abraham A, Bagwell Adams G. Association Between US State Medical Cannabis Laws and Opioid Prescribing in the Medicare Part D Population. *JAMA Intern Med*. 2018 May 1;178(5):667-672.

²⁷ Sagura LE, Mauro CM, Levy NS, et al. Association of US Medical Marijuana Laws With Nonmedical Prescription Opioid Use and Prescription Opioid Use Disorder. *JAMA Netw Open*. 2019;2(7):e197216.

²⁸ National Academies of Sciences, Engineering, and Medicine. 2017. The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research. Washington, DC: The National Academies Press.

²⁹ Khan SP, Pickens TA, Berlau DJ. Perspectives on cannabis as a substitute for opioid analgesics. *Pain Manag*. 2019 Mar 1;9(2):191-203.

³⁰ Campbell G, Hall WD, Peacock A, Lintzeris N, Bruno R, Larance B, Nielsen S, Cohen M, Chan G, Mattick RP, Blyth F, Shanahan M, Dobbins T, Farrell M, Degenhardt L. Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study. *Lancet Public Health*. 2018 Jul;3(7):e341-e350.

Along with ongoing preclinical work, two current NIDA-funded clinical trials are studying the safety and analgesic effects of combined treatment with cannabinoids and opioids.^{31,32} A third NIDA-funded clinical trial is looking at this question prospectively to assess how medical marijuana use affects opioid analgesic use in HIV+ and HIV- adults with severe or chronic pain.³³ These studies will provide individual-level information on the opioid sparing potential of cannabinoids. There remains an urgent need for effective, non-opioid treatments for pain, including the treatment of low back pain, cancer and chemotherapy-induced pain, neuropathic pain, indigestion, and arthritis-induced pain.^{34,35,36,37,38} This is an area of intense focus for NIH research.

The research regarding marijuana's effectiveness in treating PTSD appears to be limited.

a) Please explain what is currently known, particularly with respect to veterans, about the efficacy of using marijuana to treat PTSD.

Response:

NIMH is the lead Federal agency for research on mental disorders and supports a diverse research portfolio on post-traumatic stress disorder (PTSD) and related conditions. NIMH is supporting or conducting over 100 research projects relevant to posttraumatic psychopathology, including basic science research, translational and clinical research, and health care services research. NIMH-supported research involves participants across the lifespan and many different populations, including civilians, service members, and Veterans. Additionally, NIMH and other NIH Institutes and Centers, such as NIDA and the National Institute of Alcohol Abuse and Alcoholism (NIAAA), collaborate and coordinate with the Departments of Defense and Veterans Affairs in the area of service member and Veteran mental health research through the National Research Action Plan (NRAP).³⁹

NIMH is invested in identifying and developing treatments for PTSD and related conditions. While there is not currently strong evidence to support the use of marijuana to treat PTSD, preliminary research is underway to learn whether short-term treatment with low doses of tetrahydrocannabinol (THC), the primary psychoactive ingredient in marijuana that affects the cannabinoid system in our brains, might help make current cognitive behavioral treatments more effective by priming certain brain circuits prior to therapy – making it easier to learn and remember not to fear trauma reminders.⁴⁰ Additionally, NIMH has participated in trans-NIH

³¹ <https://clinicaltrials.gov/ct2/show/NCT03705559>

³² <https://clinicaltrials.gov/ct2/show/NCT03679949>

³³ <https://clinicaltrials.gov/ct2/show/NCT03268551>

³⁴ <https://clinicaltrials.gov/ct2/show/NCT02460692>

³⁵ https://projectreporter.nih.gov/project_info_description.cfm?aid=9608720&iede=47748806

³⁶ https://projectreporter.nih.gov/project_info_description.cfm?aid=9614965&iede=47748701

³⁷ https://projectreporter.nih.gov/project_info_description.cfm?aid=9796963&iede=47748842

³⁸ https://projectreporter.nih.gov/project_info_description.cfm?aid=9895227&iede=47748866

³⁹ https://obamawhitehouse.archives.gov/sites/default/files/uploads/nrap_for_oo_on_mental_health_august_2013.pdf

⁴⁰ https://projectreporter.nih.gov/project_info_description.cfm?aid=9441033

meetings that included evaluation by experts into the neurological and psychiatric effects of marijuana, other cannabinoids, and the endocannabinoid system.⁴¹

2. Uniform Regulations

Thirty-three states and the District of Columbia have legalized marijuana in some form. Each state has its own laws and regulations.

The lack of uniformity across states, in terms of the testing, labeling, or packaging of marijuana products, the strength of products that may be sold, how they may be advertised, and how they may be accessed, could lead to consumer confusion. This may also produce unintended, acute public health effects, including increased emergency room visits.

In Colorado, for instance, there was a threefold increase in marijuana-related emergency room visits between 2012 and 2016.

a) Would uniform regulations across states be helpful to ensure consumer safety and reduce public health impacts, such as emergency room visits associated with marijuana use?

Response:

At present, there is insufficient data to determine which of the myriad state regulations would be most effective in reducing the adverse public health outcomes associated with marijuana use. This is an important area of scientific investigation, reflected by NIDA's support since 2011 for a robust portfolio of marijuana policy research. In 2017, recognizing the gaps in our understanding of how changing state marijuana laws affect public health, NIDA convened an expert working group to develop a marijuana policy research agenda. The working group report⁴² included 28 recommendations for research in five broad areas, including research to: (1) develop standard measures of marijuana use; (2) better understand trends in use; (3) examine the health and social consequences of use, including motor vehicle accidents; (4) identify how product pricing, taxes, sales, promotion, and marketing affect use; and (5) develop prevention and treatment interventions that account for local variation in marijuana use and policies. NIDA is soliciting research applications on these and related marijuana policy issues⁴³ with the goal of supporting high quality science that can inform the development of evidence-based public health policies.

3. Barriers to Research

In your testimony, you noted that one of the difficulties associated with researching marijuana is that researchers are unable to legally access various strains of marijuana that are being used by individuals in states that have legalized its use. You further noted that the National Institute on

⁴¹ <https://www.drugabuse.gov/news-events/meetings-events/2016/03/marijuana-cannabinoids-neuroscience-research-summit>

⁴² National Institute on Drug Abuse. *Recommendation for NIDA's Cannabis Research Agenda: Report from the Cannabis Policy Research Workgroup*. February 6, 2018. https://www.drugabuse.gov/sites/default/files/nacda_cannabis_policy_research_workgroup_report_feb_2018.pdf

⁴³ <https://grants.nih.gov/grants/guide/notice-files/NOT-DA-19-065.html>

Drug Abuse has been working with the Drug Enforcement Administration to establish a mechanism through which researchers can legally access these strains in the future.

a) Can you please provide a status update on these ongoing conversations?

Response:

NIDA has not formally engaged the Drug Enforcement Agency (DEA) about permitting federally-funded researchers to access marijuana products on the market.

NIDA has been working with our interagency partners, including the White House Office of National Drug Control Policy (ONDCP), the FDA, and DEA, to identify opportunities for facilitating research with marijuana and other Schedule I substances, including opportunities to issue additional registrations for cultivating research marijuana. Presently, the University of Mississippi, which produces research marijuana through a contract with NIDA, is the only DEA registered marijuana manufacturer. It is not possible for the University to produce every marijuana product that is currently available in the various States. We were pleased that on August 26, 2019, the DEA signaled that it is moving forward with its review of additional grower applications⁴⁴ and that it would promulgate new regulations governing marijuana cultivation. NIDA looks forward to opportunities to provide input to the DEA as it develops a new regulatory framework that ensures an adequate and diverse supply of marijuana for research. NIDA would also remind researchers that the CSA permits researchers to import marijuana for research.

In collaboration with ONDCP, HHS, FDA, and DEA, NIDA has also been identifying ways to streamline the Schedule I research registration process.

b) In your view, is a legislative change required in order to enable researchers to legally access strains of marijuana that are being used in states that have legalized its use?

Response:

Under Federal law, researchers supported by NIDA and other Federal agencies are may not purchase marijuana available through state marijuana dispensaries, as marijuana is a Schedule I controlled substance under the CSA. Moreover, some universities have expressed reticence about allowing investigators to purchase dispensary products with non-Federal funds or do research with these products on university grounds for fear of violating Federal law. There is a significant gap in our understanding of their impact on health. The outbreak of e-cigarette or vaping product use associated lung injury (EVALI), which has been linked to informally-sourced THC-containing vape products, underscores the critical importance of facilitating researcher access to different product sources.

⁴⁴ <https://www.dea.gov/press-releases/2019/08/26/dea-announces-steps-necessary-improve-access-marijuana-research>

- c) *Would using marijuana in research that is obtained from states that have legalized its use present any challenges or safety concerns for research participants?*

Response

Marijuana available through state dispensaries is grown and processed under a variety of conditions and, like other botanical products, may include pesticides, pathogenic microbes, heavy metals, and other contaminants that could be harmful to humans. While most states with legal marijuana require product testing, there is no uniform testing standard. Likewise, product labeling varies, such that it may not be possible to determine the components of a marketed product, including the full range of cannabinoids present. Although the lack of testing and labeling standards presents challenges to conducting controlled research with these products, these challenges are surmountable. Before testing an unapproved drug or botanic product in humans, an investigator is required to submit to the FDA an investigational new drug (IND) application and to comply with FDA chemistry, manufacturing, and control requirements to ensure the proper identification, quality, purity, and strength of an investigational drug. We are aware of one study⁴⁵ for which the FDA approved an IND to conduct research with tablets containing THC and CBD derived from marijuana plants grown by a company that supplies Connecticut dispensaries. This study is not supported by the NIH, but it illustrates the feasibility of using products from suppliers of State dispensaries to develop research grade marijuana products that meet FDA's rigorous requirements. We anticipate that marijuana producers supplying dispensaries in other states would develop additional research-grade marijuana and marijuana-derived products if there was greater regulatory certainty about researchers' ability to use these products.

Senator Grassley

Dr. Volkow –

1. One of the biggest issues with marijuana is that people – particularly youth – think that since it's legalized in some states, it's therefore harmless. Marijuana and its derivatives have some medically recognized benefits, but like all drugs, it isn't without risk.
 - a. How can we in the federal government make sure that the average American citizen understands the risks associated with marijuana use, particularly as it is simultaneously more normalized yet potent?

Response:

Research is at the heart of developing evidence-based public health information. The increasing potency of marijuana and the proliferation of new marijuana products and methods for consuming them raise new public health concerns. This is underscored by the outbreak of EVALI, which has been linked to THC-containing vape products. It is imperative that scientists

⁴⁵ <https://reason.com/wp-content/uploads/2019/11/CTPharma-Yale-Study-news-release-11-8.pdf>

have the opportunity to study marijuana products that the public is using so that we can identify and communicate any risks associated with them.

Effective communication is a critical component of NIDA's mission, and we are committed to serving as a trusted source of scientific information on drug use and addiction. NIDA strives to make addiction research accessible to people in the community by strategically leveraging social media, blogs, and the news media to promote new findings, inform the public about emerging drug trends, and educate the community on addiction science. NIDA engages adolescents, through our popular teen-oriented Drugs and Health Blog, our annual National Drug and Alcohol Facts Week events that engage participating schools across the country, and Drugs & Alcohol Chat Day, in which NIDA scientists answer questions from middle- and high-school students in an all-day, real-time virtual chat. Because it can be difficult to reach adolescents directly, it is important to engage people with influence over them, including parents, teachers, and the media. NIDA produces materials aimed at helping parents and teachers communicate with children and teens about drugs, such as web-based FAQs and our Family Checkup resource, which highlights parenting skills that are effective at preventing drug use among youth. Through our NIDAMED initiative, NIDA also develops educational resources and tools for healthcare providers across disciplines—not just those working in substance use—who are at the front lines of diagnosing, preventing, and treating substance misuse and addiction.

2. A number of studies state that the risk for psychotic disorders, such as schizophrenia, increases with the frequency of marijuana use, potency of the product, and as the age at first use decreases.
 - a. What is it about marijuana that makes its users susceptible to psychotic disorders?

Response:

Research is needed to establish why individuals who use marijuana are at increased risk for psychotic disorders. The endocannabinoid system, through which marijuana exerts its effects, is thought to be involved. This system appears early in gestation and plays a critical role in brain development, especially in areas of the brain known to be involved in psychosis. One possible explanation for the link between marijuana use and psychosis is that marijuana use may lead to persistent disruptions in the endocannabinoid system, ultimately altering the developmental trajectory of circuits involved in psychosis. Importantly, a critical feature of mental illnesses, including psychotic disorders and substance use disorders, is the complicated interplay of biological and environmental factors that cause them and influence their progression. To the extent that marijuana contributes to the development of psychosis, it is likely a component cause, interacting with other known (e.g., family history) and, as of yet, unknown risk factors. Additional research is needed to identify these risk factors, determine their relative contribution to psychosis risk, and delineate the underlying mechanism by which they exert their effects.

Cornyn

Dr. Adams

Trends and Risks of High-Potency Marijuana

Your advisory raises awareness of the known and potential harms of marijuana use, especially for vulnerable populations like adolescents and pregnant women. Beyond the increased accessibility, you specifically note the increased potency of marijuana and wider variety of cannabis products being used as areas of significant public health concerns.

Could you expand on the trends you are seeing as in the onset of psychotic disorders and other mental health issues?

The scientific literature tells us that exposure to marijuana is associated with a range of psychosis outcomes from immediate, transient psychotic states that spontaneously resolve to delayed, persistent psychotic disorders such as schizophrenia (D'Souza et al, 2016). In an extensive review of the health effects of marijuana, the National Academies of Sciences, Engineering, and Medicine (NASEM) also found "...substantial evidence of a statistical association between cannabis use and the development of schizophrenia or other psychoses, with the highest risk among the most frequent users" (NASEM, 2017). The link between marijuana and psychosis has been found to be greater with earlier age of exposure to marijuana and genetic vulnerability.

Moreover, the findings of the 2018 National Survey on Drug Use and Health indicate an association between marijuana use and mental health concerns. In 2018, adults who had Any Mental Illness (AMI) or Serious Mental Illness (SMI) were more likely than those without any mental illness to be past-year users of marijuana (29.2 percent AMI and 38.9 percent SMI vs. 13.2 percent without mental illness)

- **Do cannabis concentrate and other high-THC products pose a greater public health risk than marijuana?**

In addition to risks of dependence, addiction, psychosis, and harm to the developing brain, highly concentrated products raise the risks of harm from accidental ingestion, unintentional overdose, and repetitive cycles of nausea and vomiting known as cannabinoid hyperemesis syndrome.

Perceptions of Marijuana Risks and Consequences

The advisory also notes that perceptions of the safety and health risks of marijuana have change significantly over the past few years.

How has this change in perception impacted use by adolescents and pregnant women? Can you discuss the consequences of these changes?

As of yet, it is unclear what effects the changing perception of marijuana use among adolescents and pregnant women will have on public health. One concern is that a reduced perception of harm could increase the likelihood of experimentation, which could lead to harms to the developing brain. Additionally, marijuana use remains illegal for youth under Federal law and in all states; normalization of its use raises the potential for criminal consequences in this population. In addition to the health risks posed by marijuana use, sale or possession of marijuana remains illegal under Federal law notwithstanding some state laws to the contrary.

Feinstein

Questions for Jerome Adams, MD, U.S. Surgeon General

1. Uniform Regulations

Thirty-three states and the District of Columbia have legalized marijuana in some form. Each state has its own laws and regulations. The lack of uniformity across states, in terms of the testing, labeling, or packaging of marijuana products, the strength of products that may be sold, how they may be advertised, and how they may be accessed, could lead to consumer confusion. This may also produce unintended, acute public health effects, including increased emergency room visits.

In Colorado, for instance, there was a threefold increase in marijuana-related emergency room visits between 2012 and 2016.

- a) *Would uniform regulations across states be helpful to ensure consumer safety and reduce public health impacts, such as emergency room visits associated with marijuana use?*

Uniformity of ill-informed policy ensures safety for no one. A first step in ensuring consumer safety and reducing public health impacts is to disseminate scientifically sound information to the public and relevant stakeholders. The marijuana available today is much more potent than what was available in the past. The risks of physical dependence, addiction, and harm to the developing brain increase with frequent use, exposure to high concentrations of THC, and with younger age of initiation.

2. Adolescent Marijuana Use and Risk-Perception

According to the Youth Risk Behavior Study, in states that have legalized recreational marijuana, teen use dropped between 1993 and 2017: those who said they used marijuana in the previous 30 days dropped 8 percent, while those who used it 10 or more times fell by 9 percent. However, in your testimony before the Senate Caucus on International Narcotics Control you expressed concern that perceptions of risk related to marijuana use among youth has decreased.

- a) *Given that trends in reduced perceptions of harm may often indicate future increases in adolescent drug use, are you concerned that marijuana use among adolescents could increase, despite initial decreases in states that have legalized its use?*

Contemporaneous with widespread legalization, more high school students are reporting a decline in perceived harmfulness of marijuana. Despite an initial decrease in states that have legalized its use, there is still a large number of adolescents becoming new marijuana users. Each day 3,700 adolescents aged 12 to 17 become new marijuana users, and last year over 9 million 12-25 year olds reported marijuana use in the prior month. This lowered perceived harm must be considered a risk in the context of increased access, high potency, and the large variety of forms available. To our youth, marijuana is everywhere.

Importantly, nearly one in five people who begin marijuana use during adolescence become addicted. And the earlier and more often a person uses marijuana – especially at higher THC levels – the higher the risk of harmful consequences.

- b) Given that marijuana seems to have more potential to harm the developing brain than the brain of an adult, should policies regarding marijuana use vary based on age? Is there any age at which marijuana use can be considered safe?*

We know that the brain continues to develop through the mid-twenties and that these developing brains are more vulnerable to harm. But **we need to know much more**. We need to understand the mid- and long-term health consequences of prenatal and youth exposure to marijuana, as well as more about strategies to mitigate harms. Research is also needed to understand the impact of today’s highly potent marijuana on chronic users of any age.

Cigarettes and alcohol are legal, but we know that doesn’t mean they are safe. Based on the best scientific information we have right now, marijuana use poses particular dangers to youth, but there is no age at which marijuana use can be considered “safe.”

Grassley

Surgeon General Adams

1. **One of the biggest issues with marijuana is that people – particularly youth – think that since it’s legalized in some states, it’s therefore harmless. Marijuana and its derivatives have some medically recognized benefits, but like all drugs, it isn’t without risk.**
 - a. **How can we in the federal government make sure that the average American citizen understands the risks associated with marijuana use, particularly as it is simultaneously more normalized yet potent?**

The Federal Government can produce and disseminate scientifically-sound information in formats that are easily consumable by the general public and targeted to specific stakeholders positioned to take action. Among the populations who need this information about the risks of marijuana use among youth and pregnant women are parents and parents-to-be, educators, healthcare and public health professionals, and policy makers at local, state, and national levels. The President donated his quarterly salary to support a digital ad campaign focused on parents of adolescents and on pregnant women. These ads are available for widespread use.

2. **A number of studies state that the risk for psychotic disorders, such as schizophrenia, increases with the frequency of marijuana use, potency of the product, and as the age at first use decreases.**
 - a. **What is it about marijuana that makes its users susceptible to psychotic disorders?**

Multiple studies have shown that the risk for psychotic disorders like schizophrenia rises with higher concentrations of THC, daily use, and earlier age of initiation. This association needs to be more deeply researched, including genetic and other susceptibilities.

5/21/20

Please note that my responses are shown in blue. If you have any questions I would be happy to discuss by phone (858-657-5733) or email (rfitzgerald@ucsd.edu). Thanks for your leadership in addressing these important issues.

Best regards,

Rob Fitzgerald, PhD
Professor of Pathology
UC San Diego Health

Cornyn

Fitzgerald

Impaired Driving

Dr. Fitzgerald, it has been noted that there is no scientific basis for the adoption of THC per se laws for driving. You have also mentioned the difficulties of using blood tests to establish a threshold for impairment.

- Can you discuss some approaches that states have taken to try to address impaired driving given these limitations?

Response: Several states have enacted per se legislation. Generally these states have implemented per se concentrations between 1 and 5 ng/mL of THC. At this time, there is no data to support this practice. Most states depend on officer observations, standard field sobriety tests, drug recognition expert (DRE) findings and results of blood testing to determine impairment. There are on-going studies to further evaluate these processes in relation to cannabis-related driving impairment. The combination of officer observations with toxicology lab findings is the most objective and scientific approach we have to date.

- What steps can be taken at the federal level to provide a stronger foundation for developing these policies?

Response: The following steps would be helpful:

1. Support efforts to train more police officers in the Advanced Roadside Impairment Driving Enforcement program (ARIDE). ARIDE is a NHTSA developed program that bridges training between standardized field sobriety tests and DRE exams.
2. Support efforts to train additional DREs.
3. Support forensic laboratories to enable them to acquire instrumentation required for these types of toxicology analyses.
4. Provide research funding focused on driving under the influence of cannabis and cannabis combined with alcohol. An important focus of such research should include the development of new behavioral and toxicological methods for identifying impairment and/or time since substance use. The federal government should partner with states like California, which have already begun funding these types of projects, in order to leverage federal investment.

5. Support legislation that would standardize reporting of driving under the influence of drugs, so we can get a better understanding of the national importance of this problem.

Gruber

Mental Illness and Tie to Higher THC Content

Dr. Gruber, you've noted how THC levels are rising in recreational marijuana products, CBD has declined to nearly untraceable levels, and that CBD has been shown to mitigate some of the negative effects of THC including adverse psychological symptoms.

- Do you believe that increased use of this higher-potency marijuana could increase the risks of developing mental health issues? Would that risk change depending on the age and frequency of the user?
- How impactful is the age of use to the short- and long-term risks of recreational marijuana use?

Risks for Drug Interactions

Studies have shown that cannabinoids, including CBD, can inhibit the liver's enzyme system, increasing both plasma levels and toxicity of other drugs, and potentially causing interactions with other drugs.

- Have there been sufficient studies into this risk? To what extent are we aware of adverse drug reactions between cannabinoids and prescription drugs?

Issues with Standardization in Research

Your testimony also notes that there is no consensus regarding the definition of chronic, regular, or heavy use versus casual or light use, and how that contributes to mixed findings across studies. It also notes that there isn't much standardization of measurements of marijuana.

- Have studies found a difference in outcomes based on the type of marijuana product used? For example, a study that calculates an estimate of grams of marijuana used by the subjects regardless of the product or model of use?
- What are some of the consequences of this lack of standardization?

Hennessy

Mental Illness Findings In NASEM Study

Dr. Hennessy, the National Academies report found substantial evidence of a statistical association between cannabis use and the development of schizophrenia or other psychoses. The highest risk was among the most frequent users.

- What factors contribute to this higher risk, and is it related to the higher potency of marijuana?

- Your testimony also notes that there is reason to question the directionality of the statistical association. Could you share those reasons?

The report found moderate evidence of increased symptoms of mania, hypomania in individuals diagnosed with bipolar disorder and regular cannabis use.

- Were the users taking orally administered THC, cannabis-derived products, or smoking marijuana?
- Is this evidence significant enough to advise patients with bipolar disorder to not utilize medicinal marijuana?

Evaluation of Medical Claims

The National Academies report did find conclusive evidence that orally administered THC is effective in treating some medical conditions, and that the clinical trials were utilized to gain FDA approval of the first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy. It is my sense that any medical claims related to marijuana and cannabis derived products should receive the same thorough review that this drug received before being made available.

- Do you agree with that?

Meier

IQ Decline and Adolescent Use

Dr. Meier, your study found that persistent cannabis use was associated with IQ decline from childhood to adulthood, and that IQ decline was concentrated in adolescent-onset persistent cannabis users. Persistent use is described as 50 or more uses of cannabis.

- Is there a correlation between THC content, and specifically the increased potency other witnesses have mentioned, on IQ decline along with frequency of use?

You also found that individuals who began using cannabis in adulthood did not show IQ decline.

- Were there other observed health impacts of cannabis use in that population? How much impact does frequency of use have on adults compared to adolescents?

High Potency Marijuana Health Risks

Your testimony mentions a lack of research into cannabis potency and the use of cannabis concentrates.

- What does existing research tell us about the risks of psychological dependence, addiction, and psychosis as a consequence of using concentrates?

- Is there any evidence that using concentrates could negatively impact users who have existing mental health issues?

Feinstein

Questions for Dr. Robert Fitzgerald, Clinical Pathologist, University of California, San Diego

1. Marijuana Impaired Driving

It is my understanding that marijuana impairment is difficult to detect in roadside tests, and that each state has a different standard of impairment, if it has any standard at all.

- a) *Based on your research, what are the biggest challenges in determining whether a driver is impaired by marijuana?*

Response: Let me first say that it's not quite accurate to say that each state has a different standard of impairment. While that is true when it comes to per se laws, many states strive to follow the guidelines established by the International Association of Chiefs of Police criteria regarding field sobriety tests and the determination of impairment, thus aiming to have some consistency in officer determinations.

The biggest challenges to determining if a driver is impaired by marijuana are:

1. There is no correlation between THC concentration in blood and effect on driving (unlike alcohol where there is a reasonably good relationship between blood alcohol concentration and severity of driving impairment).
 2. We have not developed an objective measure of THC impairment. The degree to which the field sobriety tests, which were developed to detect alcohol related impairment, accurately identify THC-related impairment is still a subject of research. Coming back to my response to Senator Cornyn, research aimed at the development of roadside test protocols that are specific to identifying cannabis associated driving impairment would help advance the field.
- b) *As you noted in your testimony, blood alcohol concentration is a clear indicator of alcohol-induced impairment. Is there, or will there soon be, any similar standard that can be applied to marijuana? You noted that oral fluids may be able to be used to determine marijuana impairment. Are there any drawbacks to using this testing method?*

Response: Currently there are no analogous measures of THC that are similar to a blood alcohol for driving impairment. It is possible that oral fluid and/or breath testing for THC (or a metabolite) could be developed that would indicate recent use, but I'm not convinced that they would necessarily indicate impairment. Being able to demonstrate recent use is a necessary step that could be combined with officer observations of impairment to identify people who are under the influence of marijuana. Drawbacks to oral fluid and breath testing is that results will probably vary depending on the route of administration (Smoked/vaped vs Oral).

- c) *Are drug recognition experts adequately trained to determine whether a driver is impaired by marijuana?*

Response: DREs undergo extensive training in the identification of presence of various drug classes, and their impairing effects. Due to some of the challenges in conducting research with cannabis (classified as a Schedule I drug), there are have only been limited studies examining the relationship between field sobriety and DRE evaluations and cannabis-related driving impairment. More research is needed to demonstrate how good drug recognition experts are. To date they have not been tested in large samples using a blinded randomized placebo controlled manner. We are working with the California Highway Patrol to conduct these kinds of studies. Results of this work would have implications for highway safety across the nation and it would be appropriate for the federal government to provide funds to match state investments.

2. Public Health Perspective

During the hearing, it was made clear that marijuana has the potential to cause both harms and benefits.

- a) *With this in mind, from a public health perspective, what are the biggest challenges related to marijuana, where are the most significant research gaps, and what should policymakers be focusing on moving forward?*

Response: The biggest challenge currently facing understanding effects of marijuana on human health is the inability of research institutions like the University of California to study the products that our population is exposed to. Because of federal scheduling of marijuana (schedule 1) we cannot investigate the concentrated forms of marijuana that the general public has access to, and thus have no mechanism to understand the health and public safety implications of these substances.

Policy makers should work on creating an exemption that allows established research institutions to perform studies using the products our population is exposed to. One of the primary strengths of the United States is our research engine. We need to unleash the power of our scientific enterprise to better understand both the beneficial and harmful effects of marijuana on human health. Our research universities, including in California, are reluctant to expand clinical research on cannabis because of concern that they might violate Federal law, and that the institutions and investigators may be subject to prosecution, or have their Federal awards withdrawn. Thus, creating exemptions, so that institutions can study and administer products that are legal in a State would be an important step. Related to this, the current single source of marijuana for medical research is the Federal Government itself (grown at the University of Mississippi). Expanding the supply base is important. Again, I would recommend that the federal government partner with states that have robust medicinal cannabis research enterprises to support studies on products that residents of those states have access to. Another important way to facilitate research on marijuana and health is to reschedule marijuana to reflect the emerging science. Based on the data, the most appropriate is Schedule 3.

Questions for Dr. Staci Gruber, Associate Professor of Psychiatry, Harvard Medical School

1. Comparing Medical and Recreational Use

There doesn't seem to be a great deal of information available about the differences between the use of marijuana for medical versus recreational purposes. Given that much of your research has involved subjects who use medical marijuana, can you comment on the following:

- a) *Have you found that there is a difference in the types, quantity, and concentration of marijuana products used by medical marijuana patients compared to recreational patients?*
- b) *Should these differences be taken into consideration when developing policies to address marijuana?*
- c) *Given the lack of research and information on appropriate dosing, etc., how do medical marijuana users know what products are effective for their particular condition, and is there any reason to be concerned about adverse impacts on the body?*

2. Marijuana Strains

It is my understanding that different strains of marijuana contain different chemical profiles. Depending on the specific strain, the marijuana could produce more positive than negative effects.

- a) *Can you speak to the differences in strains that contain high levels of cannabidiol compared to tetrahydrocannabinol, and vice-versa, and how these strains might have different effects on the body?*
- b) *Should different strains of marijuana be regulated differently?*

3. Veterans

You noted during your testimony that ongoing research, through the MIND study, is being conducted with respect to veterans' use of marijuana products to treat a variety of conditions, including post-traumatic stress disorder, insomnia, and chronic pain. It is my understanding that you have already conducted two studies related to veterans and that you are currently enrolling participants in the third study.

- a) *Please discuss your findings from the first two studies that have been conducted.*
- b) *Does marijuana use to treat veterans, particularly as it relates to Post Traumatic Stress Disorder (PTSD), seem to be effective? Is there any concern that marijuana use could exacerbate problems associated with PTSD?*

3. Public Health Perspective

During the hearing, it was made clear that marijuana has the potential to cause both harms and benefits.

- a) *With this in mind, from a public health perspective, what are the biggest challenges related to marijuana, where are the most significant research gaps, and what should policymakers be focusing on moving forward?*

Questions for Sean Hennessy, PharmD, PhD, University of Pennsylvania School of Medicine

1. Evidence Regarding Use of Marijuana for Medical Purposes

You were a member of the committee of the National Academies of Sciences, Engineering, and Medicine that produced the 2017 report titled “The Health Effects of Marijuana and Cannabinoids.”

Based on your work on this report:

- a) *Does enough information exist to conclude what the proper dosage and delivery mechanisms for medical marijuana patients should be?*
- b) *Does enough information exist to determine how marijuana might interact with other medications?*

2. Public Health Perspective

During the hearing, it was made clear that marijuana has the potential to cause both harms and benefits.

- a) *With this in mind, from a public health perspective, what are the biggest challenges related to marijuana, where are the most significant research gaps, and what should policymakers be focusing on moving forward?*

Questions for Dr. Madeline Meier, Assistant Professor of Psychology, Arizona State University

1. Research on Marijuana Use and IQ levels

In 2012, you authored a longitudinal study, which found that early persistent use of marijuana by adolescents could result in the loss of up to eight IQ points, which are not recoverable, even after a person stops using. It is my understanding that these findings held true, even when controlling for socio-economic status.

However, subsequent longitudinal studies involving twins, published in the Proceedings of the National Academy of Sciences, found that there was no predictable difference in the twins’ IQ when one used marijuana in adolescence and the other did not.

- a) *Can you speak to the differences in these two studies and discuss whether we should be concerned about the loss of IQ among adolescents when they are early, persistent users of marijuana?*

As a follow up, it is my understanding that you recently authored a study, which found that adolescent marijuana use is not associated with changes in the adult brain structure.

- b) *How, if at all, are the findings in this study related to the findings of your previous longitudinal study on IQ?*

2. Marijuana Strains

It is my understanding that different strains of marijuana contain different chemical profiles. Depending on the specific strain, the marijuana could produce more positive than negative effects.

- a) *Can you speak to the differences in strains that contain high levels of cannabidiol compared to tetrahydrocannabinol, and vice-versa, and how these strains might have different effects on the body?*
- b) *Should different strains of marijuana be regulated differently?*

3. Public Health Perspective

In your testimony before the Senate Caucus on International Narcotics Control, you spoke about the facts, research and conclusions at which you have arrived with your research and work regarding marijuana use. As discussed during the hearing, these facts, the research already conducted and potential future research hold the answer to policy-making regarding marijuana.

- a) *From a public health perspective, what are the biggest challenges related to marijuana, where are the most significant research gaps, and what should policymakers be focusing on moving forward?*

Grassley

Dr. Robert Fitzgerald

1. An obstacle with drugged driving is measuring impairment. You stated in your testimony that “officer observations combined with results of toxicology testing” can be used to measure impairment.
 - a. Would this assessment replace or supplement measuring THC levels in a sample? Why or why not?

Response: Since there is no correlation between concentrations of THC in blood with impairment it is essential that toxicology testing of biological specimens is combined with officer observations. Both the officer observations and the analysis of THC (and/or metabolites) in biological specimens are essential components of keeping our roads safe with respect to drugged driving. Officers can document impairment and toxicology testing can help identify the cause.

2. Drug Recognition Experts, or DREs, are the gold standard in recognizing and identifying signs of impairment. A DRE, however, is a person with his or her own subjective points of view and experiences.
 - a. How can we ensure consistency in assessment and due process protections?

Response: Currently the combination of a DRE’s findings and toxicology testing is the best way to provide objective data for identifying driving impairment. This is an imperfect system and we need to continue to investigate other methods for objectively identifying impairment.

Dr. Sean Hennessy

1. You stated in your written testimony that there is “substantial evidence” of an association between cannabis use and the development of schizophrenia or other psychoses. However, you also qualify this by stating, “there is reason to question the directionality of this association.”
 - a. Please expand on the risks of marijuana use and why its users are particularly susceptible to psychoses, and why there is a question as to the directionality of this association.

Senate Follow-Up Questions

Mental Illness and Tie to Higher THC Content

Dr. Gruber, you've noted how THC levels are rising in recreational marijuana products, CBD has declined to nearly untraceable levels, and that CBD has been shown to mitigate some of the negative effects of THC including adverse psychological symptoms.

- Do you believe that increased use of this higher-potency marijuana could increase the risks of developing mental health issues? Would that risk change depending on the age and frequency of the user?
 - *While there are no direct studies that objectively quantify real-world use of high potency products and mental health outcomes, it is likely that higher potency products could exacerbate existing or prodromal symptoms of psychotic disorders given studies which cite a dose-response relationship, such that increased potency is associated with an increased risk for psychotic symptoms. Importantly, however, in the majority of these naturalistic studies, the actual potency of cannabis products has not been directly assessed. Similarly, a number of acute administration studies show increased "psychotic-like" behaviors (i.e., feelings of paranoia) following exposure to higher potency products. However, the effects reported in these studies are only observed during acute intoxication in a laboratory setting and can therefore be considered transient. Individuals who are potentially vulnerable to developing a psychotic disorder (i.e., those with a genetic predisposition/family history of psychosis) may be at increased risk the earlier they initiate cannabis use, and the more frequently and heavily they use cannabis. Importantly though, a number of additional factors are likely to moderate outcomes. Overall, although a body of research provides important evidence suggesting that higher potency products may increase the risk for psychosis or psychotic-like behaviors, studies that directly assess and quantify the potency of the products patients are actually using are needed to elucidate the specific relationship between marijuana potency and mental health outcomes; this is best done in studies of those with and without genetic liability.*
- How impactful is the age of use to the short- and long-term risks of recreational marijuana use?
 - *In general, most agree that earlier, heavier and more frequent exposure to marijuana is related to an increased likelihood of negative consequences, particularly in terms of cognition, given that adolescents and emerging adults are still in the midst of critical brain maturation processes, which leaves them vulnerable to outside influences such as injury, illness, or drugs, including (but not limited to) marijuana.*

Risks for Drug Interactions

Studies have shown that cannabinoids, including CBD, can inhibit the liver's enzyme system, increasing both plasma levels and toxicity of other drugs, and potentially causing interactions with other drugs.

- Have there been sufficient studies into this risk? To what extent are we aware of adverse drug reactions between cannabinoids and prescription drugs?

- *Although this research is vital to determine the safety of cannabinoid-based products, empirical data is generally lacking in this area. To date, a handful of studies have identified enzymes that are strong inducers/inhibitors of the Cytochrome P450 enzyme system, which has implications for the efficacy and safety of certain conventional medications that patients may be taking concurrently with cannabinoid-based products.*

Issues with Standardization in Research

Your testimony also notes that there is no consensus regarding the definition of chronic, regular, or heavy use versus casual or light use, and how that contributes to mixed findings across studies. It also notes that there isn't much standardization of measurements of marijuana.

- Have studies found a difference in outcomes based on the type of marijuana product used? For example, a study that calculates an estimate of grams of marijuana used by the subjects regardless of the product or model of use?
 - *Historically, most studies examining the impact of marijuana use have quantified use by collecting data on number of episodes of use per week, number of "joints" or "marijuana cigarettes" smoked, or grams of marijuana used. When studies use these types of calculations, these measurements do not reflect the specific amount of each individual cannabinoid, or other components contained in cannabis plants, that a person is exposed to. Although it is more difficult to measure exposure to the compounds within a plant (samples must be sent to a laboratory for analyses, which can be logistically difficult due to Schedule I restrictions, as well as cost prohibitive), this type of data will ultimately help elucidate the unique effects of individual cannabinoids as well as other constituents and compounds found within cannabis plants. It is likely that some compounds may confer negative outcomes (e.g., THC), while other compounds such as cannabidiol and potentially certain terpenoids, may be neuroprotective. In addition, it is also possible that potential contaminants, including heavy metals, pesticides, and yeast/mold could contribute to negative outcomes.*
 - *To date, no studies have directly compared specified preset/predetermined or quantifiable amounts between product types (e.g., matched amount of specific cannabinoids within flower vs edibles vs oils). More research is needed to more fully understand how specific modes of use/routes of administration moderate the effects of cannabinoids as well as the effects of other compounds found within the cannabis plant.*
- What are some of the consequences of this lack of standardization?
 - *Due to the lack of standardization, it is difficult to answer questions regarding safe limits of cannabis use. While many studies have reported decrements among heavy, recreational cannabis users, studies often define "chronic," "heavy," or "frequent" differently. For example, these criteria are often based on descriptions/definitions from within the literature but are often somewhat arbitrary numbers that can reflect different time frames (i.e., lifetime vs monthly vs weekly use), different amounts of cannabis used (i.e., a particular amount of grams of cannabis, or a particular number of use episodes). In addition, there is no standard 'serving size' or dose of THC, CBD, or any other cannabinoids although some states, including Colorado, consider a 'standard dose' of*

edibles as 10 mg. This aspect of the lack of standardization makes it difficult to directly compare product types.

Questions for Dr. Staci Gruber, Associate Professor of Psychiatry, Harvard Medical School

1. Comparing Medical and Recreational Use

There doesn't seem to be a great deal of information available about the differences between the use of marijuana for medical versus recreational purposes. Given that much of your research has involved subjects who use medical marijuana, can you comment on the following:

- a) Have you found that there is a difference in the types, quantity, and concentration of marijuana products used by medical marijuana patients compared to recreational patients?
 - a. *Although products sold to recreational users and medical marijuana patients can be the same, recreational users primarily seek products with considerable amounts of THC, as they desire the "high" or mood altering, often euphoric or mellowing, effects of cannabis. In contrast, medical marijuana patients typically initiate use with the primary goal of symptom alleviation, and often times look to actively avoid feelings of intoxication. As such, MC patients frequently seek products with rich and varied cannabinoid profiles (e.g., high-CBD products). In fact, preliminary data from my lab's longitudinal, observational study suggests that on average, medical marijuana patients have higher exposure to CBD relative to THC. Products high in CBD and other cannabinoids in addition to THC have the potential to confer a variety of benefits. A number of studies have indicated that THC appears to serve as an effective analgesic, antiemetic, and appetite stimulant.*

- b) Should these differences be taken into consideration when developing policies to address marijuana?
 - a. *It is important to recognize that cannabis is a complex plant. As such, cannabinoid formulations will likely exert unique effects depending on which cannabinoids are contained within a product, as well as which other constituents (e.g., terpenoids, flavonoids,) are present. The impact of cannabis products are not only related to the presence of these individual compounds, but also depend on the amount of each of these constituents in a given product, their interaction with other compounds, and an individual's unique response to product administration. Therefore, research examining the actual products patients are using will help determine safety, efficacy, and side effect profiles; data from these investigations, which must employ empirically sound, controlled models (whether preclinical or clinical), should be used to help guide public policies.*

- c) Given the lack of research and information on appropriate dosing, etc., how do medical marijuana users know what products are effective for their particular condition, and is there any reason to be concerned about adverse impacts on the body?
 - a. *Currently, there is a lack of research on appropriate dosing of medical cannabis products, which is at least in part due to the fact that researchers cannot study*

commercially available cannabis-based products in research participants using clinical trial models. Moreover, as the cannabis plant contains over 100 phytocannabinoids and over 400 chemical compounds, each of which may have an impact, it is currently difficult for researchers, clinicians, and consumers to know what specific products might be most effective for a particular condition. While research remains in its infancy, some studies have suggested that individual cannabinoids demonstrate unique therapeutic properties, such as the anti-anxiety and anti-inflammatory effects of CBD, or the analgesic and anti-emetic effects of THC. More research is needed to clarify the impact of these primary cannabinoids as well as many of the other cannabinoids and compounds within the plant. When using any cannabinoid-based product, particularly those containing THC, it is recommended to "start low and go slow," meaning that medical marijuana patients should start with low doses of a product and wait to determine if a larger dose is needed. It is also important for patients who are taking other conventional medications to be aware of potential interactions between cannabinoids and their medications. For example, CBD has been shown to impact the Cytochrome P450 enzyme system, which means that CBD may strengthen or weaken the effects of many conventional medications.

b. *In terms of side effects, potential negative effects of THC have been well-documented and include the potential of increasing heart rate, inducing psychomimetic effects like hallucinations/paranoia/anxiety, and decreasing cognitive performance. Some preliminary evidence also suggests that CBD may cause drowsiness, and for some, high doses of purified CBD products may also have gastrointestinal side effects.*

2. Marijuana Strains

It is my understanding that different strains of marijuana contain different chemical profiles. Depending on the specific strain, the marijuana could produce more positive than negative effects.

- a) Can you speak to the differences in strains that contain high levels of cannabidiol compared to tetrahydrocannabinol, and vice-versa, and how these strains might have different effects on the body?
- a. *Strains, also known as cultivars, are each unique and vary with regard to concentrations of the primary constituents (THC and CBD), and with regard to other cannabinoids and compounds, including terpenoids and flavonoids, which are thought to exert their own biobehavioral effects. More research is needed to understand the effects of individual strains, but given that THC is the primary intoxicating constituent of cannabis and is often associated with negative effects at high doses (e.g., cognitive decrements, increased heart rate, paranoia, anxiety), those using high THC strains are potentially more likely to experience adverse effects related to cannabis use. High CBD strains are typically considered to have therapeutic effects, such as anti-anxiety, anti-inflammatory, and anti-epileptic properties, but a number of factors, including the amount of THC and other cannabinoids that are also present in the product, will influence the effects of a particular strain.*
- b) Should different strains of marijuana be regulated differently?
- a. *Given the potential negative impact of higher THC product, particularly on our most vulnerable consumers (i.e., youth), many have considered requiring a higher tax or age restrictions for products containing THC levels about a certain level. Conversely, some*

may consider requiring a threshold for minimum levels of CBD, which may have the ability to mitigate the effects of THC and/or confer neuroprotective properties.

3. Veterans

You noted during your testimony that ongoing research, through the MIND study, is being conducted with respect to veterans' use of marijuana products to treat a variety of conditions, including post-traumatic stress disorder, insomnia, and chronic pain. It is my understanding that you have already conducted two studies related to veterans and that you are currently enrolling participants in the third study.

- a) Please discuss your findings from the first two studies that have been conducted.
 - a. *While we have a number of ongoing studies focused on assessing the impact of cannabis and cannabinoid-based products in veterans, thus far, none have been completed to date; all are currently ongoing and remain in the data collection phase.*
- b) Does marijuana use to treat veterans, particularly as it relates to Post Traumatic Stress Disorder (PTSD), seem to be effective? Is there any concern that marijuana use could exacerbate problems associated with PTSD?
 - a. *According to available literature, evidence is mixed; there have been concerns that cannabis could exacerbate existing symptoms of PTSD, but other reports indicate that cannabis products could confer benefits. For example, small studies suggest that THC or synthetic, non-plant derived THC (e.g., nabilone) could enhance sleep quality in those with PTSD; however, the positive effects of THC for PTSD symptoms do not appear to address many of the other symptoms associated with PTSD. Studies of CBD or CBD-containing products have found evidence suggesting amelioration of symptoms such as nightmares and anxiety, and reported that CBD could be beneficial in fear extinction processes. These seemingly mixed findings are likely due to the fact that cannabis itself is a heterogeneous plant containing hundreds of cannabinoids, terpenoids, and flavonoids. Given that studies of veterans are often observational or survey-based studies, the products used by veterans in each of these studies is often not directly assessed or profiled and can vary greatly. Clinical trials assessing products specifically formulated to target symptoms of PTSD and reduce potential negative side effects (e.g., anxiety, paranoia) are needed.*

4. Public Health Perspective

During the hearing, it was made clear that marijuana has the potential to cause both harms and benefits.

- a) With this in mind, from a public health perspective, what are the biggest challenges related to marijuana, where are the most significant research gaps, and what should policymakers be focusing on moving forward?
 - a. *Currently, the legal status of cannabis contributes to a number of complexities and difficulties when conceptualizing cannabis-based research studies. In the future, reconciling federal and state law will help facilitate researchers' abilities to conduct empirically sound research. In addition, allowing researchers to study real-world*

products that are available to patients and that are actually being used will provide critical data regarding the benefits and harms associated with specific cannabinoid formulations. Future research focused on safety and efficacy of unique formulations of cannabinoids for specific medical/psychiatric conditions and symptoms is clearly needed. Research directly examining the impact of high potency products and novel, marijuana concentrates products (which contain extremely high levels of THC) are also needed. Further, given that older adults represent the fastest growing population of cannabis consumers, researchers focused on the impact of cannabis in this population is critical. Preclinical data suggests that older adults may experience unique outcomes given a number of important factors in this population; adults have slower metabolisms, high rates of comorbid conditions and conventional medication use, and often experience age-related cognitive decline as well as age-related changes in the endocannabinoid system.

**Response to Questions Submitted by Members of the
Senate Caucus on International Narcotics Control**

submitted by Sean Hennessy
University of Pennsylvania
27 May 2020

Senator Cornyn

Mental Illness Findings In NASEM Study

Dr. Hennessy, the National Academies report found substantial evidence of a statistical association between cannabis use and the development of schizophrenia or other psychoses. The highest risk was among the most frequent users.

- What factors contribute to this higher risk, and is it related to the higher potency of marijuana?
Response: Numerous factors are believed to affect one's risk of developing schizophrenia or other psychotic disorders. A 2016 meta-analysis (that is, a study of studies) conducted by Marconi and colleagues¹ examined the relationship between a person's level of cannabis use and their risk of developing schizophrenia and other psychotic disorders. That meta-analysis examined studies, published through 2013, that classified participants' self-reported cannabis use into at least three different categories—non-use plus at least two other levels. Those studies did not ask participants about the potency of the cannabis that they used, nor did they directly measure potency. Thus, the studies that found that a higher level of cannabis use is associated with a higher risk of psychosis did not include information on the potency of the cannabis.

- Your testimony also notes that there is reason to question the directionality of the statistical association. Could you share those reasons?

Response: The study committee of the National Academies of Science, Engineering and Medicine (NASEM) noted that there are at least three potential explanations for the observed associations between use of cannabis and the development of psychotic disorders: 1) cannabis use may contribute to the development of psychotic disorders; 2) psychotic disorders or their precursors may contribute to cannabis use; or 3) the same factors (e.g., genetic vulnerability, environment) may contribute to both cannabis use and to the development of psychotic disorders. A dose-response relationship between cannabis use and psychotic disorders may be present under any of these three explanations. Further, none of these explanations excludes the others—they could all be working in concert. Given that schizophrenia and other psychotic disorders may develop slowly over many years, it can be difficult to know even from longitudinal studies that measure drug use before schizophrenia was diagnosed, whether cannabis use actually preceded the emergence of early symptoms of schizophrenia in any given person. Therefore, as noted in the report (e.g., Box 12-1 on page 296), making conclusions about the direction of causation underlying such associations is challenging.

The report found moderate evidence of increased symptoms of mania, hypomania in individuals diagnosed with bipolar disorder and regular cannabis use.

¹ Marconi, A., Di Forti, M., Lewis, C. M., Murray, R. M., & Vassos, E. (2016). Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophrenia bulletin*, 42(5), 1262-1269.

- Were the users taking orally administered THC, cannabis-derived products, or smoking marijuana?

Response: The studies that examined symptoms of mania and hypomania in persons with bipolar disorder looked at smoked cannabis.

- Is this evidence significant enough to advise patients with bipolar disorder to not utilize medicinal marijuana?

Response: Decisions regarding whether or not to use medical cannabis involve weighing the potential benefits and harms in the specific person in whom use is being considered. The NASEM study committee did not assess the balance of potential benefits and harms of medical cannabis in either the general population or in specific subgroups, such as persons with bipolar disorder.

Evaluation of Medical Claims

The National Academies report did find conclusive evidence that orally administered THC is effective in treating some medical conditions, and that the clinical trials were utilized to gain FDA approval of the first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy. It is my sense that any medical claims related to marijuana and cannabis derived products should receive the same through review that this drug received before being made available.

- Do you agree with that?

Response: The NASEM report did not articulate any findings or conclusions regarding the level of review or evidence that should be required from a regulatory perspective to either support medical claims for cannabis or cannabis-derived products, or to support the availability of cannabis or cannabis-derived products for medical use. Given the unique history and cultural context of cannabis in the US, the issues concerning its regulation are complex. Personally, I have not engaged in sufficient consideration or discussion of these issues to have formed well-founded views on this question.

Senator Feinstein

1. Evidence Regarding Use of Marijuana for Medical Purposes

You were a member of the committee of the National Academies of Sciences, Engineering, and Medicine that produced the 2017 report titled “The Health Effects of Marijuana and Cannabinoids.”

Based on your work on this report:

- Does enough information exist to conclude what the proper dosage and delivery mechanisms for medical marijuana patients should be?*

Response: No. Even for the few FDA-unapproved uses for which there is at least moderate evidence for the effectiveness of cannabis or cannabis-derived products, there is very little evidence about the comparative effects of different doses or of different mechanisms of delivery. This represents a significant knowledge gap concerning therapeutic uses of cannabis and cannabis-derived products.

b) *Does enough information exist to determine how marijuana might interact with other medications?*

Response: No. Although the 2017 NASEM report did not specifically address the question of drug-drug interactions, there are a number of mechanisms by which THC, CBD, and other constituents of cannabis and cannabis-derived products might be expected to interact with prescription drugs.² However, very little research has been performed to evaluate such interactions, including their health effects in real-world patient populations.

2. Public Health Perspective

During the hearing, it was made clear that marijuana has the potential to cause both harms and benefits.

a) *With this in mind, from a public health perspective, what are the biggest challenges related to marijuana, where are the most significant research gaps, and what should policymakers be focusing on moving forward?*

Response: The 2017 NASEM report examined the available evidence concerning the benefits and harms of cannabis and cannabis-derived products. A common theme of our findings was that the available evidence was sparse and of uneven quality. To support and improve the cannabis research agenda, the NASEM study committee made recommendations to address research gaps, improve research quality, improve surveillance capacity, and address research barriers.

To specifically address your question, the study committee recommended that public agencies, philanthropic and professional organizations, private companies, and clinical and public health research groups provide funding and support for a [national cannabis research agenda](#) that addresses key evidence gaps. Prioritized research objectives should include, but need not be limited to:

Clinical and Observational Research

- Examine the health effects of cannabis use in at-risk or under-researched populations, such as children and youths and older populations, pregnant and breastfeeding women, and heavy cannabis users.
- Investigate the pharmacokinetic and pharmacodynamic properties of cannabis, modes of delivery, different concentrations, in various populations, including the dose–response relationships of cannabis and THC or other cannabinoids.
- Determine the harms and benefits associated with understudied cannabis products, such as edibles, concentrates, and topicals.
- Conduct well-controlled trials on the potential harmful and beneficial health effects of using different forms of cannabis, such as inhaled (smoked or vaporized) whole cannabis plant and oral cannabis.
- Characterize the health effects of cannabis on unstudied and understudied health endpoints, such as epilepsy in pediatric populations; symptoms of posttraumatic stress disorder; childhood and adult cancers; cannabis-related overdoses and poisonings; and other highpriority health endpoints.

Health Policy and Health Economics Research

- Identify models, including existing state cannabis policy models, for sustainable funding of national, state, and local public health surveillance systems.

² Foster, B. C., Abramovici, H., & Harris, C. S. (2019). Cannabis and cannabinoids: Kinetics and interactions. *American Journal of Medicine*, 132(11), 1266-1270.

- Investigate the economic impact of recreational and medical cannabis use on national and state public health and health care systems, health insurance providers, and patients.

Public Health and Public Safety Research

- Identify gaps in the cannabis-related knowledge and skills of health care and public health professionals, and assess the need for, and performance of, continuing education programs that address these gaps.
- Characterize public safety concerns related to recreational cannabis use and evaluate existing quality assurance, safety, and packaging standards for recreational cannabis products.

In addition, to ensure that sufficient data are available to inform research on the short- and long-term health effects of cannabis use (both harmful and beneficial effects), the committee recommended that the Centers for Disease Control and Prevention, the Substance Abuse and Mental Health Services Administration, the Association of State and Territorial Health Officials, the National Association of County and City Health Officials, the Association of Public Health Laboratories, and state and local public health departments fund and support improvements to federal public health surveillance systems and state-based public health surveillance efforts.

Senator Grassley

1. You stated in your written testimony that there is “substantial evidence” of an association between cannabis use and the development of schizophrenia or other psychoses. However, you also qualify this by stating, “there is reason to question the directionality of this association.”
 - a. Please expand on the risks of marijuana use and why its users are particularly susceptible to psychoses, and why there is a question as to the directionality of this association. Response: The NASEM report did indeed note that there is substantial evidence of a statistical association between cannabis use and the development of schizophrenia and other psychotic disorders (Conclusion 12-1; page 295). The committee noted that at least three potential mechanisms may explain these associations: 1) cannabis use may contribute to the development of psychotic disorders; 2) psychotic disorders or their precursors may contribute to cannabis use; or 3) the same factors (e.g., genetic vulnerability, environment) may contribute to both cannabis use and the development of psychotic disorders. None of these explanations excludes the others—they could all be working in concert. Given that schizophrenia and other psychotic disorders can develop slowly over many years, it can be difficult to know even from longitudinal studies that measured cannabis use before schizophrenia was diagnosed whether cannabis use actually preceded the emergence of early symptoms of schizophrenia in any given person. Therefore, as noted in the report (e.g., Box 12-1 on page 296), making conclusions about the direction of causation underlying such associations is challenging.

Senate Caucus on International Narcotics Control Hearing
Marijuana and Public Health

October 23, 2019

Written Statement from:
Robert L. Fitzgerald, PhD
Professor of Pathology
University of California-San Diego



Introduction

Senators Cornyn and Feinstein, and Members of the Caucus it is a pleasure to be here today to discuss issues related to the use of marijuana and driving. As a way of a brief introduction, my first job out of graduate school was as a forensic toxicologist in Virginia helping to determine the cause and manner of death in Medical Examiner cases. At the Medical Examiner's office, I saw the devastating effects of driving under the influence on a routine basis. I also had the opportunity to work with State and Local police along with prosecution and defense attorneys to present scientific data in courts of law. Currently I am clinical toxicologist at UC San Diego where my research focuses on developing analytical methods to measure concentrations of THC and metabolites following recent marijuana exposure. I am part of a large team of investigators at the UCSD Center for Medical Cannabis Research (CMCR) focused on understanding both beneficial and detrimental effects of cannabis on human health. We recently completed enrolling subjects in one of the largest studies to date looking at the effect of smoked marijuana on driving performance and are in the initial stages of analyzing data.

The relationship between marijuana use and driving impairment is complex because of the unique pharmacokinetic and pharmacodynamic properties of delta-9-tetrahydrocannabinol (THC). With ethanol there is a clear relationship between amount of alcohol consumed, blood concentrations, and effects on driving performance. With marijuana these types of relationship are much more complex. The relationship between blood THC concentrations and crash risk has not been established, but there is a clear understanding that THC impairs driving performance. The question that remains is how to best identify drivers who are impaired by marijuana. There

are no perfect solutions and legislative directives must balance keeping our roadways safe with due process.

Problems with determining the relationship between concentrations of THC and impairment is that levels of THC in blood vary widely depending on the route of administration, the time of sampling after dosing and the characteristics of the individual using marijuana. Generally, smoked marijuana causes effects that start shortly after inhalation and last about 3 hours, while subjects who eat marijuana start feeling effects about an hour later and can have effects up to 8 hours. Unlike alcohol which is cleared with 24 hours of drinking, THC and several metabolites accumulate in the body with repeated dosing so frequent users have baseline concentrations that exceed the per se limits currently used in some states for driving under the influence. After smoking, THC concentrations in blood change rapidly and our studies have documented the poor relationship between blood concentrations of THC and measures of impairment. Studies like this led the National Safety Council to put out a position statement in 2017 that reads:

“It is further concluded that due to rapid changes in blood THC concentrations over time, there is no minimum safe threshold blood concentration below which a driver can be considered to have been unaffected while driving following recent marijuana use. Consequently, there is no scientific basis for the adoption of THC per se laws for driving.” This statement was also supported by the International Association of Police Chiefs. Despite these position statements, 18 States currently have some form of per se statutes.

How do we keep our roads safe? In California prosecution of driving under the influence of drugs is currently based on officer observations combined with results of toxicology testing. This practice will likely continue for the foreseeable future.

Since there is no reasonable expectation that THC or a metabolite of THC will be useful for per se impairment an alternative would be to develop methods to identify “recent use” biomarkers. The biological specimens that could be used to determine if a driver has recently used marijuana are blood, breath, and oral fluid. The primary advantages of breath and oral fluid over blood is that they can be collected at the roadside at the time of a traffic stop as opposed to blood which typically takes about 90 minutes to collect. This is an important consideration because unlike ethanol, concentrations of THC can fall by more than 90% in this short timeframe. There are a variety of ongoing efforts to identify markers of recent use.

In respect of my time limit I would like to close my initial statement by mentioning two items that this caucus needs to be aware of so they can help shape appropriate regulations.

1. Due to federal restrictions, investigators cannot study the cannabis products our population is exposed to. This is a critically important public health issue that needs to be changed.
2. Currently there is no standardized data collection for driving under the influence of drugs. Without good data it is difficult to develop good policy.

I hope my testimony was helpful and look forward to answering any questions members of the caucus may have.

**Testimony of Dr. Staci Gruber Before the Senate Caucus on International Narcotics Control
“Marijuana and America’s Health: Questions and Issues for Policy Makers” October
23, 2019**

The term “marijuana” typically describes *all* constituents derived from the plant *Cannabis Sativa L.*, which contains more than 100 phytocannabinoids that interact with the body’s natural endocannabinoid system (ECS). Delta-9-tetrahydrocannabinol (THC), the primary psychoactive constituent of MJ, is mainly responsible for the subjective “high” felt by recreational MJ users who often seek strains and products with high concentrations of THC. Given that the ECS affects growth, differentiation, positioning, and connectivity among neurons, exposure to exogenous cannabinoids such as THC may disrupt neural development, especially during adolescence.

However, preliminary evidence also suggests that MJ and its constituents likely hold extraordinary potential for the treatment of a number of medical conditions¹. Cannabidiol (CBD), the primary nonintoxicating constituent of the plant, has become well-known for its role in treating intractable pediatric-onset seizure disorders², and has demonstrated promise in treating other medical conditions including pain and multiple sclerosis³, as well as psychiatric conditions including anxiety⁴ and psychosis^{5,6}. CBD has been shown to mitigate some of the negative effects of THC, including adverse psychological symptoms⁷ and structural alterations in the brain^{8,9}. It is of note that while THC levels are rising in *recreational* MJ products, CBD levels have declined to nearly undetectable levels¹⁰.

Despite a body of evidence demonstrating structural and functional brain alterations among MJ users, more than 24 million Americans report past month MJ use¹¹. Current deliberations over the legalization of MJ often highlight the potential benefits of medical marijuana (MMJ), and with the majority of states legalizing MMJ, it is not surprising that perceived risk related to MJ use is at an all-time low. In fact, recent US national survey data indicate that more high school seniors use MJ daily (5.9%) than smoke cigarettes (4.2%), more than 37% of seniors reported past-year MJ use, and only 29% of all seniors surveyed thought regular MJ use was harmful¹². Further, almost 9% of the national population aged 12 or

older currently use MJ¹¹, which is potentially concerning given critical neurodevelopmental changes that take place throughout adolescence. During adolescence, a period often marked by increased risk-taking behaviors including experimentation with substance use, brain regions, particularly those associated with executive functioning (e.g., problem solving, planning, inhibition), undergo processes that refine and strengthen neural networks, which continue until at least the mid-20s^{13,14}. Throughout emerging adulthood, white matter volume and integrity also increase, which are associated with improvements in neural conductivity^{15,16}. As adolescence is marked by ongoing neuromaturational processes and given increasing evidence that the adolescent brain is more vulnerable to the effects of drugs than the adult brain, *those at the greatest risk for adverse consequences represent a vast and vulnerable population of MJ consumers, a combination that poses serious public health concerns.*

To date, the majority of data regarding the impact of MJ is derived from studies of individuals with chronic, heavy recreational use; given public health concerns regarding adolescent use, many studies have specifically examined adolescent users or those with adolescent onset of MJ use. These studies have yielded a large body of research documenting the neurocognitive impact of recreational MJ use on the brain using both neuropsychological assessment and neuroimaging techniques, which have helped to clarify the underlying structural and functional alterations associated with recreational MJ use. Given heterogeneity across study findings, potential moderating variables must be taken into account given overall implications for public policy and considerations for continued research efforts.

Neurocognitive Impact of Recreational MJ Use

Cognition

Numerous studies have documented the effects of MJ across a wide range of cognitive domains¹⁷⁻²⁰. With regard to studies of memory function, several reviews indicate that recreational MJ use appears to impact a number of individual aspects of memory^{18,21,22}; however, findings are most robust for measures of verbal learning, where decrements have been observed in terms of encoding, recall, and recognition²². Despite strong evidence for verbal memory impairment among recreational MJ consumers, findings from

other areas of memory function, namely associative and visuospatial memory, are less clear^{21,23,24}. Studies of executive function which examine response inhibition, planning, and decision-making, generally report decrements in MJ users²⁵⁻³². Further, several investigations also report that poorer executive function is a predictor of MJ use^{33,34} and MJ-related problems³⁵. Although only a small number of studies have examined processing speed, most have observed deficits in MJ users^{36,37,38} relative to non-users. Findings with regard to overall intelligence are largely inconsistent. While some studies have reported lower IQ among recreational MJ users relative to non-users^{37,39}, more recent longitudinal studies with larger sample sizes challenge these findings. In one investigation of twins discordant for MJ use, MJ users demonstrated lower IQ relative to non-users, but MJ-using twins failed to show significantly greater IQ decline relative to their abstinent siblings, suggesting that the observed decline in IQ might be attributable to familial factors, rather than a direct result of MJ use⁴⁰. Similarly, a second large-scale, longitudinal study⁴¹ did not find IQ differences between MJ users and controls after adjusting for confounding variables.

Brain Function

Neuroimaging techniques have facilitated researchers' ability to clarify the underlying neural substrates associated with cognitive decrements in MJ users. Using a variety of paradigms, researchers have studied functional correlates across cognitive domains. While the direction and magnitude of findings are often variable, overall, MJ use is typically associated with altered patterns of neural activation across multiple brain regions. For example, during measures of executive function, a number of studies have reported altered activation in the frontal cortex^{30,42-44}. Although many have examined verbal memory using traditional neuropsychological measures, the majority of fMRI studies have utilized spatial working memory tasks. Interestingly, MJ users generally demonstrate similar behavioral performance compared to non-users on these paradigms, yet neural alterations have been observed across studies^{24,45-48}, suggesting that less efficient neural strategies may be used by MJ users in order to achieve the same level of performance as non-users. Other aspects of cognition proposed to be associated with drug use, including associative memory, error monitoring, and reward processing have also been examined using fMRI methods in

recreational MJ users. Overall, functional correlates of each of these processes appear to be altered in MJ users relative to non-MJ users⁴⁹.

Brain Structure

Brain imaging techniques have also afforded researchers the opportunity to examine the impact of MJ use on brain structure, including measures of both grey and white matter. Studies assessing the structural impact of MJ use often report bidirectional findings, which are typically related to the brain region under examination⁵⁰. Interestingly, however, alterations are most often observed in areas with high densities of CB1 receptors⁸ and may also be influenced by age of onset and increased MJ use⁵¹. A recent review reported that while larger cerebellar and striatal volumes have been observed in MJ users, regular MJ users often exhibit reductions in grey matter volume in several other regions, particularly in the hippocampus⁸. Importantly, studies have found that structural alterations in a number of brain regions appear to be related to increased executive dysfunction⁵²⁻⁵⁵ and poorer verbal memory⁵⁶.

White matter, critical for efficient communication between brain regions, has also been assessed among MJ-using populations. In general, reduced white matter fiber tract integrity, measured using diffusion tensor imaging (DTI) techniques, has been observed in several prefrontal, limbic, parietal and cerebellar tracts in adolescent and emerging adult MJ users⁵⁷⁻⁶⁰. A relationship between earlier age of onset of MJ use and lower white matter integrity has also been reported⁵⁷⁻⁶⁰. Interestingly, these alterations have also been correlated with impulsivity^{59,60} and appear to be a risk factor for poorer executive function and for cannabis use disorders, specifically in adolescent users⁵⁷.

Variables Moderating the Impact of MJ Use on the Brain

Age of onset of MJ use

As noted, overall, investigations have revealed functional and structural alterations associated with MJ use, but a number of studies have also reported that decrements observed in adults tend to be more significant, or persist for longer periods in those who began using MJ during adolescence^{29,61}. This is not surprising given the fact that the brain is neurodevelopmentally vulnerable during adolescence and sensitive

to exposure to drugs, alcohol, illness, and injury. Additionally, some investigations have noted that earlier age of MJ onset appears to be inextricably linked to higher frequency of use and amount of MJ used³⁰, suggesting that increased MJ use may be a trait characteristic specific to early onset users. As such, individuals with earlier MJ onset may have an “additive vulnerability,” marked by a brain that is susceptible to the impact of MJ coupled with an increased likelihood to engage in higher levels of MJ use, relative to those with later MJ onset. Age of MJ onset is therefore an important variable to include in research endeavors as individuals who begin using MJ during adolescence are characterized by relatively “immature” brains and a tendency to use MJ more regularly, potentially posing a greater risk for cognitive decrements. Further, as differences between MJ users and non-users are often attributable to those with early versus late MJ onset^{27,62-64}, collecting data regarding onset of MJ use is likely to help reduce heterogeneity of study findings in future investigations.

Exposure to MJ: Frequency, Magnitude, Potency & Novel Modes of Use

Increased frequency and magnitude of MJ use have been shown to be predictive of poorer cognitive performance^{30,33}. To date, most studies regarding MJ use have examined the impact of heavy, chronic recreational MJ use. Accordingly, conclusions regarding the effects of MJ use on the brain are generally reflective of chronic, heavy use and may not necessarily be generalizable to light or more casual MJ users. However, it is important to recognize that there is no consensus regarding the definition or criteria required for “chronic,” “regular,” or “heavy” use versus “casual” or “light use.” Discrepancies among what constitutes heavy relative to light MJ use has likely contributed to mixed findings across studies. Further, although most studies base assessments of MJ use on current number of days of MJ use or number of episodes of use per week, some investigators utilize estimates based on longer periods of time, such as lifetime smoking episodes. Each of these definitions account for frequency of use, but none specifically account for magnitude or amount of cannabis consumed, which can be difficult to assess especially across multiple products types. Unlike alcohol or other drugs, there is no standardized measure of MJ, which stems from a variety of difficulties in calculating exposure to MJ. For example, some derive the magnitude of MJ

consumed by calculating the total number of joints smoked or "puffs" taken, while others calculate an estimate of actual grams of MJ used, which is becoming increasingly difficult with the advent of novel products and varied modes of use. Even if individuals can quantify the number of grams of MJ used, it does not account for other factors that influence overall exposure.

Individuals often use MJ products of various strengths, or potencies. Over the last several decades, the potency of recreational MJ, measured as THC concentration, has increased exponentially. Analyses of recreational MJ products revealed that between 1995 and 2017 levels of THC more than quadrupled, increasing from 4% to 17%¹⁰. In addition, highly potent products termed "concentrates" have also had a surge in popularity in recent years, raising additional concerns about the impact of recreational MJ use on the brain. These products are made by extracting THC from MJ flower to yield products with extremely high levels of THC that can exceed 80%⁶⁵. Concentrated products, including "dabs" (the colloquial name for concentrated oil created by extracting THC from flower-based MJ products), shatter, wax, budder, and others all have significantly higher potency relative to conventional flower products⁶⁶. Although no studies thus far have directly examined the impact of concentrates on the brain, survey studies have associated the use of concentrates with negative physiological consequences,⁶⁷ stronger intoxicating effects⁶⁸, and higher levels of physical dependence⁶⁹ and self-reported depression and anxiety⁷⁰. In addition, one study assessing the relationship between brain structure and potency of MJ flower products (classified as either "high" or "low" potency by self-report) noted alterations in corpus callosum white matter microstructure in high-potency MJ users compared to low-potency users and controls⁷¹. Findings suggest that use of high potency MJ products, including concentrates, may impart negative consequences on the brain. This raises concern that adverse consequences associated with MJ use may be more significant now than in the past, particularly among young users.

Length of abstinence

Throughout the literature, studies have employed a range of abstinence periods, generally ranging from 12 hours to one month, in order to examine the residual effects of MJ use. Length of abstinence may

also influence study findings, as studies have shown changes in cognition over the course of abstinence periods. While some have reported recovery of function after one to three months of MJ abstinence,^{37,72} others have shown that decrements are sustained over time¹⁸. Additional research is needed in this area, particularly studies examining the impact of *extended* abstinence periods.

Chronologic Age: the impact of MJ use in older adults

Historically, increasing rates of MJ use have been noted among adolescents and young adults, which raised public health concerns given their neurodevelopmental vulnerability, driving research efforts to focus on youth and young adult populations. Recently, however, with expanded legalization across the US for both medical and recreational use, rates of use are now climbing fastest among older adults. According to data from the National Survey of Drug Use and Health (NSDUH), from 2002-2014, the proportion of adults aged 55 to 64 who reported MJ use in the past year increased by 455% from 1.1% to 6.1%; among those 65 and older, this proportion also increased dramatically, rising from 0.3% to 1.3%⁷³. In comparison, rates among 18- to 25-year-olds rose only 13% in the same period, while rates among 12-17 year-olds actually *decreased* 10%. Despite the prevalence of MJ use among older adults, consequences of use are relatively unknown in this population, although preclinical evidence suggests that THC may impact older individuals differently. One preclinical study reported a *reversal* of age-related cognitive decline in mature and old mice treated with low doses of THC, while the same exposure resulted in cognitive decrements among young mice⁷⁴. It is of note, however, that older adults may also have specific vulnerabilities with regard to MJ use. As overall metabolism slows with age, MJ may take longer to “clear the body,” increasing the likelihood of experiencing higher levels of intoxication or an adverse event. Further, cannabinoids, including CBD, can inhibit the liver’s cytochrome P450 enzyme system, increasing both plasma levels and toxicity of other drugs and potentially causing drug-drug interactions⁷⁵. This is important, as approximately one-third of all prescription drugs in the US are used by older adults⁷⁶. Additional studies aimed at identifying the specific impact of MJ use in older adults are clearly warranted, especially given the shifting landscape of legal recreational and medical use in a growing number of states.

Can the Effects of Recreational MJ Use be Generalized to Medical MJ Use?

Historically, THC, the primary intoxicating constituent of MJ, has been the most commonly studied cannabinoid. Recreational users typically seek products high in THC, given their goal to “alter their current state of being” or “get high.” In contrast, MMJ patients are typically *not* interested in getting high, but instead seek symptom relief. Accordingly, MMJ patients are inclined to use products with varied cannabinoid constituent profiles, which often include those with high levels of CBD and other non-intoxicating cannabinoids, as well as THC. While CBD has been shown to mitigate some of the negative effects related to THC⁹ and has been hypothesized to have tremendous therapeutic potential for a variety of conditions and indications¹, studies investigating the properties of additional cannabinoids, including cannabigerol (CBG), cannabichromene (CBC), and cannabinol (CBN), also cite positive effects, such as anti-inflammatory and neurogenic effects⁷⁷⁻⁸⁰. In addition to the unique effects of each individual cannabinoid, many posit the existence of an “entourage effect,” which describes the synergistic action that occurs in the presence of multiple cannabinoids and terpenoids⁸¹. Terpenoids, the essential oils responsible for the flavor and fragrance components of cannabis, also exert their own biobehavioral health effects. This potential entourage effect may help explain why products from whole-plant extractions appear to be more efficacious than isolated cannabinoid compounds^{82,83}.

Although additional research is needed to fully understand the effects of individual cannabinoids as well as interactions between cannabinoids, terpenoids, flavonoids and other compounds present in the plant, differences between recreational and medical users’ goals of use and choice of products raise the question as to whether the documented effects of recreational MJ use can be generalized to MMJ use. Despite the literature on recreational MJ use, few studies thus far have specifically examined the impact of MMJ on the brain, which may differ from recreational use given a number of factors, including but not limited to goal of use, product choice, and age of the consumer. Recent work from the first longitudinal, observational study of MMJ patients suggests that following three months of MMJ treatment, patients exhibit improvements in mood, quality of life, and sleep disturbance as well as *improved* cognitive performance on measures of executive function relative to baseline^{84,85}. Additionally, in the first study to use neuroimaging techniques to

examine functional correlates of MMJ use, three months of MMJ treatment was related to an apparent normalization of brain activation during the completion of the Multi-Source Interference Test (MSIT), a robust measure of cognitive control⁸⁴. These improvements, which are in stark contrast to previous findings in recreational MJ users, particularly those with adolescent onset, may be related to potentially protective factors such as the presence of CBD and other therapeutic cannabinoids in MMJ patients' products or are perhaps attributable to the fact that most MMJ patients are adults and beyond the period of neurodevelopmental vulnerability when they initiate use. Further, these MMJ patients reported significant symptom alleviation and a notable decrease in the use of conventional medication (including opioids) following three months of MMJ treatment; these factors may also contribute to the cognitive improvements observed in this population. Additional research is needed to fully explore mechanisms of action among medical MJ patients in order to identify specific factors which moderate the adverse effects of MJ primarily observed in young, recreational users.

Marijuana and Public Policy

The rapid pace of legalization efforts has caused policy to outpace science, and while additional research is needed, it is imperative to use scientific evidence to guide policy decisions. Studies of recreational MJ use report decrements in cognitive performance and alterations in brain structure and function, and most agree that individuals who begin to use MJ in adolescence or those with earlier onset of use are more likely to demonstrate neurobiologic alterations relative to those who initiate use later in life. This finding is consistent with work demonstrating that the adolescent brain is not fully mature during adolescence and thus more vulnerable to the effects of drugs and alcohol than adults. It is critical for policymakers to carefully consider age-related guidelines to help prevent or reduce adolescent exposure. In addition, advertising of MJ products should not target youth, and safe guidelines for packaging of MJ products should be established to prevent accidental ingestion by children.

Policymakers are encouraged to engage in dialogue regarding safe limits of MJ use. In addition to frequency and magnitude of MJ used, safe limits of MJ use should consider potency of MJ products used

and novel modes of administration, specifically those designed to deliver large doses of THC very quickly. Some have considered increased tax rates for higher potency products or limiting the total amount of THC within products available to specific consumer populations (e.g., young adults). Given that a number of cannabinoid constituents have potentially beneficial and neuroprotective effects, it is also important to determine whether implementing minimums for certain constituents, such as CBD, could help to mitigate some of the adverse effects related to THC. In light of data demonstrating a significant increase in THC and decline in CBD within recreational products, reversing this trend could prove to be helpful.

Barriers to Cannabis Research

In order to fully understand the potential benefit and possible risks associated with cannabis use, researchers *should be able to study actual cannabis products currently available to consumers* for both recreational and medical use. However, despite a growing need for information to help inform public policy and safe use guidelines, a number of barriers currently hinder research efforts. First, the Schedule I status of MJ poses significant challenges. Currently, cannabis and all cannabinoids derived from plants containing >.3% THC by weight, fall under Schedule I of the CSA, the most restrictive category, despite the fact that numerous constituents, particularly CBD, are non-intoxicating and have been deemed "safe" by a number of sources^{86,87}. While MJ may be legal in a particular state for medical and/or recreational/adult purposes, MJ remains illegal at the Federal level making it difficult for scientists to gain access to appropriate products for investigation. The Schedule I status of MJ can also lead to delays in conducting research, as multiple approvals are required, including applying for and receiving a Schedule I license, and a number of other safeguards must be in place to prevent potential diversion, such as storage, security, and surveillance considerations.

Current regulations stipulate that all cannabis to be used in clinical trials must be obtained from a single Federal source, currently the National Institute on Drug Abuse (NIDA). Although the DEA announced in 2016 that it would accept applications for non-NIDA entities to become registered to manufacture MJ and related products to supply researchers in the US, NIDA currently remains the only source of cannabis

material for researchers. Over the last several years, NIDA's Drug Supply Program (DSP) has exponentially expanded the number of conventional MJ flower products (and one high CBD extract) available to researchers, which vary in constituent composition (low, medium, high THC, CBD, etc.) and potency. However, investigations using only products from NIDA's drug supply may suffer from a lack of ecological or external validity, as potency and constituent profiles and ratios may not be consistent with consumers' products. Further, the majority of products available through the DSP are in conventional flower form, and do not reflect the wide range and types of products/modes that MJ consumers and patients often use. Mechanisms allowing cannabis growers, providers or dispensaries to have their products tested, vetted, and ultimately made available to researchers for use in clinical research studies are a potential step in facilitating the assessment of actual MJ products used by consumers, including concentrate products, edibles, topicals, and tinctures, as well as products supplied by medical and recreational dispensaries.

Conclusions

Decades of research have focused on the impact of recreational MJ use, documenting cognitive decrements and structural and functional brain alterations in chronic, heavy users. These changes are most evident among adolescent users or those with early onset of MJ use, as adolescence represents a critical period of neurodevelopment, making youth more vulnerable to exogenous influences, including MJ. Accordingly, frequency and magnitude of use, product choice, potency, mode of use, and age of the consumer are all likely to influence the effects of MJ on the brain. It is important, however, to recognize that cannabis is a diverse and complex plant comprised of hundreds of constituents, many of which are likely to exhibit unique effects when studied alone as well as in the presence of other cannabinoids, terpenoids, flavonoids, and other compounds. Despite the range of effects conferred by individual constituents, many of which are non-intoxicating and have no diversion potential, cannabis and cannabinoids extracted from plants with >0.3%THC by weight is currently treated as a single entity and classified as a Schedule I substance, the most restrictive drug class, significantly hindering research efforts. While the impact of recreational MJ use among adolescents and early onset users is often the focus of research investigations, resulting in a body of

literature, the impact of medical MJ use is vastly understudied. Investigations are needed to clarify the impact of MMJ on the brain and health-related outcomes (e.g. changes in conventional medication use, impact on pain, sleep, quality of life, mental health conditions, etc.), both short- and long-term consequences of high potency products and novel modes of use, effects of recreational and medical MJ use in older adults, and the efficacy and safety of existing products as well as those in development, ideally using clinical trial models. As the nation has warmed toward both medical and adult recreational MJ, the need for empirically sound data is critical to help patients and consumers make informed decisions about their use.

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Testimony by Sean Hennessy before the Senate Caucus on International Narcotics Control
October 23, 2019

Good afternoon. My name is Sean Hennessy and I am a pharmacist-epidemiologist and faculty member at the University of Pennsylvania. I was a member of the 16-person committee that wrote the report entitled *The Health Effects of Cannabis and Cannabinoids*¹ that the National Academies of Science, Engineering and Medicine released in January 2017.

More than 150 years ago, the National Academy of Sciences was created through a congressional charter signed by Abraham Lincoln to serve as an independent, authoritative body outside the government that could advise the nation on matters pertaining to science and technology. It later expanded to include engineering and medicine. Every year, approximately 6,000 National Academies members and volunteers serve *pro bono* on consensus study committees or convening activities. The National Academies' consensus study process is considered the gold standard of independent, nonpartisan, evidence-based advice.

Our committee conducted a comprehensive review and synthesis of the existing evidence regarding the potential health effects—both therapeutic and harmful—of cannabis and cannabis-derived products. Our 487-page report lists nearly 100 different conclusions about these effects. It also lists four recommendations to address research gaps, improve research quality, improve surveillance capacity, and address research barriers. I'd like to briefly summarize what our committee found and recommended. I have attached a copy of the report's highlights for your reference.

For each potentially therapeutic or harmful health effect that we examined, our committee classified the evidence as either *conclusive*, *substantial*, *moderate*, *limited*, or as *no or insufficient evidence*.

Potential Therapeutic Effects

We found *conclusive evidence* that orally administered tetrahydrocannabinol (THC) is effective in treating chemotherapy-induced nausea and vomiting. Synthetic THC (dronabinol) and a synthetic analogue of THC (nabilone) are both FDA-approved for this use.

We found *substantial evidence* that some cannabis products are effective for the treatment of chronic pain in adults. Of the trials examined, 13 studied a product called *nabiximols* (an oral-mucosal cannabis extract containing equal amounts of THC and CBD), 7 studied cannabis flower that was either smoked or vaped, 5 studied orally administered synthetic THC, and 3 studied THC oramucosal spray.

We found *substantial evidence* that orally administered cannabinoids (nabiximols and nabilone) can improve patient-reported symptoms of muscle spasticity in persons with multiple sclerosis.

We found *moderate evidence* that cannabis-derived products, primarily nabiximols, can improve short-term sleep in persons with sleep disturbance associated with obstructive sleep apnea, fibromyalgia, chronic pain, and multiple sclerosis.

¹ National Academies of Sciences, Engineering, and Medicine. 2017. *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research*. Washington, DC: The National Academies Press. doi:10.17226/24625.

We found only *limited evidence* that cannabis and oral cannabinoids can increase appetite and reduce weight loss associated with HIV/AIDS; that oral cannabinoids can improve clinician-measured muscle spasticity in persons with multiple sclerosis; that oral THC can improve symptoms of Tourette syndrome; that oral CBD can improve anxiety symptoms in individuals with social anxiety disorders; and that nabilone can improve symptoms of posttraumatic stress disorder.

There were many conditions for which we found *no or insufficient evidence* that cannabis or cannabis-derived products were effective, including cancers, irritable bowel syndrome, and Parkinson disease.

After we issued our report, the results of clinical trials were made available that served as the basis for the approval by the US Food and Drug Administration of concentrated CBD oil (Epidiolex®) for use as part of a multi-drug treatment for two rare and severe forms of epilepsy.² For reasons of transparency, I note that I served as a consultant for Greenwich Biosciences, Inc. in 2018 and received consulting fees that were less than the \$5000 threshold for a “significant financial interest” set by the US Department of Health and Human Services.

Potential Harmful Health Effects

We found *substantial evidence* of a statistical association between recent cannabis use and an increased risk of motor vehicle crashes.

We found *substantial evidence* of a statistical association between maternal cannabis smoking and lower birth weight of the offspring.

We found *substantial evidence* of a statistical association between long-term cannabis smoking and worse respiratory symptoms including cough, increased sputum production, wheeze, and more frequent chronic bronchitis episodes.

We found *substantial evidence* that initiating cannabis use at an earlier age is a risk factor for the development of problem cannabis use.

We found *substantial evidence* of a statistical association between cannabis use and the development of schizophrenia or other psychoses, with the highest risk among the most frequent users. However, there is reason to question about the directionality of this association.

We found *moderate evidence* of a statistical association between acute cannabis use and impairment in learning, memory, and attention.

We found *moderate evidence* of a statistical association between regular cannabis use and increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders.

² <https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-comprised-active-ingredient-derived-marijuana-treat-rare-severe-forms>, accessed 16 October 2019.

We found *moderate evidence* of a statistical association between cannabis use and a small increased risk for the development of depressive disorders.

We found *moderate evidence* of a statistical association between cannabis use and increased incidence of suicidal ideation, suicide attempts, and completed suicide.

We found *moderate evidence* of a statistical association between regular cannabis use and increased incidence of social anxiety disorder.

We found *moderate evidence* that during adolescence the frequency of cannabis use, oppositional behaviors, a younger age of first alcohol use, nicotine use, parental substance use, poor school performance, antisocial behaviors, and childhood sexual abuse are risk factors for the development of problem cannabis use.

We found *moderate evidence* of a statistical association between cannabis use and the development of substance dependence and/or a substance abuse disorder for substances, including alcohol, tobacco, and other illicit drugs.

We found *moderate evidence* of a statistical association between cannabis use and an increased risk of overdose injuries among pediatric populations in U.S. states where cannabis is legal according to state law.

Barriers to Research on the Effects of Cannabis and Cannabis-derived Products

Our committee identified four challenges to conducting research on the health effects of cannabis:

1. There are specific regulatory barriers, including the classification of cannabis as a Schedule I substance, that impede the advancement of cannabis and cannabinoid research.
2. It is often difficult for researchers to gain access to the quantity, quality, and type of cannabis product necessary to address specific research questions on the health effects of cannabis use.
3. A diverse network of funders is needed to support cannabis and cannabinoid research that explores the beneficial and harmful health effects of cannabis use.
4. To develop conclusive evidence for the effects of cannabis use on short- and long-term health outcomes, improvements and standardization in research methods are needed.

Recommendations

Our committee made the following four recommendations:

1. To develop a comprehensive evidence base on the short- and long-term health effects of cannabis use (both beneficial and harmful effects), public agencies, philanthropic and professional organizations, private companies, and clinical and public health research groups should provide funding and support for a national cannabis research agenda that addresses key gaps in the evidence base.
2. To promote the development of conclusive evidence on the short- and long-term health effects of cannabis use (both beneficial and harmful effects), agencies of the U.S. Department of Health and Human Services should jointly fund a workshop to develop a set of research standards and benchmarks to guide and ensure the production of high-quality cannabis research.

3. To ensure that sufficient data are available to inform research on the short- and long-term health effects of cannabis use, the federal, state, and local health authorities should fund and support improvements to federal public health surveillance systems and state-based public health surveillance efforts.
4. The Centers for Disease Control and Prevention, National Institutes of Health, U.S. Food and Drug Administration, industry groups, and nongovernmental organizations should fund the convening of a committee of experts tasked to produce an objective and evidence-based report that fully characterizes the impacts of regulatory barriers to cannabis research and that proposes strategies for supporting development of the resources and infrastructure necessary to conduct a comprehensive cannabis research agenda.

Thank you for your attention and the opportunity to discuss these issues. I look forward to answering your questions.

January 2017

efforts to support the advancement of research, and address the current barriers to cannabis research.

Report

HIGHLIGHTS

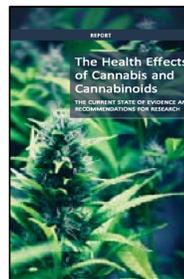
The Health Effects of Cannabis and Cannabinoids

The Current State of Evidence and Recommendations for Research

Recent years have seen a rapid rise in the medical and recreational use of cannabis: a broad term that can be used to describe the various products and chemical compounds (e.g., marijuana, cannabinoids) derived from different species of the cannabis plant. Despite increased cannabis use and a changing state-level policy landscape, conclusive evidence regarding the short- and long-term health effects—both harms and benefits—of cannabis use remains elusive.

A lack of definitive evidence has resulted in insufficient information on the health implications of cannabis use, causing a significant public health concern for vulnerable populations such as adolescents, pregnant women, and others. Unlike with substances such as alcohol or tobacco, no accepted standards exist to help guide individuals as they make choices regarding if, when, where, and how to use cannabis safely and, in regard to therapeutic uses, effectively.

With support from a host of federal, state, philanthropic and nongovernmental organizations, the National Academies of Sciences, Engineering, and Medicine convened an ad hoc, expert committee to develop a comprehensive, in-depth review of the most recent evidence regarding health effects of using cannabis and cannabis-derived products. In the resulting report, *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*, the committee presents nearly 100 research conclusions. The committee also formulated recommendations to expand and improve the quality of cannabis research efforts, enhance data collection



Despite increased cannabis use and a changing statelevel policy landscape, conclusive evidence regarding the short- and long-term health effects— both harms and benefits— of cannabis use remains elusive.

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THE STUDY PROCESS

The committee conducted an extensive search of literature databases to identify relevant articles published since the 1999 release of the National Academies report *Marijuana and Medicine: Assessing the Science Base*. As a result of their search efforts, the committee considered more than 10,000 scientific abstracts for their relevance to the report. Given the large scientific literature on cannabis, the breadth of the statement of task, and other constraints of the study, the committee gave primacy to recently published systematic reviews and high-quality primary research for 11 groups of health topics and concerns, including therapeutic effects for a variety of diseases and conditions; cancer incidence; respiratory disease; prenatal, perinatal, and neonatal outcomes; psychosocial and mental health concerns, and others.

The committee was charged to conduct a comprehensive, in-depth review of health topics with the greatest public health impact rather than to conduct multiple systematic reviews, which would have required a lengthy and robust series of processes. The committee did, however, adopt key features of that process: a comprehensive literature search, assessments by more than one person of the quality of the literature and the conclusions, pre-specification of the questions of interest before conclusions were formulated, standard language to allow for comparisons between conclusions, and declarations of conflict of interest via the National Academies conflict-of-interest policies.

Because of the practical steps taken to narrow a very large literature to one that was manageable within the timeframe available to the committee, there is a possibility that some literature was missed. Furthermore, some research may not be reflected in this report if it did not directly address the health endpoint research questions that were prioritized by the committee.

THE COMMITTEE'S CONCLUSIONS

The committee arrived at nearly 100 different research conclusions related to cannabis or cannabinoid use and health, organizing these into 5 categories: conclusive, substantial, moderate, limited, and no/insufficient evidence.

For a definition of these levels of evidence and a full listing of the conclusions, please see the "Committee's Conclusions" document by visiting the report's website at [nationalacademies.org/CannabisHealthEffects](https://www.nationalacademies.org/CannabisHealthEffects).

THE COMMITTEE'S RECOMMENDATIONS

Based on their research conclusions, the committee members formulated four recommendations that outline priorities to inform a research agenda. The recommendations prioritize research approaches and objectives to:

- address current research gaps, highlighting the need for a national cannabis research agenda that includes clinical and observational research, health policy and health economics research, and public health and public safety research;
- identify actionable strategies to improve research quality and promote the development of research standards and benchmarks;
- highlight the potential for improvements in data collection efforts and the enhancement of surveillance capacity; and
- propose strategies for addressing the current barriers to the advancement of the cannabis research agenda.

The full text of the committee's recommendations appears on the pages that follow.

CONCLUSION

This is a pivotal time in the world of cannabis policy and research. Shifting public sentiment, conflicting and impeded scientific research, and legislative battles have fueled the debate about what, if any, harms or benefits can be attributed to the use of cannabis or its derivatives. This report provides a broad set of evidence-based research conclusions on the health effects of cannabis and cannabinoids and puts forth recommendations to help advance the research field and better inform public health decisions.

To read the full report, please visit [nationalacademies.org/CannabisHealthEffects](https://www.nationalacademies.org/CannabisHealthEffects).

RECOMMENDATIONS

Recommendation 1: To develop a comprehensive evidence base on the short- and long-term health effects of cannabis use (both beneficial and harmful effects), public agencies, philanthropic and professional organizations, private companies, and clinical and public health research groups should provide funding and support for a national cannabis research agenda that addresses key gaps in the evidence base. Prioritized research streams and objectives should include, but need not be limited to:

Clinical and Observational Research

- Examine the health effects of cannabis use in at-risk or under-researched populations, such as children and youth (often described as less than 18 years of age) and older populations (generally over 50 years of age), pregnant and breastfeeding women, and heavy cannabis users.
- Investigate the pharmacokinetic and pharmacodynamic properties of cannabis, modes of delivery, different concentrations, in various populations, including the dose–response relationships of cannabis and THC or other cannabinoids.
- Determine the benefits and harms associated with understudied cannabis products, such as edibles, concentrates, and topicals.
- Conduct well-controlled trials on the potential beneficial and harmful health effects of using different forms of cannabis, such as inhaled (smoked or vaporized) whole cannabis plant and oral cannabis.
- Characterize the health effects of cannabis on unstudied and understudied health endpoints, such as epilepsy in pediatric populations; symptoms of posttraumatic stress disorder; childhood and adult cancers; cannabis-related overdoses and poisonings; and other high-priority health endpoints.

Health Policy and Health Economics Research

- Identify models, including existing state cannabis policy models, for sustainable funding of national, state, and local public health surveillance systems.
- Investigate the economic impact of recreational and medical cannabis use on national and state public health and health care systems, health insurance providers, and patients.

Public Health and Public Safety Research

- Identify gaps in the cannabis-related knowledge and skills of health care and public health professionals, and assess the need for, and performance of, continuing education programs that address these gaps.
- Characterize public safety concerns related to recreational cannabis use and evaluate existing quality assurance, safety, and packaging standards for recreational cannabis products.

Recommendation 2: To promote the development of conclusive evidence on the short- and longterm health effects of cannabis use (both beneficial and harmful effects), agencies of the United States Department of Health and Human Services, including the National Institutes of Health and the Centers for Disease Control and Prevention should jointly fund a workshop to develop a set of research standards and benchmarks to guide and ensure the production of high-quality cannabis research. Workshop objectives should include, but need not be limited to:

- The development of a minimum dataset for observational and clinical studies, standards for research methods and design, and guidelines for data collection methods.
- Adaptation of existing research-reporting standards to the needs of cannabis research.
- The development of uniform terminology for clinical and epidemiological cannabis research.
- The development of standardized and evidence-based question banks for clinical research and public health surveillance tools.

Recommendation 3: To ensure that sufficient data are available to inform research on the short- and longterm health effects of cannabis use, (both beneficial and harmful effects), the Centers for Disease Control and Prevention, the Substance Abuse and Mental Health Services Administration, the Association of State and Territorial Health Officials, National Association of County and City Health Officials, the Association of Public Health Laboratories, and state and local public health departments should fund and support improvements to federal public health surveillance systems and state-based public health surveillance efforts. Potential efforts should include, but need not be limited to:

- The development of question banks on the beneficial and harmful health effects of therapeutic and recreational cannabis use and their incorporation into major public health surveys, including: the National Health and

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Nutrition Examination Survey, National Health Interview Survey, Behavioral Risk Factor Surveillance System, National Survey on Drug Use and Health, Youth Risk Behavior Surveillance System, National Vital Statistics System, Medical Expenditure Panel Survey, and the National Survey of Family Growth. • Determining the capacity to collect and reliably interpret data from diagnostic classification codes in administrative data (e.g., International Classification of Diseases-10)

- The establishment and utilization of state-based testing facilities to analyze the chemical composition of cannabis and products containing cannabis, cannabinoids, or THC.
- The development of novel diagnostic technologies that allow for rapid, accurate, and noninvasive assessment of cannabis exposure and impairment. • Strategies for surveillance of harmful effects of cannabis for therapeutic use.

Recommendation 4: The Centers for Disease Control and Prevention, National Institutes of Health, Food and Drug Administration, industry groups, and nongovernmental organizations should fund the convening of a committee of experts tasked to produce an objective and evidence-based report that fully characterizes the impacts of regulatory barriers to cannabis research and that proposes strategies for supporting development of the resources and infrastructure necessary to conduct a comprehensive cannabis research agenda. Committee objectives should include, but need not be limited to:

- Proposing strategies for expanding access to research-grade marijuana, through the creation and approval of new facilities for growing and storing cannabis.
- Identifying nontraditional funding sources and mechanisms to support a comprehensive national cannabis research agenda.
- Investigating strategies for improving the quality, diversity, and external validity of research-grade cannabis products.

Health and Medicine Division

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Good afternoon, Mr. Chairman and members of the Caucus. Thank you for inviting me to contribute my knowledge about adolescent vulnerability to cannabis effects on cognitive functioning.

Summary

What We Know:

1. Cannabis use is associated with cognitive deficits that persist beyond the period of acute intoxication
2. Cannabis-related cognitive deficits are subtle
3. More frequent, persistent, and earlier-onset cannabis use is associated with larger cognitive deficits

What We Still Need to Know:

1. What are the mechanisms underlying cannabis-related cognitive deficits?
2. What are the parameters of cannabis use that determine the magnitude and persistence of cognitive deficits (quantity, frequency, age-of-onset, duration, THC content)?
3. Does cognitive functioning recover with abstinence?
4. Are there individual differences in susceptibility to cannabis-related cognitive deficits?

Cannabis Effects on Cognitive Function

Cannabis intoxication results in temporary cognitive impairment,¹⁻³ but it is less clear if cannabis use results in enduring cognitive impairment – impairment that persists beyond the period of acute intoxication. Studies comparing heavy cannabis users with nonusers have collectively shown that heavy cannabis users, even when not intoxicated by cannabis, perform worse on cognitive tests, including tests of learning and memory, attention, and other executive functions.⁴⁻⁶ The magnitude of cognitive deficits in these heavy cannabis users is small,⁴⁻⁶ though some evidence suggests that cognitive deficits might be larger among more frequent, chronic, and earlier-onset cannabis users.^{3,7-12} Some evidence suggests that cognitive deficits might resolve with prolonged abstinence.^{5,6,13}

The extant evidence base draws largely on studies that compared heavy cannabis users with nonusers on cognitive test performance, and these studies have two commonly cited limitations. First, the studies lack information on initial cognitive functioning before the onset of cannabis use. Therefore, the studies do not address the possibility that cognitive differences between cannabis users and comparison individuals represent pre-existing rather than cannabis-induced deficits. Second, the studies rely on cannabis users' retrospective reports of their frequency, quantity, age-of-onset, and duration of cannabis use, with reports often obtained years after initiation of heavy use. Therefore, retrospective reports of cannabis use might not be accurate.

To redress these limitations, prospective longitudinal studies are needed. Prospective longitudinal studies assess cognitive functioning in youth before the initiation of cannabis use, obtain prospective information about cannabis use as the sample is followed over a number of years, and then reassess cognitive functioning again, after some individuals in the sample have developed a persistent pattern of cannabis use. The most comprehensive prospective longitudinal study of cannabis use and cognitive functioning was published by our group in 2012 (Meier et

al., 2012).¹⁴ Our study found that persistent cannabis use was associated with IQ decline from childhood to adulthood, and IQ decline was concentrated in adolescent-onset persistent cannabis users. Here I (1) describe our 2012 study and explain the findings, (2) address questions about whether cannabis-associated IQ decline could be accounted for by factors such as low socioeconomic status and poor childhood self-regulation, and (3) explain why the study is unique and why we need more studies like it.

Cannabis and IQ (Discussion of Meier et al., 2012)

The Findings: We studied the association between persistent cannabis use and IQ decline and asked whether IQ decline was concentrated among adolescent-onset cannabis users. Findings come from the Dunedin Multidisciplinary Health and Development Study. The Study has followed a group of 1,037 children, who were born in 1972-73 in Dunedin, New Zealand, from birth to age 38 years, with 96% of the sample taking part at age 38. IQ was tested at age 13, before cannabis use, and again at age 38, after some study members had used cannabis for years.

We found that:

1. Persistent cannabis use was associated with IQ decline from childhood to adulthood, and IQ decline was concentrated among adolescent-onset persistent cannabis users. For example, individuals who began using cannabis in adolescence (before age 18) and used it for years thereafter showed an average 8-point IQ decline from childhood to adulthood (circled in red in the figure). Individuals who used cannabis short-term in adolescence showed only weak evidence of IQ decline (3-point IQ decline; circled in black dashes in the figure). Individuals who began using cannabis in adulthood (after age 18) did not show IQ decline (gray bars), even when they used persistently.

In the figure below, 1 diagnosis = the study member met criteria for cannabis dependence at only one of the five assessment phases (ages 18, 21, 26, 32, 38); 2 diagnoses = the study member met criteria for cannabis dependence at two of the five assessment phases; 3+ diagnoses = the study member met criteria for cannabis dependence at three or more of the five assessment phases. More diagnoses = greater persistence.

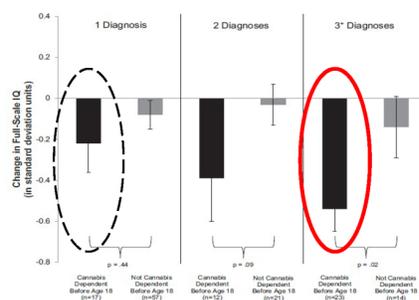


Fig. 2. Adolescent vulnerability. Shown is change in full-scale IQ (in SD units) from childhood to adulthood among study members with 1, 2, or 3+ diagnoses of cannabis dependence as a function of age of onset of cannabis dependence. Individuals with adolescent-onset cannabis dependence (black bars) experienced greater IQ decline than individuals with adult-onset cannabis dependence (gray bars). IQ decline of approximately -0.55 SD units among individuals with adolescent-onset cannabis dependence in the 3+ group represents a decline of 8 IQ points. Error bars = SEs.

2. Quitting or reducing cannabis use did not appear to fully restore intellectual functioning among adolescent-onset former persistent cannabis users.
3. IQ decline could not be explained by alcohol or other drug use or by reduced years of education among persistent cannabis users.
4. IQ decline could also not be explained by low childhood socioeconomic status or poor childhood self-regulation.¹⁵
5. Third-party informants (e.g., friends, relatives) reported noticing more attention and memory problems in everyday life among persistent cannabis users (e.g. losing focus when they should be paying attention, forgetting to do errands, return calls, pay bills).

Why are these findings important? The importance of “before and after” IQ testing. Previous studies have suggested that adolescents may be particularly vulnerable to the effects of cannabis on cognitive functioning.^{8-10,16-18} However, until our study, research had not been able to rule out the possibility that poorer cognitive test performance among adolescent-onset cannabis users predates cannabis use initiation. We showed that regardless of their initial (pre-cannabis) test performance, adolescent-onset persistent cannabis users performed worse than non-users and adult-onset cannabis users on cognitive tests in adulthood.

What is the size of the IQ decline? The extent of IQ decline among adolescent-onset persistent cannabis users (8 IQ points) is non-trivial. For example, an average person has an IQ of 100, placing them in the 50th percentile for intelligence compared to their same-age peers. If this average person loses 8 IQ points, they drop from the 50th to the 29th percentile for intelligence.

Why is an 8-point decline in IQ significant? Research has shown that IQ is a strong predictor of a person’s access to a college education, their lifelong total income, their access to a good job, their performance on the job, and even early death.^{19,20} Individuals who lose 8 points may be disadvantaged, relative to their same-age peers, in many important aspects of life. In fact, the adolescent-onset persistent cannabis users from the Dunedin Study experienced downward social mobility. That is, they ended up in occupations that were less prestigious, less skilled, and less well paid than their parents’ occupation.²¹

How many people does this affect? Only approximately 2% of the 1,037 individuals born in one year in Dunedin became adolescent-onset persistent cannabis users. Thus, any effect of cannabis on IQ is confined to a relatively small segment of the population. Nonetheless, findings are concerning given that fewer adolescents today believe that regular cannabis use presents a serious health risk.²²

What should we do? We should direct efforts toward delaying the onset of cannabis use in young people and encourage cessation, particularly for cannabis users who began using in adolescence.

What additional research is needed? Additional research is needed to answer the following questions:

1. *What are the mechanisms underlying cannabis-related IQ decline?*
One hypothesis is that cannabis use causes brain changes that result in IQ decline.

Further, adolescents might be particularly vulnerable to the effects of cannabis because cannabis use might disrupt critical neuromaturational processes (e.g., synaptic pruning [culling of weak/unused synapses, which might result in more efficient information processing] and white matter development [which is important for efficient brain signaling]) that occur during adolescence.^{13,18} Our 2012 study on cannabis and IQ lacked brain imaging data, and so we could not test this hypothesis. Findings from extant brain imaging studies of cannabis users and comparison individuals have been somewhat inconsistent,²³ but functional imaging studies have found evidence of altered brain activity in cannabis users in at least some brain regions,^{23,24} and structural imaging studies have consistently found that cannabis users have lower hippocampal volume.^{23,25,26} The consistent finding of lower hippocampal volume among cannabis users is interesting because the hippocampus has a high density of cannabinoid receptors and is involved in learning and memory. Nonetheless, most brain imaging studies lack data from before cannabis initiation, leaving open the possibility that differences between cannabis users and non-users in terms of brain structure or function reflect pre-existing differences. Overall, there is a clear need for large-scale longitudinal studies to follow youth from before to well after cannabis initiation and to combine cognitive testing with brain imaging. The Adolescent Brain and Cognitive Development Study (ABCD Study) was launched, in part, to meet this need.

Although adolescence is receiving attention as a developmental period of heightened vulnerability to cannabis effects, there are likely other sensitive periods in development. For example, cannabis exposure during prenatal development is receiving increased attention, and evidence suggests that the children of mothers who used cannabis during pregnancy show poorer cognitive functioning.²⁷ Another example is that cannabis use in older adulthood might be associated with serious cognitive consequences. With continued follow-up of the Dunedin Study cohort, who are now age 45, our team can answer new questions about cannabis effects on the aging brain.

2. *What are the parameters of cannabis use that determine the magnitude and persistence of cognitive deficits?*

Additional work is needed to identify the frequency, quantity, age-of-onset, and duration of cannabis use that is sufficient to produce cognitive deficits. Findings from our 2012 study on cannabis use and IQ suggest that cannabis use that begins before age 18 and continues for many years is associated with IQ decline from childhood to adulthood, but short-term cannabis use in adolescence might not be associated with IQ decline (see above Figure). Several recent longitudinal studies,²⁸⁻³⁰ including a study from our group using data from a different cohort,³¹ found little evidence of cannabis-related IQ decline in adolescence. Importantly, these studies do not conflict with our 2012 study. Rather, the studies collectively suggest that short-term cannabis use in adolescence might not be associated with IQ decline, but long-term cannabis use from adolescence onward might.

A caveat is that the adolescents in these recent longitudinal studies had relatively low levels of cannabis use. For example, adolescents were classified as cannabis users if they had ever used cannabis or if they had used cannabis 50+ times. It is possible that cannabis-related IQ decline in adolescence might only become apparent after heavier use. Consistent with this, an earlier longitudinal study of youth followed to adolescence found evidence of IQ deficits among heavy adolescent cannabis users (>5 joints per week) but not lighter uses.³²

One parameter of cannabis use that has received almost no research attention is cannabis potency, which refers to the THC content of cannabis. (THC is the main psychoactive constituent of cannabis.) In our 2012 study on cannabis and IQ, the cannabis users had access to low-potency cannabis -- 3.5% THC.³³ Today's teenagers have access to cannabis with much higher potency. For example, the average THC content of confiscated marijuana (flower) in the US was 12% in 2014,³⁴ and the average THC content of marijuana sold in US dispensaries is now ~20%.^{35,36} In addition, work from my group showed that nearly 1 in 4 adolescents have used cannabis concentrates,³⁷ which are cannabis plant extracts with unprecedentedly high THC content.^{38,39} Cannabis concentrates have estimated average THC content of ~40-70%,³⁸ but THC content of concentrates can exceed 80%. Because THC has been shown to have dose effects on drug reinforcement (e.g., liking of the drug), cognitive impairment, and psychotic-like experiences,⁴⁰⁻⁴³ there is speculation that use of cannabis with higher THC content might increase risk for addiction, cognitive deficits, psychosis, and other adverse consequences.^{41,44-49} However, an alternative hypothesis is that higher THC cannabis might not pose greater risks, because cannabis users might titrate their use (use less cannabis when THC content is high). My recent work showed that cannabis users who used concentrates had higher rates of physiological dependence (symptoms of addiction) on cannabis than cannabis users who did not use concentrates.⁵⁰ However, additional research on this topic is needed. Moreover, research is needed to ascertain if cannabidiol (CBD), another constituent of cannabis, might attenuate the negative effects of THC.^{51,52}

To summarize, research is needed to understand how cannabis frequency, quantity, duration, age-of-onset, and potency impact cognitive functioning. To do this work, cannabis researchers must work together to develop standardized measures of each of these cannabis parameters.

3. *Does cognitive functioning recover with abstinence?*

In our 2012 study, we found that adolescent-onset persistent cannabis users performed worse in adulthood than in childhood even after they had quit or reduced their use in the year leading up to cognitive testing in adulthood. This suggests that quitting or reducing use might not fully restore functioning among adolescent-onset persistent cannabis users, but longer-term follow-up is needed. In general, the evidence on recovery with abstinence is mixed. Some studies have found evidence of cognitive deficits among

cannabis users who were abstinent for approximately a month or more.⁵³⁻⁵⁶ Yet, studies that compared heavy cannabis users with comparison individuals have collectively found little evidence of cognitive deficits among longer-term abstinent cannabis users.^{5,6} Carefully designed studies are needed to understand the extent and time course of recovery associated with quitting cannabis, and to understand if recovery depends on age-of-onset of use, duration of use, or other cannabis use parameters.

4. *Are there individual differences in susceptibility to cannabis-related cognitive deficits?*

One intriguing possibility is that some individuals are less likely than others to experience negative effects of cannabis. Research is needed to identify these individuals and to isolate the factors that offer them protection. For example, evidence suggests that some people might be genetically less susceptible than others to experiencing cannabis-related cognitive deficits.^{57,58} This could have significant implications for prevention. Relatedly, research is needed on sex differences in vulnerability to cannabis effects on cognitive function.⁴⁰ For example, one recent study found that an earlier age of onset of cannabis use was associated with poorer memory in women but not men.⁵⁹

Appendix

Supporting Details for Meier et al., 2012: How we measured cannabis use. We measured cannabis use in two ways: cannabis dependence and regular cannabis use. Persistence of cannabis dependence was defined as the total number of study waves out of five (ages 18, 21, 26, 32, and 38) at which a study member met DSM criteria for cannabis dependence. Study members were grouped according to their number of dependence diagnoses: (a) those who never used cannabis at any study wave and thus could not have become dependent; (b) those who used cannabis at least once at one or more study waves but never diagnosed; (c) those who diagnosed at one wave; (d) those who diagnosed at two waves; and (e) those who diagnosed at three or more waves.

Cannabis dependence is a substance use disorder as defined in the Diagnostic and Statistical Manual of the American Psychiatric Association (known as DSM-IV). The purpose of the DSM-IV diagnosis is to predict a patient's future prognosis, and to identify which patients are most in need of treatment. A diagnosis of cannabis dependence generally reflects an individual's continued use of cannabis despite experiencing significant health, social, and/or legal problems related to cannabis use.

Persistence of regular cannabis use. Because some people use cannabis on a regular basis but never develop problems, we also examined IQ decline as a function of persistent regular cannabis use. This was defined as the total number of study waves out of five at which a study member reported using cannabis four or more days per week (the majority of days in a week). Study members were grouped as those who: (a) never used cannabis; (b) used but never regularly; (c) used regularly at one wave; (d) used regularly at two waves; and (e) used regularly at three or more waves.

Results were similar for persistent cannabis dependence and persistent regular cannabis use.

How we defined adolescent-onset cannabis use. We defined adolescent-onset cannabis in two ways: 1) cannabis dependence before age 18 or 2) weekly cannabis use before age 18. Results were similar across both definitions.

How we measured IQ. We assessed intelligence in childhood (ages 7, 9, 11, and 13) and again in adulthood at age 38 using standard tests for the field.

How we measured everyday life cognitive functioning. Study members nominated people "who knew them well." These informants were mailed questionnaires and asked to complete a checklist, including whether the study member had problems with their attention (e.g., "can't concentrate, mind wanders) and memory (e.g., forgets to do errands, return calls, pay bills) over the past year at age 38.

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**Written Testimony of VADM Jerome M. Adams, M.D., M.P.H., U.S. Surgeon General and
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Caucus on International Narcotics Control
October 23, 2019**

Chairman Cornyn, Co-Chairwoman Feinstein and members of the Caucus on International Narcotics Control, we appreciate the opportunity to share the content of the recent Surgeon General's Advisory on Marijuana Use and the Developing Brain with you, and to join national experts to discuss this complex issue that demands our attention and action. Recent increases in access to marijuana and in its potency, along with misperceptions of its safety, endanger our most precious resource, our nation's youth.

Background

Marijuana, or cannabis, is the most commonly used illicit drug in the United States. In 2018, 43.5 million people reported using marijuana in the past year.¹ Marijuana acts by binding to cannabinoid receptors in the brain to produce a variety of effects, including euphoria, intoxication, and memory and motor impairments. These cannabinoid receptors are part of an extensive endocannabinoid system that regulates a wide range of functions, including brain development.

The endocannabinoid system appears relatively early during fetal development. As the fetal brain grows, this system influences how brain cells develop and connect with one another, and it plays a major role in the formation of brain circuits including those important for decision making, mood, and responding to stress.² Not surprisingly, animal studies have shown that in utero exposure to marijuana can interfere with the proper development and regulation of brain circuitry. Moreover, the endocannabinoid system is a critical regulator of the neuronal hardwiring that translates experience throughout the teen years and young adulthood into mature brain architecture. This helps explain why the developing brain is particularly vulnerable to chronic exposure to delta-9-tetrahydrocannabinol (THC), the component of marijuana responsible for euphoria, intoxication, and addiction.

Marijuana and its related products are widely available in multiple forms, with varying concentrations of constituent chemicals, the most salient of which are known collectively as "cannabinoids". In addition to varying levels of THC, marijuana also contains cannabidiol (CBD). While pure CBD is not intoxicating and does not lead to addiction, its long-term effects are largely unknown. In addition to THC and CBD, the marijuana plant also contains hundreds of other cannabinoid and non-cannabinoid components, many of which have not been studied extensively.

Marijuana has changed over time; the marijuana available today is much more potent than what was available in the past. The THC concentration in commonly cultivated marijuana plants increased three-fold between 1995 and 2014 (4 percent and 12 percent, respectively),⁴ and marijuana available in dispensaries in some states has average concentrations of THC between 17.7 percent and 23.2 percent.⁵ Concentrated products, commonly known as dabs or waxes, are widely available to recreational users today and may contain between 23.7 percent and 75.9 percent THC.⁶

The risks of physical dependence, addiction, and other negative consequences increase with frequent use, exposure to high concentrations of THC⁷ and with younger age of initiation. Higher doses of THC are more likely to produce anxiety, agitation, paranoia, and psychosis.⁸ Use of edible marijuana can increase the risk of unintentional overdose due to its lengthy absorption time and delayed effect, often prompting the user to take a second dose. Edibles, which may have the appearance of desserts or snacks, are also increasingly a cause of accidental ingestion by children⁹ and adolescents.¹⁰ In addition, chronic users of marijuana with a high THC content are at risk for developing a condition known as cannabinoid hyperemesis syndrome, which is marked by severe cycles of nausea and vomiting.¹¹ The increase in the THC content of marijuana, combined with the growing availability of loosely regulated cannabis products, has led to a worrisome upward trend in the rate of calls to poison control centers and emergency department visits over the past decade.

Surgeon General's Advisory on Marijuana Use and the Developing Brain

On August 29, 2019, the Surgeon General's Advisory on Marijuana Use and the Developing Brain was issued to emphasize the importance of protecting our Nation from the health risks of marijuana use in adolescence and during pregnancy. This advisory is intended to raise awareness of the known and potential harms that the increasing availability of highly-potent marijuana in multiple, concentrated forms poses to the developing brain of youth and young adults who consume it. These harms can be long-lasting and costly to individuals and to our society, impacting mental health and educational achievement and raising the risks of addiction and other psychiatric disorders. In addition to the health risks posed by marijuana use, the sale or possession of marijuana remains illegal under federal law, notwithstanding some state laws to the contrary.

Marijuana Use during Pregnancy

Pregnant women use marijuana more than any other illicit drug. In a national survey, marijuana use in the past month among pregnant women doubled (3.4 percent to 7 percent) between 2002 and 2017¹², although this trend may be starting to reverse based on the most recent data reported in the National Survey on Drug Use and Health. In a study conducted in a large health system in California, marijuana use rose by 69 percent (4.2 percent to 7.1 percent) between 2009 and 2016 among pregnant women, with the highest rates of use occurring among pregnant women under the age of 25. These researchers found that 22 percent of pregnant girls under the age of 18 and 19 percent of pregnant women ages 18-24 used marijuana in 2016.¹³ Alarming, many retail dispensaries recommended marijuana to pregnant women for morning sickness.¹⁴

Since the THC in marijuana crosses the placenta, it may disrupt the important role the endocannabinoid system plays in fetal brain development and in maintaining a healthy pregnancy.² Moreover, the placenta itself has cannabinoid receptors, which might contribute to restricted fetal growth with cannabis use during pregnancy³⁴. Indeed, studies have shown that marijuana use in pregnancy is associated with adverse outcomes, including lower birth weight and¹⁶ and preterm delivery.³⁵ For example, The Colorado Pregnancy Risk Assessment Monitoring System reported that maternal marijuana use was associated with a 50 percent increased risk of low birth weight regardless of maternal age, race, ethnicity, education, and tobacco use.¹⁶

The American College of Obstetricians and Gynecologists holds that “[w]omen who are pregnant or contemplating pregnancy should be encouraged to discontinue marijuana use. Women reporting marijuana use should be counseled about concerns regarding potential adverse health consequences of continued use during pregnancy.”¹⁷ In a 2018 clinical guidance statement, the American Academy of Pediatrics recommended that health professionals “...advise all adolescents and young women that if they become pregnant, marijuana should not be used during pregnancy.”¹⁸

While cannabis use *during* pregnancy is associated with increased risk of adverse birth outcomes, later effects on the child due to exposure to THC through breastmilk are still unclear. This is in part due to challenges disentangling the long-term effects associated with marijuana exposure *in utero* versus during nursing. Although additional research is needed in this area, there is ample reason for caution, as THC has been detected in breastmilk for up to six days after the last recorded use. Additionally, marijuana smoke contains many of the same harmful components as tobacco smoke;²² no one should smoke marijuana or tobacco around a baby.

Marijuana Use during Adolescence

Each day in 2018, 3700 adolescents aged 12 to 17 became new users of marijuana.¹ Although marijuana use declined among 8th graders and remains unchanged among 10th and 12th graders compared to five years ago, high school students’ perception of the harm from regular marijuana use has been steadily declining over the last decade.²⁴ In 2018, only about a third (34.9 percent) of adolescents aged 12 to 17 perceived great risk from weekly marijuana use.¹ During this same period, a number of states legalized adult and/or so-called medicinal use of marijuana, though it remains illegal under federal law. Importantly, medical marijuana laws may allow for use at a younger age than adult recreational laws. The legalization movement may be impacting youth perception of harm from marijuana.

The human brain continues to develop from before birth into the mid-20s and is vulnerable to the effects of addictive substances.^{25, 26} Frequent marijuana use during adolescence is associated with structural and functional changes in areas of the brain involved in attention, memory, decision-making, and motivation, and in deficits in attention and memory.²⁷ Marijuana can also impair learning in adolescents. Chronic use is linked to declines in IQ and school performance, which may jeopardize professional and social achievements, and life satisfaction.²⁹ Regular use of marijuana in adolescence is linked to increased rates of school absence and drop-out, as well as suicide attempts.²⁹

Marijuana use is also linked to both overall risk for and early onset of psychotic disorders, such as schizophrenia. The risk for psychotic disorders increases with frequency of use, potency of the marijuana product, and younger age of initiation.³⁰ Adolescent marijuana use is also associated with other substance use.^{31, 32} In 2017, teens 12-17 reporting frequent use of marijuana showed a 130 percent greater likelihood of misusing opioids.²³ 2018 data from 8th, 10th, and 12th graders show that a third reported lifetime cannabis use and almost a quarter reported lifetime use of concentrated products. Adolescents using concentrates show higher rates of other substance use and risk factors for substance use-related problems.³³ Marijuana’s increasingly widespread availability in multiple and highly potent forms, coupled with a false and dangerous perception of safety among youth, merits a nationwide call to action.

Research Supported by the National Institutes of Health's (NIH) National Institute on Drug Abuse (NIDA)

NIH supports a broad range of research aimed at understanding the public health effects of marijuana use at all stages of life. NIDA's portfolio includes research on the pharmacology of THC and other cannabinoids in the marijuana plant; the molecular mechanisms underlying the effect of marijuana use on the brain, including its development; epidemiologic studies to elucidate the prevalence and patterns of marijuana use; research to understand the brain changes associated with cannabis addiction and other adverse effects such as amotivation, an unwillingness to participate in normal social situations; research on the potentially beneficial effects of marijuana and its constituent compounds; applied research aimed at preventing and treating cannabis misuse and addiction; as well as research aimed at understanding how marijuana policies affect public health.

There is still much we do not know about the impact of marijuana exposure during the vulnerable periods of adolescence and pregnancy; therefore, these remain key areas of focus for NIDA. Two current studies with great potential to advance knowledge in these areas are the Adolescent Brain Cognitive Development (ABCD) study and the HEALthy Brain and Child Development (HBCD) study. ABCD, the largest long-term study of brain development and child health in the United States, is expected to yield an unprecedented amount of information about normal brain development and how it is affected by substance use—including use of marijuana—and other childhood experiences. The ABCD study has recruited over 11,000 children ages 9-10 and is following them into early adulthood. By integrating structural and functional brain imaging with genetic and biological markers, along with psychological, behavioral, and other health assessments, ABCD will increase our understanding of the many factors that can enhance or disrupt a young person's life trajectory. Complementing ABCD is the HBCD Study, which is currently in its planning phase. HBCD would establish a large cohort of pregnant women and assess maternal and child outcomes over the course of at least 10 years. In parallel to the ABCD study, findings from this cohort will help researchers understand both normal childhood brain development as well as the long-term impact of prenatal and postnatal drug and environmental exposures.

Key Messages and Critical Actions

No amount of marijuana use during pregnancy or during youth when the brain is under development is known to be safe. Until and unless more is known about the long-term impact, the safest choice for pregnant women and youth is not to use marijuana. Although women generally tend to limit drug use during pregnancy, education efforts on marijuana's adverse effects during pregnancy should be expanded and improved. Pregnant women and youth—and those who love them—need the facts and resources to support healthy decisions. It is critical to educate women and youth, as well as family members, school officials, state and local leaders, and health professionals, about the risks of marijuana.

Science-based messaging campaigns and targeted prevention programming are urgently needed to ensure that risks are clearly communicated and amplified by local, state, and national organizations. Clinicians can help by asking about marijuana use, and by informing pregnant women, new mothers, young people, and those vulnerable to psychotic disorders of the risks associated with marijuana use. Clinicians can also prescribe safe, effective, and FDA-approved treatments for nausea, depression, and pain during pregnancy.

What we know now about the impact of marijuana exposure during adolescence, as well as during prenatal development is enough to warrant concern and action. Still, further research is needed to understand the full effects of marijuana exposure on biological, cognitive, and social development, especially the mid- and long-term consequences of prenatal and youth exposures. The wide and ever-increasing array of cannabis products used both recreationally and for therapeutic purposes also raise significant public health concerns, particularly when used by young people and pregnant women. Additional research aimed at evaluating the health effects of these products is critical.

Thank you for the opportunity to share this summary of the current trends in marijuana use among youth and pregnant women; the state of the evidence regarding the harms to developing brains; and the steps we can take together to understand more about and to mitigate those harms in order to protect our youth, the future of our nation. I am happy to answer any questions you may have.

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