Testimony of Dr. Staci Gruber Before the Senate Caucus on International Narcotics Control

"Marijuana and America's Health: Questions and Issues for Policy Makers"

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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 conditions[1]. Cannabidiol (CBD), the primary non-intoxicating constituent of the plant, has become well-known for its role in treating intractable pediatric-onset seizure disorders[2], and has demonstrated promise in treating other medical conditions including pain and multiple sclerosis[3], as well as psychiatric conditions including anxiety[4] and psychosis[5,6]. CBD has been shown to mitigate some of the negative effects of THC, including adverse psychological symptoms[7] 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 levels[10].

Despite a body of evidence demonstrating structural and functional brain alterations among MJ users, more than 24 million Americans report past month MJ use[11]. 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 harmful[12]. Further, almost 9% of the national population aged 12 or older currently use MJ[11], 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 domains[17-20]. 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 recognition[22]. 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 users[25-32]. Further, several investigations also report that poorer executive function is a predictor of MJ use[33,34] and MJ-related problems[35]. 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 use[40]. Similarly, a second large-scale, longitudinal study[41] 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 users[49].

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 examination[50]. Interestingly, however, alterations are most often observed in areas with high densities of CB1 receptors[8] and may also be influenced by age of onset and increased MJ use[51]. 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 hippocampus[8]. Importantly, studies have found that structural alterations in a number of brain regions appear to be related to increased executive dysfunction[52-55] and poorer verbal memory[56].

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 users[57-60]. A relationship between earlier age of onset of MJ use and lower white matter integrity has also been reported[57-60]. 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 users[57].

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 used[30], 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 products[66]. 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 effects[68], and higher levels of physical dependence[69] and self-reported depression and anxiety[70]. 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 controls[71]. 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 time[18]. 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 mice[74]. 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 interactions[75]. This is important, as approximately one-third of all prescription drugs in the US are used by older adults[76]. 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 <u>Recreational</u> MJ Use be Generalized to <u>Medical</u> 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 THC[9] and has been hypothesized to have tremendous therapeutic potential for a variety of conditions and indications[1], 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 effects[77-80]. 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 terpenoids[81]. 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 control[84]. 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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