DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Mixed Signals: The Administration's Policy on Marijuana, Part Four

Scientific Focus on the Adverse Health Effects of Marijuana Use

Witness appearing before the

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Mr. Chairman and Members of the Subcommittee. Thank you for inviting the National Institute on Drug Abuse (NIDA), a component of the National Institutes of Health (NIH), to participate in this hearing to share what research tells us about the health effects of marijuana use. In light of the rapidly shifting landscape regarding marijuana use for medical and recreational purposes, it is more important than ever to spread accurate information about marijuana's health effects and to conduct the research needed to fill the gaps in our knowledge.

Background

Marijuana is the most commonly used illicit drug in the United States, with about 12 percent of people aged 12 and over reporting use in the past year.[1] Rates of use are particularly high (and increasing) in teenagers, corresponding to a diminishing perception of the drug's risks by this age group.[2] In 2009, current (past-month) use of marijuana by 12th graders surpassed cigarette smoking, and according to the 2013 Monitoring the Future (MTF) survey of high school students, 6.5 percent of 12th graders report using marijuana daily or near-daily. [3]

MTF indicates a growing perception among young people that marijuana is a relatively harmless drug, and according to a recent Pew survey, a large majority of adults (69 percent) view alcohol as more dangerous than marijuana.[4] Many studies have reported detrimental effects from marijuana use, but others have not or have left much open to interpretation, and although research is actively underway to address these questions, the extent of marijuana's harms remains hard to specify with as much precision as would be ideal.

We must be careful drawing conclusions from past research on marijuana's effects for several reasons. First, alcohol and tobacco are linked to more morbidity and mortality in our society than other drugs in part due to their widespread availability as legal substances. It is likely that, were patterns of marijuana use by people of all ages to become comparable to that of these other legal

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[1] SAMHSA. Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health. , 2013.
[2] MTF
[3] Johnston LD, O'Malley PM, Bachman JG, J.E. S (2013) Overview: key Findings on Adolescent Drug use. 1975-2013. In: Monitoring the Future national Survey Results on Drug Use (University of Michigan).
[4] Pew Research Center, April 2014, "America's Changing Drug Policy Landscape"; available at http://www.people-press.org/files/legacy-pdf/04-02-14%20Drug%20Policy%20Release.pdf

substances, statistics regarding marijuana's impact on automobile accidents (*i.e.,* compared to alcohol), lung diseases (*i.e.,* compared to tobacco), or treatment needs for those addicted (compared to both alcohol and tobacco) would look much different than they do currently. Another reason we must be careful drawing conclusions from past research on marijuana's effects is the dramatic increase in concentrations of the marijuana plant's main psychoactive ingredient, tetrahydrocannabinol (THC) seen over the past couple decades, along with the new ways of administering high THC content (*e.g.,* electronic cigarette devices). The potency of an average marijuana cigarette has steadily increased from roughly 3 percent THC in the early 1990s to 12.5 percent THC in 2013:[5] During this same period, the potency of marijuana extracts (also known as "hash oil") has also climbed to what are now staggering levels: The average marijuana extract contains over 50 percent THC, with some samples containing more than 80 percent THC.[6] This means some historical findings about health and developmental effects from marijuana use may not be relevant when trying to predict effects on contemporary users. A rapid rise in emergency room (ER) admissions linked to marijuana use attests to the greater dangers of acute use than have been seen in the past. There were 128,857 ER visits related to marijuana use in 2011, nearly double the number from 2004 (65,699) and comparable to the number of visits in 2011 related to heroin use (122,517); in the same year, 606,653 visits were related to alcohol use.[7]

Despite some areas of uncertainty, a substantial body of research, most of it supported by NIDA, enables us to say with some confidence that marijuana use may result in a wide range of adverse consequences for health, safety, and other domains, and that by interfering with the endocannabinoid system—an important neuronal signaling system that processes critical information in the brain and the rest of the body—it may have particularly harmful long-term effects when it is used heavily (*e.g.,* on a daily or near-daily basis) during adolescence.[8] I would like to review in this testimony what scientific research enables us to say about the adverse acute (short-term) and chronic (long-term) effects of marijuana use.

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[5] ElSohly MA (2014) Potency Monitoring Program Quarterly Report Number 124. Reporting Period: 12/16/2013 -03/15/2014 National Institute on Drug Abuse. Contract Number: NO 1 DA-1 0-7773. (HHS, ed): National Center for Natural Products Research, a Division of the Research Institute of Pharmaceutical Sciences.
[6] Id.
[7] SAMHSA. Drug Abuse Warning Network, 2011: National Estimates of Drug-Related Emergency Department Visits. 2011.
[8] FERGUSSON D. M., BODEN J. M. Cannabis use and later life outcomes. Addiction 2008;103:969-76 2008: 103: 969-976.

Acute Effects of Marijuana Use

Health and Safety. Although the reported incidents of death due to the acute influence of marijuana are limited, increasing numbers of ER visits related to marijuana (on its own or in combination with other substances) have been reported. Among the possible causes are involvement in accidents, acute psychotic reactions (paranoia, perceptual distortions, loss of touch with reality), and heart attacks in people with cardiovascular risks or disease.[9] The reported rise in ER visits may be related to the increase in THC content in marijuana, the use of vaporizers that allow users to administer very highly concentrated extracts, and, particularly in the case of children and inexperienced users, the consumption of food products (*e.g.,* candies and baked goods) that contain marijuana extracts. Also troubling are the customary effects of marijuana intoxication, including impairments in memory, judgment, and decision-making ability, which compromise an individual's functioning in various ways that can indirectly have damaging or even devastating impact on their life and health. For example, as is true of alcohol and other drugs, marijuana can increase the likelihood of engaging in risky behaviors such as unsafe sex, which raises the risk of contracting or transmitting sexually transmitted diseases (STDs) including human immunodeficiency virus (HIV).[10] However, the most pronounced immediate threat from marijuana use is through impacting driving ability.

Marijuana significantly impairs coordination and reaction time and is the illicit drug most frequently found to be involved in automobile accidents, including fatal ones.[11] Controlled driving simulation studies have found a direct relationship between blood THC concentration and impaired performance.[12] Recent marijuana smoking and/or blood THC concentrations of 2-5 ng/mL are associated with substantial driving impairment.[13] A meta-analysis of multiple studies

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[9] Thomas G, Kloner RA, Rezkalla S. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: what cardiologists need to know. Am J Cardiol 2014;113:187-90.

[10] Andrade LF, Carroll KM, Petry NM (2013). Marijuana use is associated with risky sexual behaviors in treatment-seeking polysubstance abusers. American Journal of Drug and Alcohol Abuse 39:266-271.

[11] Brady JE, Li G (2014) Trends in Alcohol and Other Drugs Detected in Fatally Injured Drivers in the United States, 199-2010," American Journal of Epidemiology [Epub ahead of print].

[12] Lenné M, Dietze P, Triggs T, Walmsley S, Murphy B, Redman J. The effects of cannabis and alcohol on simulated arterial driving: Influences of driving experience and task demand. Accid Anal Prev 2010;42:859-66.

[13] Hartman RL, Huestis MA. Cannabis effects on driving skills. Clin Chem 2013;59:478-92.

found that the risk of being involved in an accident roughly doubles after marijuana use.[14] For comparison, one study found that drivers with a blood alcohol level above 0.08 percent, the legal limit in most countries, are at a five-fold risk for having an accident and that this increases to 27-fold for drivers under 21.[15] Accident-involved drivers with THC in their blood, particularly higher levels, are three to seven times more likely to be responsible for the accident than drivers who had not used drugs or alcohol.[16] The risk associated with marijuana in combination with alcohol appears to be greater than that for either drug by itself.[17]

School Performance. By impairing critical cognitive functions including learning, memory, and problem solving—effects which may last for days after acute intoxication[18]—marijuana use may compromise the ability to function in school settings. Its wide use by teenagers (22.7 percent of 12th graders report past-month use[19]) makes marijuana of particular concern when it comes to individual academic success. Failing to learn in school, even as a result of temporary cognitive impairment, interferes with the ability to advance educationally and thus may explain associations that have been found between regular use of marijuana and poorer school performance.[20] The 6.5 percent of 12th graders reporting daily or near-daily marijuana use in the MTF survey likely underestimates the prevalence of regular use among all 17-18-year-olds, as regular marijuana users are more likely to drop out of school[21] and thus not be included in the survey.

Long-Term/Chronic Use

The deleterious impact of marijuana on cognitive performance appears to extend beyond the effects of acute intoxication, accumulating among those who use marijuana heavily and/or over

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[14] Ramaekers JG, Berghaus G, van Laar M, Drummer OH. Dose related risk of motor vehicle crashes after cannabis use. Drug Alcohol Depend 2004;73:109-19.
[15] Peck RC, Gebers MA, Voas RB, Romano E. The relationship between blood alcohol concentration (BAC), age, and crash risk. J Safety Res 2008;39:311-9.
[16] Ramaekers J, Berghaus G, van Laar M, Drummer O. Dose related risk of motor vehicle crashes after cannabis use. Drug Alcohol Depend 2004;73:109-19.
[17] Hartman RL, Huestis MA. Cannabis effects on driving skills. Clin Chem 2013;59:478-92.
[18] Crean RD, Crane NA, Mason BJ. An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. J Addict Med 2011;5:1-8.
[19] MTF
[20] Lynskey M, Hall W (2000) The effects of adolescent cannabis use on educational attainment: a review. Addiction 95:1621-1630.
[21] Bray, J.W., Zarkin, G.A., Ringwalt, C. and Qi, J.F. The relationship between marijuana initiation and dropping out of high school. Health Econ., 9 (2000), pp. 9–18

the long-term, particularly when use is initiated during adolescence. This may reflect the impact THC exposure has on brain development. The human brain undergoes a continuous and protracted process of development from the prenatal period through childhood and adolescence, and it is not done maturing until the mid-20s. Throughout this period the brain is strongly influenced by everything the individual experiences, and its ongoing maturation makes it more vulnerable to the adverse long-term effects of exposure to substances, including THC. The harmful impact of heavy or long-term THC exposure on the developing brain is supported by considerable animal research and a lesser but growing amount of research in humans.

Effects on brain development from prenatal exposure. As the brain is developing, the endocannabinoid system plays a key role in the formation of synapses, and the ability of exogenous cannabinoids (*e.g.,* those found in marijuana) to interfere with this signaling system may explain the alterations in brain development seen in animals prenatally exposed to THC. Studies in rats show that prenatal THC exposure can perturb the establishment of connections between neurons and connections among different parts of the brain[22], including the ventral tegmental area, which contains the dopaminergic cells necessary for responding to natural rewards and responsible for the addictive effects of drugs.[23] The extent to which prenatal exposure to marijuana produces similar effects in humans is still poorly understood. Although an estimated 9 to 22 percent of pregnant women have used marijuana and some studies have linked prenatal exposure to subtle negative effects on higher-order thinking, including problem-solving, memory, planning, impulsivity, and attention, it is difficult to disentangle the effects of marijuana use from various confounding factors, such as a mother's use of other drugs or alcohol.[24]

Effects on brain development in adolescence. We know more about the effects of THC on brain development in adolescence. As in the case of prenatal exposure, studies in rats show that early exposure (comparable to adolescence in human development) to THC is associated with an altered reward system, which increases the likelihood that an animal will self-administer other

[22] Tortoriello G, Morris CV, Alpar A, et al. Miswiring the brain: Δ9-tetrahydrocannabinol disrupts cortical development by inducing an SCG10/stathmin-2 degradation pathway. EMBO J 2014 Jan 27 [Epub ahead of print] 2014.
[23] Dinieri JA, Hurd YL. Rat models of prenatal and adolescent cannabis exposure. Methods Mol Biol 2012;829:231-42.
[24] Brown HL, Graves CR. Smoking and marijuana use in pregnancy. Clin Obstet Gynecol 2013;56:107-13. Jutras-Aswad D, DiNieri JA, Harkany T, Hurd YL. Neurobiological consequences of maternal cannabis on human fetal development and its neuropsychiatric outcome. Eur Arch Psychiatry Clin Neurosci 2009;259:395-412.

drugs (*e.g.,* heroin) when given the opportunity. And imaging studies in humans show that those individuals who consumed marijuana regularly during adolescence (compared to those who did not consume marijuana during adolescence) display impaired neural connectivity in specific brain regions involved in a broad range of cognitive functions like memory, learning, and interoceptive awareness.[25] These neural effects may help explain why adolescent onset of frequent and persistent marijuana use was associated with a significant drop in IQ scores in a large longitudinal study conducted in New Zealand.[26]

We still do not know the full extent of the impact of early marijuana use on long-term cognitive ability and associated life outcomes. Some studies suggest impairments in memory and attention after lengthy heavy marijuana use persist and worsen with increasing years of regular use or with initiation during adolescence; other evidence suggests long-term cognitive deficits could be reversible or remain subtle and not disabling if chronic users discontinue their marijuana use. Inconsistency among studies may be due to the many factors that can modulate the actual relationship between adolescent marijuana use and psychosocial harm (*e.g.,* genetic background, parental and built environment, etc.). Early marijuana use is associated with impaired school performance and increased risk of leaving school early, a harbinger of the established links between heavy marijuana use and other adverse life outcomes including lower income, higher unemployment, greater welfare dependence, increased criminal behavior, and diminished life satisfaction.[27] Whether and to what extent these links are causal remains for further research to determine.

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[25] Batalla A, Bhattacharyya S, Yücel M, et al. Structural and functional imaging studies in chronic cannabis users: a systematic review of adolescent and adult findings. PLoS One 2013;8:e55821.

[26] Meier MH, Caspi A, Ambler A, Harrington H, Houts R, Keefe RS, McDonald K, Ward A, Poulton R, TE. (2012) Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc Natl Acad Sci U S A 109:E2657-2664.

[27] Brook JS, et al. (2013) Adult work commitment, financial stability, and social environment as related to trajectories of marijuana use beginning in adolescence. Subst Abus. 34:298-305. Brook JS, Lee JY, Finch SJ, Brook DW.Developmental trajectories of marijuana use from adolescence to adulthood: relationship with using weapons including guns. Aggress Behav. 2014 May-Jun;40(3):229-37.

Addiction and other substance use. Approximately nine percent of people who experiment with marijuana will become addicted to it.[28] The number goes up to about one in six among those who start using marijuana as teenagers, with 25-50 percent among those who smoke marijuana daily becoming addicted.[29] The evidence clearly indicates that frequent marijuana use can and often does lead to addiction. According to the 2012 National Survey on Drug Use and Health (NSDUH), an estimated 2.7 million Americans 12 and older met diagnostic criteria for marijuana dependence (equivalent to addiction). Marijuana's ability to cause addiction in some (vulnerable) individuals is consistent with its ability to trigger withdrawal symptoms, including craving, irritability, anxiety, sleeping difficulties, and feeling generally ill or depressed—symptoms that make it hard to quit the drug and cause some people to relapse after they have tried to quit.[30]

The risk of marijuana addiction is increased in young people, particularly when they use the drug regularly. Compared to those who start using marijuana in adulthood, those who start as teenagers are roughly two to four times more likely to experience cannabis addiction symptoms within two years after their first use of the drug. And marijuana addiction, in turn, predicts increased risk of using other illicit drugs.[31] There is suggestive animal evidence that abuse of marijuana in adolescence could facilitate subsequent addictive behaviors in adulthood. For example, animal studies show that early THC exposure can weaken the dopamine system in the reward areas of the brain—an effect that, in humans, would explain early marijuana initiates' increased likelihood of developing other substance use disorders later in life.[32]

However, other drugs, such as alcohol and nicotine, also prime the brain for a heightened response to other substances, and thus could also be categorized as gateway drugs. There may be nothing

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[28] Anthony, J.; Warner, L.A.; and Kessler, R.C. *Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: Basic findings from the National Comorbidity Survey.* Exp Clin Psychopharmacol 2:244–268, 1994.
[29] Hall, W.; and Degenhardt, L. *Adverse health effects of non-medical cannabis use.* Lancet 374:1383–1391, 2009. Hall, W. *The adverse health effects of cannabis use: What are they, and what are their implications for policy?* Int J of Drug Policy 20:458–466, 2009.
[30] Gorelick DA, Levin KH, Copersino ML, et al. Diagnostic criteria for cannabis withdrawal syndrome. Drug Alcohol Depend 2012;123:141-7.
[31] Agrawal A, Neale MC, Prescott CA, Kendler KS. A twin study of early cannabis use and subsequent use and abuse/dependence of other illicit drugs. Psychol Med 2004;34:1227-1237
[32] Agrawal A, Neale MC, Prescott CA, Kendler KS (2004) A twin study of early cannabis use and subsequent use and abuse/dependence of other illicit drugs. Psychol Med 34:1227-1237

special about marijuana in this respect: One interpretation of the links between early marijuana (or tobacco or alcohol) use and subsequent substance use trajectories would be that those who are more vulnerable to substance use may simply be more likely to start with substances that are readily available. Resulting social interactions with other drug users may then make them more likely to try other substances.

Other Mental and Physical Health Effects Associated with Marijuana Use

Mental illness risk. There is an association between regular marijuana use and anxiety and depression. However, it is inherently difficult to confidently demonstrate causality in studies that link marijuana use and mental illness. There is a stronger link between marijuana use and psychoses (including schizophrenia), particularly if users have a preexisting vulnerability to that disease.[33] Marijuana can also worsen the course of schizophrenia. The disease trajectory can be negatively affected by stronger potency, heavier use, and younger onset, which may advance the time of an initial psychotic episode by anywhere from two to six years.[34] It is possible that heavy marijuana use may arise from some of the same factors that predict increased risk of mental illness, rather than being a cause.

Cancer and other diseases. An area of obvious concern given that marijuana is most commonly smoked is its short- and long-term impacts on lung health. Large airway inflammation, increased airway resistance, and lung hyperinflation are associated with marijuana smoking, and regular marijuana smokers report more symptoms of chronic bronchitis than non-smokers.[35] Smoking marijuana may also reduce the immunological competence of the user's respiratory system, increasing the likelihood of acquiring respiratory infections, including pneumonia.[36]

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[33] Caspi, A. et al. (2005) 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 X environment interaction. Biol Psychiatry 57:1117-1127. Di Forti, M. et al. (2012) Confirmation that the AKT1 (rs2494732) Genotype Influences the Risk of Psychosis in Cannabis Users. Biol Psychiatry 72:811–816. Compton, M. (2014) Teen Marijuana Use Linked to Earlier Psychosis Onset. Medscape May 14, 2014.

[34] Casadio, P., Fernandez, C., Murray, R.M., Di Forti, M. (2011) Cannabis use in young people: The risk for schizophrenia. Neuroscience and Biobehavioral Reviews 35:1779–1787.

[35] Tashkin DP. Effects of marijuana smoking on the lung. Ann Am Thorac Soc 2013;10:239-47.

[36] Owen KP, Sutter ME, Albertson TE. Marijuana: respiratory tract effects. Clin Rev Allergy Immunol 2014;46:65-81.

At this point, however, the long-term impact of low levels of marijuana exposure on respiratory health does not appear to be significant, and we do not yet know if even heavy marijuana smoking over a long period of time raises a person's risk for lung cancer. One study found that users who smoked the equivalent of one joint or one pipeful of hashish per day for at least 30 years (or "30 joint-years") had a higher rate of lung and several upper respiratory and digestive tract cancers; however, this association did not hold up after potential confounding factors like cigarette smoking were adjusted for.[37]

Research is however showing a link between adolescent marijuana use and rare but fast-growing form of testicular cancer (non-seminomatous testicular germ cell tumor) in young men. One case-control study showed that any lifetime use of marijuana approximately doubled the risk for this cancer[38], and another study found that risk increased with frequent use and earlier initiation of use.[39]

Marijuana use has also been associated with vascular disease that may put a user at higher risk for heart attack, stroke, and transient ischemic attacks after using marijuana, although we do not fully understand the mechanisms by which this may occur.[40]

What Is NIDA Doing About Marijuana?

Information dissemination and outreach. A critical component of NIDA's mission is to ensure the rapid and effective dissemination of research results to significantly improve prevention, treatment, and policy as it relates to drug abuse and addiction. To inform and educate the public on marijuana and its potential harms, NIDA has published a number of reports about marijuana for professional care providers and policy makers as well as easy-to-read fact sheets and

[37] Hashibe M, et al (2006) Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study. Cancer Epidemiol Biomarkers Prev 15:1829-1834.

[38] Lacson, J. C. A., Carroll, J. D., Tuazon, E., Castelao, E. J., Bernstein, L. and Cortessis, V. K. (2012), Population-based case-control study of recreational drug use and testis cancer risk confirms an association between marijuana use and nonseminoma risk. Cancer, 118: 5374–5383. doi: 10.1002/cncr.27554

[39] Daling, J. R., Doody, D. R., Sun, X., Trabert, B. L., Weiss, N. S., Chen, C., Biggs, M. L., Starr, J. R., Dey, S. K. and Schwartz, S. M. (2009), Association of marijuana use and the incidence of testicular germ cell tumors. Cancer, 115: 1215–1223. doi: 10.1002/cncr.24159

[40] Thomas G, Kloner RA, Rezkalla S. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: what cardiologists need to know. Am J Cardiol 2014;113:187-90.

informational pamphlets aimed at young people and parents. Other dissemination efforts include serving as a resource for the press, responding to public information queries, conducting, social media outreach, and coordinating public education initiatives such as National Drug Facts Week.

NIDA's marijuana research portfolio. NIDA funds a wide range of research on marijuana and on THC and other cannabinoid chemicals, including:

- Patterns and trends in marijuana use and attitudes, particularly among adolescents
- Short- and medium-term effects of THC on the brain and behavior
- Driving under the influence of cannabis
- Long-term effects of prenatal and adolescent cannabis exposure on brain development
- The development and impact of prevention programs on marijuana use
- Screening and brief assessment for marijuana abuse to prevent escalation
- Medications and behavioral treatments for cannabis use disorder
- The working of the brain's cannabinoid system, including its role in pain and HIV
- Potential therapeutic uses of THC and other cannabinoids in treatment of pain, HIV, and addiction (see section below)
- Social, behavioral, and public health impacts of state-level policy changes related to marijuana (*i.e.,* both "medical marijuana" and recreational use)

Research on the therapeutic benefits of cannabis and cannabinoids. THC and other chemicals in the marijuana plant have a potentially wide range of medicinal properties, and thus the possible therapeutic uses of marijuana are a subject of increasingly intense interest by researchers and the wider public. The challenge is to learn how to optimally harness the potential medical benefits of marijuana's chemical constituents without exposing healthy or sick people to the various intrinsic risks of smoking or otherwise ingesting marijuana in its crude form (particularly when product quality, composition, purity, and dosing are inconsistently standardized and regulated, as may be the case with "medical marijuana"). While acknowledging that smoked marijuana has been anecdotally reported to be useful in certain cases (*i.e.,* in stimulating appetite, particularly in AIDS-related wasting syndrome; in combating chemotherapy-induced nausea and vomiting, severe pain, and some forms of spasticity), the authoritative Institute of Medicine report on "Marijuana and

Medicine" stressed the greater potential of non-smoked, rapid-onset delivery systems for cannabis and urged the field to concentrate on investigating the therapeutic potential of synthetic or pharmaceutically pure cannabinoids, not smoked marijuana.[41]

As of January 31, 2014, seven NIH institutes are supporting 54 NIH active grants related to the therapeutic uses of cannabis or cannabinoids, (approximately half of them were funded by NIDA), in 9 different disease categories. Many of these studies are using animal models or cell culture systems. The vast majority are examining the medical benefits of individual cannabinoid chemicals derived from or related to those in the marijuana plant, not the plant itself, although a handful of studies use unprocessed plant material. Individual cannabinoid chemicals may be isolated and purified from the marijuana plant or synthesized in the laboratory, or they may be naturally occurring (endogenous) cannabinoids found in the body (*i.e.,* as part of the endocannabinoid signaling system) and modified using other, non-cannabinoid chemicals.

FDA-approved medicines based on THC for the treatment of wasting syndrome and to control nausea in chemotherapy patients are already available, and there is currently a great deal of active interest in developing medications based on another constituent of the cannabis plant called cannabidiol (CBD). This non-psychotropic chemical does not directly interact with cellular receptors of the body's endocannabinoid signaling system, on which THC acts, and it may even mitigate some of the psychoactive effects of THC. CBD has shown some promise in controlling seizures in children with severe forms of epilepsy (Dravet and Lennox-Gastaut syndromes), and preliminary trials of a CBD-based drug are currently underway, although those trials are not funded by NIH.

Limitations and Need for Further Research

Most of the long-term effects of marijuana use summarized in this testimony have been observed among those who use the drug heavily and/or over a long period of time, but most of the human studies so far have not been large or prospective, and various (often hidden) confounding

[41] IOM (1999) Marijuana and Medicine: Assessing the Science Base. Janet E. Joy, Stanley J. Watson, Jr., and John A. Benson, Jr., Editors. Division of Neuroscience and Behavioral Health, Institute of Medicine. NATIONAL ACADEMY PRESS Washington, D.C.

factors—including the frequent use of marijuana in combination with other drugs—often make it difficult to establish causality or determine the strength of marijuana's unique effects. This is particularly the case when trying to assess the true impact of intrauterine exposure to marijuana or understand the relationship between marijuana use and mental illness, as discussed earlier. There is also the difficulty, also mentioned, of knowing the current relevance of published study findings of long-term outcomes that were conducted when the potency of the cannabis available was less than what it is today.

Research is needed in several areas. For example, it is important to learn more about long-term marijuana use by vulnerable populations, such as those who may use marijuana for medical purposes (despite the limited scientific evidence, as yet, for these benefits)—such as AIDS patients, cardiovascular disease patients, patients with multiple sclerosis or other neurodegenerative diseases, and elderly persons. We do not yet know if people whose health has been compromised by disease or its treatment (*e.g.,* chemotherapy) are at greater risk for adverse health outcomes from marijuana use. We also need to know more about the potential harms of marijuana to individuals prenatally exposed to the drug.

More research is also needed to shed light on the influence of marijuana policy on public health and other outcomes. Our understanding of the impact of marijuana policy on market forces (*e.g.,* youth-targeted advertising, the allure of new sources of tax revenue, pricing wars, and the emergence of FDA-approved cannabis-based medicines) is very limited, as is our understanding of how perception, use, and outcomes interrelate around this drug. Getting a better grasp of this will be crucial, given the striking decades-long trend in epidemiological data (Monitoring the Future)[42] showing that whenever adolescents report diminished perception of risk, prevalence of teen marijuana use increases. Would current or anticipated shifts in culture/policy around marijuana cause more young people to be regularly exposed to cannabis and thus use it more than they already do?

[42] Johnston LD, O'Malley PM, Bachman JG, J.E. S (2013) Overview: key Findings on Adolescent Drug use. 1975-2 013. In: Monitoring the Future national Survey Results on Drug Use (Michigan, U. o., ed).

Most importantly, there have thus far been no large-scale longitudinal studies beginning in childhood, prior to first exposure to marijuana, that track individuals through adolescence and examine links between drug use behaviors and brain development and other outcomes. NIDA in partnership with the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Cancer Institute (NCI), and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) has recently proposed a large, prospective study that would use current brain-imaging and other technologies to study the impact of marijuana and all other forms of substance use on teenagers. This study, provisionally called the National Longitudinal Study of the Neurodevelopmental Consequences of Substance Use, will follow a large cohort, beginning in late childhood, prior to drug exposure, through young adulthood. By gathering neuroimaging data as well as a broad range of substance use, mental health, and other outcomes such as IQ and cognition, the study will clarify the impact of marijuana use on development, reveal the effects of multiple substance exposures, and disentangle the effects of marijuana and other drugs from various confounding factors (particularly prior exposure to substances), as well as giving us insight into the mechanisms by which substances change the brains of young users.

Conclusion

Scientific research has linked marijuana use to a range of significant adverse effects on health and well-being. For example, its acute effects during intoxication interfere with cognitive and motor processes needed for driving a vehicle, and thus marijuana use significantly raises the risk for automobile accidents. Frequent marijuana use during adolescence may have a prolonged or even permanent deleterious impact on brain function and may jeopardize a young person's educational, professional, and social achievements. Like other drugs of abuse, marijuana can be addictive. Additionally, marijuana use is associated with increased risk of some psychiatric conditions as well as various pulmonary and vascular health effects. We still need to understand more fully to what extent rising potency of marijuana may exacerbate these risks.

The health impact of any substance (legal or illegal) is determined not only by its inherent toxicity and how it acts in a user's brain but also by how available and socially acceptable it is, how it is advertised/marketed, how people use it (and how often), and so on. Alcohol and tobacco—legal

substances—provide a useful perspective here, since these two substances overwhelmingly account for the greatest burden of drug-associated death and disease due in part to their widespread access afforded by their legal status.. As state policies around marijuana shift, it is reasonable to predict that increasing numbers of people will use the drug, including young people, and thus that increasing numbers of Americans will experience the types of consequences discussed above.[43]

We appreciate the opportunity to testify on the health effects of marijuana. The key to minimizing negative outcomes lies, on one hand, in the intensification of efforts to educate the public about the real dangers associated with marijuana use and, on the other, in the deployment of multipronged, evidence-based strategies to prevent and treat the abuse of and addiction to marijuana and other drugs.

Thank you again for inviting me here today, and I look forward to any questions you may have.

[43] Richter KP, Levy S. Big Marijuana - Lessons from Big Tobacco. N Engl J Med. (2014, June)
Morris RG, TenEyck M, Barnes JC, Kovandzic TV. The effect of medical marijuana laws on crime: evidence from state panel data, 1990-2006. PLoS One. 9(3):e92816. (2014)
Schuermeyer J et al. Temporal trends in marijuana attitudes, availability and use in Colorado compared to non-medical marijuana states: 2003-11. Drug Alcohol Depend. 140:145-55. (2014)
Salomonsen-Sautel Set al. Trends in fatal motor vehicle crashes before and after marijuana commercialization in Colorado. Drug Alcohol Depend.140:137-44. (2014)