Recreational Marijuana and Cognitive Decline:

What Every Clinical Neurologist Needs To Know

The first installment of a two-part series exploring the impact of recreational and medical marijuana on cognitive function and neurological disorders.

BY RONALD DEVERE, MD, FAAN

In the last decade, marijuana has gone from being totally illegal in the United States to legalization for medical use in 23 states and for recreational use in four jurisdictions (including Washington, DC). Even the Surgeon General expressed interest in what science will learn about marijuana, noting that review of preliminary data show its benefit for certain medical conditions and symptoms. Given this pattern, it is very likely that more states will legalize its medical and unrestricted use in coming years.

A growing sentiment in public opinion toward marijuana, particularly among adolescents, is that it is a harmless substance for pleasure that should not be regulated or considered illegal. Marijuana is currently the most common "illicit" drug in the US, with around 12 percent of people 12 years of age or older reporting use in the last few years (with the highest rates of use in the young).[1] However, a recent study examined the perceptions and use of marijuana among young people in the US between 2002 and 2013 and found that fewer adolescents between the ages of 12 an 14 years report using marijuana (six percent in 2002 and 4.5 percent in 2013), while more disapprove of marijuana (74 percent in 2002 and 79 percent in 2013). Young adults (ages 18 to 25 years) have trended in a different direction, with 41 percent disapproving it 2002 and 23 percent disapproving it in 2013; however, no increased use was noted in this age group.[2]

As clinical neurologists, we must be aware of and understand the neurological consequences to our patients—young and old—in their use of this agent in both recreational and medical capacities. The regular recreational use

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of marijuana as previously stated is more common in the younger population.[1] The cognitive consequences have been much more studied in this population, as it appears that marijuana can cause havoc in those with developing brains. While recreational use is much less common in the elderly, we need to know what role medical marijuana can play in clinical neurology, especiallyits effects on cognitive function.

Over the span of two articles, I will strive to distill important clinical facts on marijuana use in all age groups. While I will examine the neurological disorders that may benefit from medical marijuana in the next article (appearing in the November/December 2015 issue), here I will focus on the impact of recreational use on the brain.

BACKGROUND AND CHEMICAL INGREDIENTS OF MARIJUANA

Before we proceed with more information about marijuana, some comments are necessary about the human ECS system. This is a signaling system that includes cannabinoid receptors, endogenous receptor ligands and their synthesizing and degrading enzymes. The core function of the ECS system has been described as "relax, eat, sleep, forget, and protect," which is shorthand for the diversity of processes involving the system. This system regulates neuronal excitability, inflammation in pain circuits, and helps regulate movements, appetite, aversive memory extinction, immunomodulation, mood, awake and asleep cycle, hypothalamic-pituitary adrenal modulation, blood pressure, bone density, tumor surveillance and neuroprotection. Additionally, "runners high," the effects of osteopathic manipulative therapy, and electro-acupuncture are mediated by the ECS.[4]

Although its use dates back as far as possibly 3000 BCE, very little was known about marijuana up until half a century ago. In 1963, a young organic chemist from Israel, Raphael Mechoulam, working at the Weitzman Institute in Tel Aviv, discovered the important ingredients. With the help of the Israeli police, he confiscated five Kilos of Lebanese Hashish. He had isolated an array of substances, which he injected separately in Rhesus Monkeys. Only one substance made aggressive monkeys calm and mildly sedated. Further testing revealed that the two main substances were Tetrahydrocannibal (THC), which is psychoactive, and Cannabidiol (CBD), which has other effects for medical conditions but is not psychoactive. THC produces euphoria but it can also produce psychosis. Cannabidiol has antianxiety and possibly antipsychotic effects.[5] Marijuana's therapeutic effects depend on the concentration of THC in a given formulation as well as the ratio of THC to cannabidiol, because of cannabidiol's ability to mitigate the psychoactive effects of THC. As a result, the THC-cannabidiol ratio for many strains of marijuana has been engineered to achieve the desired effects. To make things a little more confusing, there are more than 60 pharmacological active cannabinoids besides cannabidiol.

ADVERSE EFFECTS OF RECREATIONAL MARIJUANA

1. **Risk of Addiction**. The evidence in the literature suggests that long-term non-medical Marijuana use can lead to addiction. One in six who use marijuana as teenagers and 25-50 percent that smoke it daily will develop an addiction.[6] According to the 2012 National Survey on Drug Use and Health, 2.7 million people 12 years and older met criteria for marijuana dependence, 5.1 Million met criteria for dependence on any illicit drug, and 8.6 million met dependence criteria for alcohol.[7] Cannabis withdrawal syndrome has been found in heavy chronic users. Abrupt cessation symptoms begin in one to two days, reach peak in two to six days and resolve in a few weeks. Symptoms include irritability, insomnia, dysphoria, craving and anxiety, which makes cessation very difficult. Unlike opioid withdrawal, aches, pain, and muscle spasms are uncommon.[8]
2. **Effect on the Developing Brain**. The brain continues to develop from the prenatal period to approximately age 21.[9] Exposure to THC during prenatal or adolescent stages in animals appears to recalibrate the sensitivity of the reward system to other drugs and impairs axonal connections between neurons.[10] Adults who smoked marijuana as adolescents have fewer fibers in specific brain regions, including the Precuneus (an area important for alertness and self-conscious awareness) and the Fimbria (an area of the hippocampus important for learning and memory). Decreased nerve fiber connections have also been noted in the prefrontal networks responsible for executive function (includes inhibitory control, habits, routines, and behavior).[11] Cannabis effects are mediated by two types of receptors designated CB1 and CB2. These receptors are part of the normal ECS system. The CB1 receptors are distributed in the hippocampus, prefrontal cortex, anterior cingulate, basal ganglia, cerebellum, association cortices, spinal cord and peripheral nerves. CB1 activation prominently modulates cognition and memory, per-

WHAT ARE THE NEUROBIOLOGICAL MEDIATORS OF COGNITIVE IMPAIRMENT BY MARIJUANA?

The exact mechanism is not totally clear. Acetylcholine (ACH) participates in many CNS functions including attention, working memory, motivation and reward through nicotinic and muscarinic receptors. Cholinergic neurons are either projection neurons terminating diffusely in the brain including the hippocampus, prefrontal cortex, or interneurons, which are located in the striatum and nucleus accumbens.[21] We know that ACH is implicated in other cognitive impaired disorders such as Alzheimer's, vascular and Parkinson's dementia. THC inhibits cholinergic transmission in the brain and impairs working memory similar to the use of scopolamine, a cholinergic antagonist.[22] CB1 receptors as previously mentioned are on cholinergic terminals and control ACH release.[23] Cannabis induced reduction of ACH in the hippocampus and medial prefrontal cortex correlated with impaired working memory.

ception, control of motor function and analgesia.[3] The CB2 receptors are found mainly on cells in the immune system, which may in part explain cannabinoids effect on pain and inflammation. Their activation modulates and inhibits pro-inflammatory cytokine production, leading to blockade of neutrophil and macrophage migration. CB2 receptor expression on CNS microglia may explain cannabinoid efficacy in reducing cytokine mediated neuroinflammation.[3] Both of these receptors are located in the presynaptic terminals and modulate and inhibit release of other neurotransmitters including GABA, dopamine, glutamate, norepinephrine, and acetycholine. They also indirectly affect gamma-aminobutyric acid, n-methyl d aspartate, opioid and serotonin receptors.

3. **Cognitive Function in Adolescent and Young Adult Marijuana Users**. As previously mentioned, THC is the most potent product in marijuana, and its concentration ranges from 0.5 percent to five percent. Hashish has THC levels a bit higher, from two percent to eight percent. In Hash oil the concentration of THC can be very high, from 15 percent to 25 percent. In a landmark study, Meier et al. followed 1,037 individuals in New Zealand from birth to age 38 years.[12] They ascertained information regarding cannabis use through interviews at ages 18, 21, 32, and 38 years. They conducted neuropsychological testing at age 13, before initiation of cannabis use and at age 38, after a pattern of persistent cannabis use had developed. In their study, they ruled out other important confounding factors, such as acute or residual cannabis intoxication, tobacco dependence, hard drug dependence (heroin, cocaine and amphetamines), alcohol dependence, and schizophrenia. They also controlled for years of education and obtained ADLs from third-party informants. Additionally, they determined whether persistent users who quit or reduced cannabis use were able to restore their cognitive deficit. Each study member served as her or his own control.

The summary of the long study came to the following conclusions:

1. Study members who never used cannabis had a slightly higher IQ.
2. Those with cannabis dependence at the first three or four follow-up visits experienced significant cognitive decline from three to eight IQ points. This was noted in the persistence of cannabis users and those with cannabis dependence.
3. The greatest neuropsychological impairments were in executive function and processing speed. When informants were given assessment sheets in regard to ADLs of the study patients, more impairment in attention and memory problems were noted in the cannabis dependence group.
4. Adolescent onset users under 18 years of age tended to become more persistent users and showed more cognitive impairment than the adult onset users (ages 25 and greater). This older group had much less cognitive decline at the end of the study.
5. Adolescent cannabis users regardless of dependence or used infrequently, at time of cessation for a year showed continued cognitive decline. This was not noted in the adults who stopped using cannabis.
6. Cognitive decline in adolescence was not based on cannabis users completing less education.
7. Strong suggestion that cannabis use in adolescence is toxic to a developing brain.
8. Major educational effort should be directed toward delaying cannabis use by young people.

> "While it is clear that cannabis has an impact on cognitive function for young people, no pertinent studies have been conducted investigating cognitive function in mid-adult and elderly recreational users."

There are a number of limitations in this extensive study. For instance, the use of cannabis is based on the history from individuals not on a biologic marker and underreporting is a possibility. Additionally, it did not account for the potency of cannabis, however, one study revealed that cannabis seized by police in New Zealand appears to be similar to the US.[13]

COGNITIVE DECLINE AND ATTENTION LOSS

The notion of cognitive decline in users of cannabis was the driving factor in another study in which investigators did an extensive evidence based review of the acute and long term effects of cannabis use on executive cognitive function (attention, concentration, decision making, impulsivity, working memory and verbal fluency).[14]

The acute effects noted during the first six hours after use in chronic light cannabis users (2.5% THC cigarettes) showed significant impairment in attention and concentration. However, chronic heavy cannabis users who were abstinent showed impaired information processing and attention that normalized after acutely smoking cannabis. This suggested that abstinence following chronic cannabis use may result in a deficit in information processing which normalizes after

acute use. Along the same lines, there is some evidence that acute cannabis use has observable deficits in planning and decision making as relates to response speed and accuracy and impulsive behavior.[15] Other studies have also shown impairment in working memory—worse the higher the THC dose. There is no evidence that verbal fluency was impaired in acute users.[16]

In light of these studies, impairing effects of cannabis intoxication on attention and concentration is stronger in less experienced cannabis users than those established with drug tolerance. Attention and concentration in those with established drug tolerance is disrupted more by acute abstinence than acute cannabis administration due to adaption to chronic heavy cannabis use.

The residual effects of Cannabis use on executive function have been studied in various capacities, from seven hours after use to 20 days after use.[14] Three out of four studies showed impaired attention, longer reaction times, and time to complete tasks compared to controls. In one study, investigators examined focus and attention capacities in cannabis users right before work and immediately after work at the beginning and the end of a work week.[17] Compared to controls, cannabis users had impaired attention and information processing both at the beginning and end of the workweek, correlating with duration of cannabis use. This confirms that even with abstinence, some deficits remain. In the category of decision-making and impulsivity, studies only with 12-hour abstinence were done which showed impairment.

One study found no abnormalities in working memory or verbal fluency after 19 hours abstinence in light and heavy cannabis users.[18]

These studies suggest that attention and concentration are impaired in cannabis users, but not enough studies have been done to evaluate executive function in light and heavy cannabis users after abstinence of roughly three weeks.

Reviewing the long-term effects of Cannabis on executive function, several studies found no attention of concentration impairment in patients who remained abstinent between 28 days and one year.[19,20] Two studies found impairment in attention but the reviewing authors stated that this could have been secondary to basic information processing rather than higher level of attention. It is worth noting that information processing has not been studied in long-term cannabis abstinence.

One study with 25 days of abstinence of cannabis found impaired decision making and risk taking compared to controls. Inhibition and impulsivity was not shown to be impaired. Only one study analyzed working memory and it didn't show any abnormalities. Verbal fluency was studied after 28 days of cannabis abstinence, and early onset of cannabis users (under age 17) had significant impairment in verbal fluency compared to controls.

Although this is an area deserving of more investigation, these studies indicate that cannabis appears to cause some impaired executive function after three weeks of abstinence and beyond. The most enduring and detectable deficits are seen in decision making, concept formation, and planning. Those subjects with chronic heavy cannabis use especially beginning before age 17 show the most enduring effects.

CONCLUSION

While it is clear that cannabis has an impact on cognitive function for young people, no pertinent studies have been conducted investigating cognitive function in mid-adult and elderly recreational users. However, the next segment in this article series will explore the larger number of studies evaluating the potential benefits of medical marijuana for various conditions. ■

Ronald Devere, MD, FAAN is Director of the Alzheimer's Disease and Memory Disorders Center in Austin, TX.

1. Volkow, Nora D. et al. Adverse Health Effects of Marijuana Use. NEJM, 370; 23, June 5, 2014
2. Salas-Wright, Christopher et al. Trends in disapproval and use of Marijuana among adolescents and young adults in the U.S. A. American Journal of Drug and Alcohol Abuse Vol 41 Issue 5 2015, page 392-404.
3. Rose Mark BS, MA et al. Medical Marijuana and other Cannabinoids. 2014 NetCE. Course #95170, Sacramento California, pages 1-38
4. Sparling P.B. et al, Exercise activates the Endocannabinoid system. Neuroreport. 2003; 14 (17) :2209-2211
5. Bhattacharyya, S. et al. Opposite Effects of Delta-9- Tetrahydroncannabinol and Cannabidiol on human brain function and psychopathology. Neuropsychopharmacology, 2010; 35 (3):764-774.
6. Hall, W. et al, Adverse Health Effects of non-medical cannabis use. Lancet 2009 ;374: 1383-91
7. Center for Behavioral Health Statistics and Quality. National survey on drug use and health. Rockville MD: substance Abuse and Mental Health Services Admin 2013.
8. Gorelick DA, et al. Diagnostic Criteria for Cannabis Withdrawl Syndrome. Drug Alcohol Dependency 2012, ; 123 (1-3): 141-147.
9. Gogtay N, et al. Dynamic Mapping of Human Cortical Development during Childhood through early adulthood. Proceedings Natl Academy of Science, USA, 2004; 101: 8174-9.
10. Tortoriello G et al, Miswiring the Brain, Delta 9 tetrahydrocannabinol disrupts cortical development by inducing an SCG10 /stathmin-2 degradation pathway. EMBO J. 2014; 33:668-85.
11. American J of Drug Alcohol Abuse 2013; 39: 382-91.
12. Meier M.H. et al, Persistent cannabis users show neuropsychological decline from childhood to midlife. PNAS published online august 27, 2012. E2657-E2664.
13. Mclaren J. et al, Cannabis Potency and contamination, A review of the Literature. Addiction Journal, 2008, 103: 1100-1109.
14. Crean, Rebecca D. et al, Evidence Based Review of Acute and Long term Effects of Cannabis Use on Executive Cognitive Functions. Journal of Addiction medicine. 2011, March 1; 5(1) ; 1-8
15. Ramaekers, J.G. et al. High Potency Marijuana Impairs Executive Function and Inhibitory Motor Control. Neuropsychopharmacology 2006; 31 (10): 2296-303.
16. Hart CL. et al, Effects of Acute Smoked Marijuana on Complex Cognitive Performance. Neuropsychopharmacology 2001; 25(5); 757-65
17. Wadsworth EJK et al, Cannabis Use, Cognitive performance and Mood in a Sample of Workers. Journal of Psychopharmacology 2006; 20(1):14-23.
18. Pope HG. Et al, The Residual Cognitive effects of Heavy Marijuana Use in College Students. JAMA 1996; 275(7): 521-7.
19. Lyons MJ et al, Neuropsychological Consequences of regular Marijuana Use: A twin Study. Psychological Medicine 2004; 34 (7): 1239-50.
20. Verdejo-Garcia AJ. et al, Effects of MDMA, Cocaine and Cannabis use severity on Distinctive Components of Executive Function in Polysubstance Abusers: a multiple regression Analysis. Addiction Behavior 2006, 31(8): 1373-82
21. Mesulam MM. The Cholinergic Innervation of the Human Cortex Prog Brain Res 2004; 145:67-78
22. Varvel SA. et al, Differentia Effects of Delta 9-THC on spatial reference and working memory in mice. Psychopharmacology (Berl) 2001; 157 (2): 142-150.
23. Degroot A, et al. CB1 receptor antagonism increases Hippocampal acetylcholine release: site and mechanism of action. Molecular Pharmacology 2006; 70(4): 1236-1245.