

# A Scientific Perspective on Marijuana on the Eve of Its Legalization

## NAADAC Interview of Dr. Darryl S. Inaba, PharmD, CADC-V, CADC III

In June 2015, NAADAC interviewed Dr. Inaba regarding the effects and actions of marijuana in the human body.



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**NAADAC:** It seems that the push for medical and legal recreational use of marijuana is reaching a tipping point, what do you think about this development?

**DR. INABA:** I think that people are again ignoring the science and medical community about marijuana as they did when marijuana was made illegal during the mid-1930s. As a clinician who has worked with those who experience medical, emotional and social problems from its use for the past 40 years, I am concerned about the life consequences that legalization will have on those who are vulnerable to developing problems from its use, especially youth users who are most at risk. Current data indicate that 8–10 % of people who use the marijuana will develop Cannabis Use Disorder (CUD) and will not be able to stop using it without treatment. (Borgelt, Franson, Nussbaum, & Wang, 2013; National Institute on Drug Abuse (NIDA), 2013; American Psychiatric Association, 2000). Currently over 300,000 people a year are being treated for this condition. About 17% of all those who are treated for substance-related and addictive disorders in the United States list marijuana as their primary and many list it as their secondary or tertiary drug of choice. It is, in fact, the substance most often listed by the 1.8 to 1.9 million treated for addiction each year in this country. (Substance Abuse and Mental Health Services Administration (SAMHSA), 2014). The majority of clients I have treated for CUD during the past 40 years were self-referred, not criminally-referred into treatment. They entered

treatment because marijuana was causing severe dysfunction and disruption in their lives and they desperately wanted to stop despite the great ridicule they were getting from others calling them a “wussy” who should go out and get a real addiction like heroin or meth before needing any help to stop.

Science and medicine also documents an availability of more powerful marijuana products than were generally available in the past. “Dabs,” “Spice,” “Edibles” with a greater concentration of THC or more powerful synthetic cannabinoids are creating more health problems than during the 1960s when marijuana abuse first exploded in the general population of this country. (Center for Disease Control and Prevention (CDC), 2015; Gray, 2014). The greater availability of more potent THC, powerful and often undetectable synthetics, along with the evolving legalization of marijuana will certainly increase the number of

people who will be seeking treatment. That issue is not being seriously considered by the legalization movement. Our treatment programs are already overloaded with long waiting lists for people who seek and need addiction treatment services. Further, how will the increased need for treatment services be financed?

In the late-1930s, the push was on to make cannabis an illegal drug. Newspaper reporters from the Hearst newspaper chain and prohibitionists were looking for a new cause. In response Mayor La Guardia of New York City put a commission together to examine the problem and make recommendations. Cannabis had been recognized as a beneficial medical substance in many pharmacopeia references and it had been used for thousands of years to treat patients for a variety of ailments. So the question was: should it be banned for use in medicine as well as for recreational use? After a rigorous review, the Commission found that there was no cause for a total ban as there were viable medical applications for its use. Science and medicine lost that battle and Congress passed the Marijuana Tax Act of 1937 prohibiting its use and availability for medical as well as recreational purposes.

Fast forward to the present day, society, and especially politics are again ignoring medicine and science regarding the general availability of marijuana. More information about both the positive and the negative effects of marijuana on the brain and body has been discovered in the past few years than the previous thousands of years of its use. We are starting to identify the great medical effects of the non-psychoactive chemicals in pot like cannabidiol (CBD) and the brain damaging effects of it psychoactive chemicals like Delta-9-tetrahydrocannabinol ( $\Delta^9$ -THC). All this is being ignored while influence for its legalization by BIG TOBACCO and ALCOHOL, whom William F. Buckley referred

to as “The Merchants’ Of Death,” is winning the day. The potential financial opportunity to big business from having another addictive substance to market is probably irresistible. Society needs to be reminded that America suffers more than 500,000 deaths each year due to medical and life problems associated with its legal drugs of addiction, tobacco and alcohol and only about 40,000 annual deaths due to the abuse of illicit drugs on its streets.

**NAADAC: There does seem to be a virtual flood of new studies and reports regarding marijuana, but they all seem to often contradict each other and promote more confusion than clarity about its effects. Why does marijuana research result in such conflicting controversial reports?**

**DR. INABA:** Marijuana is a nightmare for empirical scientists’ to study accurately. It is not a single chemical but a virtual smorgasbord of hundreds to thousands of biologically active compounds. Though there are only three species of the cannabis plant, there are vast numbers of strains, varieties, and hybrids that are in continuous development, each with varying levels of different molecules and compounds that the marijuana plant produces. Further, the varying concentrations of marijuana compounds are influenced by different growing techniques, how they are used, and even how long they have been stored after harvesting until they are used. A single marijuana plant contains some 480 or so biologically active chemicals, 66 of which are **phytocannabinoids** (cannabinoids produced by plant), and 80 to 100 psychoactive chemicals. (University of Washington Alcohol & Drug Abuse Institute (ADAI) and Australia National Cannabis Prevention and Information Centre, 2011). Each individual’s genetics or biology also influence the effects of marijuana. When it is taken into the body, greater than 100 psychoactive metabolites can be produced from the body’s attempt to break down and eliminate it. Smoking marijuana creates an additional 2,000 or so chemicals from the combusted processes and most of those chemicals also have biologic impact on the brain and body. Another major concern about the chemicals present in street marijuana is that rodenticides, insecticides and other pesticides that are often used in their production usually remain in the plant and negatively impact the body. Fungi, bacteria, and residual solvents used in extraction processes are also found to contaminate marijuana products even in states that have legalize and regulate their sale. Since much of the research done on marijuana does not or cannot control for these many variables, there continues to be tremendously conflicting and controversial results about its effects.

In 1988, scientists Devane and Howlett (1988) identified two major types of receptors for the cannabinoids in the brain and body: **CB<sub>1</sub>** and **CB<sub>2</sub>**. CB<sub>1</sub> receptors are responsible for the feelings of euphoria when marijuana is used. These are located the cortex and sub cortical areas of the brain, but there are no cannabinoid receptors in brain stem, the part of the brain that controls heart rate and breathing. Other psychoactive drugs like opiates and cocaine have major receptors in brain stem but not cannabis, which is why an overdose from marijuana rarely results in death as seen with other drug overdoses. I say rarely because high potency marijuana and synthetic cannabinoids are now being increasingly linked to suicides, accidents, homicides, drowning, heart attacks, seizures and even testicular cancer. CB<sub>1</sub> receptors also activate the brain’s addiction pathway and are responsible for marijuana’s addictive properties.

**Delta-9-tetrahydrocannabinol ( $\Delta^9$ -THC)** a major compound found in all marijuana plants is the primary activator of CB<sub>1</sub> receptors. CB<sub>2</sub> receptors are mainly outside of the brain and may be responsible for most of the medically beneficial effects reported with medical marijuana treatment. The CB<sub>2</sub> receptors are more often activated by another major compound found in marijuana plants, **cannabidiol (CBD)**. CBD actually opposes many of the effects of THC including the euphoric effects. CBD is not considered to be psychoactive and it interacts with the immune system, has anti-seizure, pain relief, anti-nausea and many other positive health benefits. Thus, I think that there is a real future for actual medical cannabinoids because CBD and other unique chemicals in the cannabis plant may be a treasure trove of future medicinal compounds. However, in my opinion, medical marijuana does not include rolling up some “nugs” or “shake” in a Zig Zag and smoking it as medicine, since there are also hundreds of medically harmful compound in the plant as well.

**NAADAC: Why does addiction to marijuana, now classified in psychiatry as Cannabis Use Disorder, continue to be dismissed by many in both the general and even some scientific communities?**

**DR. INABA:** Cannabis is a psychoactive substance that has been in continuous use throughout the world for longer than most other drugs. It was used in Chinese medicine thousands of years ago and archeologists have even found still active molecules of its chemicals in Egyptian mummies. The funny thing about its long history of use is that we still barely know how it works and what it does to the brain. The most curious thing for me as an addiction treatment provider is that regular marijuana users continue an ardent denial about it even being a drug. They think of marijuana as an herb, a food, an economic entrepreneurial opportunity, or even that it is a political or constitutional right for all Americans to be able to use it. Very few, users and non-users, think of marijuana as being a drug. Opium, cocaine, alcohol, LSD and most abused psychoactive drugs come from botanical sources and no one has any problems thinking of them as drugs. Why then isn’t marijuana respected as being a drug as well?

As an addiction treatment professional and a clinical pharmacist, I know that the most psychoactive cannabinoid in marijuana is Delta-9-tetrahydrocannabinol ( $\Delta^9$ -THC). This compound, this drug, and many of the other cannabinoids in marijuana do cross the blood brain barrier to produce a long list of psychoactive effects: it impairs coordination, memory, depth perception, the ability for the eye to track movement and other abilities that decreased one’s ability to drive.  $\Delta^9$ -THC is an abuseable/addictive psychoactive substance that should not be used especially by adolescents, pregnant women, and people with a history of addiction and/or those who have mental health problems without careful medical supervision. Despite these issues and many current scientifically validated studies about adverse mental and physical effects of cannabinoids, many people do not believe that there are any negative problems associated with the use of marijuana or its primary psychoactive substance,  $\Delta^9$ -THC. They do not see it as an addictive drug despite the evidenced-based, Diagnostic and Statistical Manual of Mental Disorders specifying 11 symptoms plus 7 signs of withdrawal effects as diagnostic criteria for those experiencing Cannabis Use Disorder. (American Psychiatric Association, 2013).

### NAADAC: How can chemicals produced in the cannabis plant have so many different effects on the human body and brain?

**DR. INABA:** To answer this key question we need to look at what is now known about phytocannabinoids found in the plant and the endocannabinoids present in the human body from a neuropharmacological perspective. It has only been about 25 years since research scientists first discovered the biological receptor sites that interact with the chemical compounds produced by the Cannabis plant, the phytocannabinoids in marijuana. It turns out that our brain and body cells have unique receptor sites known as G protein-coupled receptors for these compounds that are on the pre-synaptic axons fibers of neurons.

Within five years of that discovery, Raphael Mechoulam, who had much earlier identified CBD and  $\Delta^9$ -THC as active phytocannabinoids in the plant, then discovered anandamide, which is a natural biologically produced brain communication neurotransmitter that  $\Delta^9$ -THC and other phytocannabinoids emulated in the body. (Devane et. al., 1992).

So, all of us already have natural chemicals in our brains that produce the same effects as  $\Delta^9$ -THC. Very much like the opiates mimicking endorphins or methamphetamine releasing the brain natural catecholamine stimulants to produce their effects, the marijuana chemicals are mistaken for and act like natural neurotransmitters naturally produced by brain cells.

After anandamide, also known as AEA was discovered, scientists found an additional set of natural neurotransmitters (2AG, AGE, NADA, and OAE) that act like the various chemicals in marijuana. These natural brain marijuana-like chemicals are known as the **endocannabinoids**. Phytocannabinoids artificially activate these same receptors that are in our brain and body for our natural endocannabinoids. Research has also discovered a vast number of CB<sub>1</sub> and CB<sub>2</sub> marijuana receptors throughout the human body, not just in the brain. These cannabinoid receptors are actually the most abundant receptors in the human body even more prevalent than opiate endorphin/enkephalin/dynorphin receptors. Thus, the chemical compounds found in marijuana have a very diverse range on effects on the human body. These phytocannabinoid compounds can have both positive and negative effects. Also, each individual may have different variances in the type, density and number of CB<sub>1</sub> and CB<sub>2</sub> receptors as well as unique biologic processes that differ from each other. Thus, different people can have vastly different effects from the same batch and amount of marijuana used.

### NAADAC: How does marijuana use result in Cannabis-Use Disorder as codified by the Diagnostic and Statistical Manual of Mental Disorder (DSM-5)?

**DR. INABA:** Marijuana is abused for its euphoric effects. The brain mistakes the infusion of its artificial phytocannabinoids as an excessive release of its natural endocannabinoids. The first endocannabinoid discovered was named anandamide which is Sanskrit for supreme joy. In response to what the brain mistakes as excessive activity of its natural endocannabinoids when marijuana is abused, it progressively shuts down production, storage and release of its natural endocannabinoids. The brain always strives to maintain balance of its neurochemical system which is known as **homeostasis**. Brain cells also shut down their cannabinoid receptors through a process known as “down regulation.” A pot user has to therefore continually use more and more or stronger and stronger

marijuana to fool the brain that its endocannabinoid functioning is at homeostasis. But, as they continue to use more their natural endocannabinoids continue to be depleted and they become potentially dependent on marijuana to feel functional. This unbalanced functioning of the brain is known as **allostasis**.

Phytocannabinoids in marijuana also cause an imbalance of other natural neurotransmitters like dopamine. Dopamine in the brain's addiction pathway is imbalanced by all addictive drugs. Marijuana first exaggerates dopamine release to hijack the brain's reward and survival instincts resulting in compulsion to keep using marijuana. But continued use results in its depletion similar to the allostasis that develops with abuse of other addictive substances. Dopamine depletion results in craving, obsession to use and the drive to start using again when marijuana use is discontinued. Addictive use of marijuana produces tolerance, physical dependence and even withdrawal symptoms.

Current research documents that 8% to 10% of the people who use marijuana will become addicted to it. (American Psychiatric Association, (2000); Anthony & Helzer, 1991; Anthony, Warner, & Kessler, 2004). Since most people who use marijuana will not develop addiction, many users will vigorously deny marijuana addiction. Vulnerability for Cannabis Use Disorder is determined by a combination of genetics, environmental stresses (e.g. early childhood trauma, or even poor nutrition), and the allostasis impact of continued use. We treat several clients with Cannabis Use Disorder at my program in Oregon, and most are self-admitted to treatment complaining that they can't stop using it though it is causing them significant consequences and disrupting their quality of life activities. The current waiting list to get into the residential treatment services of the Oregon Addictions Recovery Center where I work is four months long.

### NAADAC: Has science identified any other solid health consequences from heavy use of marijuana?

**DR. INABA:** Marijuana interferes with a person's ability to complete tasks requiring multiple steps to achieve a goal. It impairs depth perception, can suppress short term memory ability, and has many other detrimental mental effects when someone is under its influence. Standard deviation of lateral position (SDLP) equivalent to 0.08 level of alcohol use while driving has also been documented. These acute effects impair driving ability. (Hartman et al., 2015). Regular heavy use of marijuana has recently been shown to produce cognitive problems and even an 8 point drop in IQ — the same IQ drop experienced from lead poisoning! This IQ loss has been shown to be chronic effects that persist into midlife even if the user stops using after their adolescent years. (Meier et al., 2012). Increased risk for heart attack, seizures, testicular cancer, acute psychosis, and even schizophrenia has been fairly well documented with early age, high-potency marijuana, edible marijuana products, or use of the synthetic marijuana compounds (Andeasson, et al., 1987; Arseneault, et al., 2002). I have even treated clients who have experienced very painful and scary uncontrolled vomiting from its use known as **Cannabis Hyperemesis Syndrome** (Chen & McCarron, 2013). I have also treated clients who developed **Hallucinogen Persisting Perceptual Disorder** (HPPD), which is a prolonged “bad trip” resulting from its use. (Halpern & Pope, Jr., 2003).

As a health and addiction treatment professional, I am especially concerned about the increased use of marijuana along with decreased perception that its use can cause any harm by the youth population. Preadolescents who start using marijuana and other addictive substances at an age of 10 to 12 are 5 to 6 times more liable to develop some form of substance-use disorder and other health consequences in their lives than others who delay their first use until they at least graduate from high school. (Falls, 2007). The deluge of current laws legalizing unconstrained medical and recreational cannabis use has decreased the perception of marijuana as being harmful in any way to the user. This has opened the door to increase abuse of marijuana especially in the population most vulnerable to its adverse consequences, our youth.

**NAADAC: Do you have any other major concerns about marijuana use as America seems on the verge of legalizing its recreational use?**

Dr. Inaba: I have grave concerns about the rapid increase in the concentration of  $\Delta^9$ -THC potency of marijuana and its various commercial products available to those who use it. Back in the 1960s, street marijuana samples tested to an average of about 1–2%  $\Delta^9$ -THC. By the late 1980s, genetic manipulation, sinsemilla and other enhanced growing processes, resulted in an average concentration of 4–6%  $\Delta^9$ -THC. Currently the Marijuana Potency Monitoring Project at the University of Mississippi reports an average concentration of about 15% from thousands of samples seized by law enforcement throughout the United States. A recent report of 600 Colorado marijuana samples submitted for premarket testing found an average concentration of almost 19% with some containing up to 30%. This Colorado report also found toxins, rodenticides, and even heavy metals contaminants from the chemicals and fertilizers used to increase concentration of  $\Delta^9$ -THC in mari-

juana. CBD concentrations of these same samples were found to be much less than what had previously existed. Decreased CBD was accomplished via genetic modifications and was done since CBD counteracts the desired psychoactive effects of  $\Delta^9$ -THC. Fungi were also found to contaminate many of the Colorado commercial marijuana samples. (Briggs, 2015).

Then, there is the increasing problem of extracts with extremely high concentrations of 9-THC known as dabs, BHO, honey oil, or wax. Dabbing is a process of extracting and concentrating  $\Delta^9$ -THC using butane, alcohol, water, or another solvent. This results in an oil or a wax-like product that can contain 80% to 95% concentrations of  $\Delta^9$ -THC. I have treated clients with terrible and long-lasting psychological and traumatic effects from smoking dabs. Some users have experienced a heart attack or feel like they are about to have a heart attack. A current client had six emergency room visits in a two month period suffering from painful Cannabis Hyperemesis Syndrome that could not be controlled with any emergency anti-vomiting medication when he used a high potency marijuana product.

Marijuana “Edibles” are  $\Delta^9$ -THC extract infused candies, cookies, soft drinks, energy drinks, etc. for oral use instead of smoking. Attraction to abusing cannabis as “Edibles” has exploded across the country. These products often contain much more THC per candy bar, gummy bear, or soft drink can/bottle than is usually available when a marijuana cigarette or “joint” is smoked. A usual recreational dose of  $\Delta^9$ -THC is generally accepted to be 10 mg. and these products were mandated to contain that  $\Delta^9$ -THC concentration per serving. Purveyors of these products comply with this by labeling their “Edible” candy bar or can of soft drink to contain 10 mg. per servings but then have multiple servings per unit of sale. Thus, a single “Edible” gummy bear is listed as containing 4 servings per each individual gelatin candy and I know of no one who would slice a gummy

bear into 4 parts and only chew a single slice to satisfy their sugar or marijuana needs.

Finally, there is the uncontrollable problem of synthetic cannabinoids. Street chemist can potentially create countless numbers of designer synthetic marijuana-like compounds. There are at least nine different chemical families with compounds that can be redesigned to act like super-potent THC at cannabinoid brain receptors. Disguised and sold as incense, potpourri, aromatherapy, and even as e-cigarettes cartridges, these chemicals have been tested to be anywhere from 5 to 800 times more potent than THC. Worst of all, most of these extremely potent forms of new cannabis products like dabs, Edibles and even the odorless and flavored e-cigarette cartridges appear to be marketed toward adolescents and young users who have still developing brains making them much more vulnerable to the new found toxic health consequences from exposure to chemical compounds in marijuana.

We are definitely in a new era of marijuana or cannabinoid abuse and the future doesn’t look too good. Why society continues to ignore science and medical community findings regarding the potential harm of cannabis use or even that it is a drug with potential negative as



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well as positive effects is completely baffling to me. Maybe it's all part of the addictive process that Bill W of A.A. once accurately described as: Cunning, Baffling, and Powerful.

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- Current data indicates what percentage of people who use marijuana will develop Cannabis Use Disorder (CUD)?
  - 8–10%
  - 12–18%
  - 20–25%
  - 50–58%
- Congress passed the Marijuana Tax Act, prohibiting its use and availability for any purpose in what year?
  - 1934
  - 1932
  - 1937
  - 1938
- How many species of the cannabis plant exist?
  - 2
  - 3
  - 6
  - Infinity
- A single marijuana plant contains some \_\_\_\_\_ or so biologically active chemicals.
  - 15
  - 220
  - 375
  - 480
- \_\_\_\_\_ are the cannabinoid receptors that are responsible for the feeling of euphoria when marijuana is used.
  - THC
  - CB<sub>1</sub>
  - CB<sub>2</sub>
  - AEA
- \_\_\_\_\_ are the cannabinoid receptors that are mainly outside of the brain and may be responsible for most of the medically beneficial effects reported with medical marijuana treatment.
  - THC
  - CB<sub>1</sub>
  - CB<sub>2</sub>
  - AEA
- \_\_\_\_\_ is not considered to be psychoactive and it interacts with the immune system, has anti-seizure, pain relief, anti-nausea and many other positive health benefits.
  - CBD
  - CB<sub>1</sub>
  - CB<sub>2</sub>
  - AEA
- What are the natural brain marijuana-like chemicals known as?
  - Phytocannabinoids
  - Endocannabinoids
  - Tetrahydrocannabinol
  - Cannabinoids
- Which receptors are actually the most abundant receptors in the human body?
  - endorphin
  - encephalin
  - dynorphin
  - CB<sub>1</sub> and CB<sub>2</sub>
- The Marijuana Potency Monitoring Project at the University of Mississippi reports an average concentration of about \_\_\_\_\_ from thousands of samples seized by law enforcement throughout the United States.
  - 10%
  - 15%
  - 20%
  - 25%