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REVIEW

WHY NOT POT?
A Review of the Brain-based Risks of Cannabis

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ABSTRACT

In this review, we provide a historical perspective on marijuana, and survey contemporary research investigating its potential negative effects on the brain. We discuss the evidence regarding cannabis dependence, driving under the influence of cannabis, underachievement, inducing (or worsening) certain psychiatric conditions, and the potential for progression to use of more dangerous drugs—summarized by the acronym DDUMB, a cognitive tool that may help healthcare providers in their risk/benefit discussions with patients who use cannabis. We also review and discuss the impact of marijuana use on target populations, including adolescents (who are at increased risk of harm); heavy users; and people suffering from—or at high risk of—mental illness. While cannabis presents certain subjective, health-related, and pecuniary benefits to users, growers, and other entities, it is also associated with several brain-based risks. Understanding these risks aids clinicians and their patients in making informed and balanced decisions regarding the initiation or continuance of marijuana use.

INTRODUCTION

"I have argued that every human being is born with an innate drive to experience altered states of consciousness periodically . . . this drive is a most important factor in our evolution, both as individuals and as a species."

Andrew Weil
The Natural Mind: A Revolutionary Approach to the Drug Problem

Marijuana, also known as cannabis or pot, is the most commonly used drug worldwide and is a fraught topic in contemporary society.[1] A variety of forces—economic,[2] legislative,[3] technological,[4] and even horticultural[5]—have markedly changed the politics, polemics, and public perception of pot. The resultant upsurge of cannabis use in some parts of the United States has already had a collateral impact on individual and societal health,[6] similar to that seen with the prescription opiate epidemic.[7] Balancing these myriad forces—all of which drive greater societal acceptance of marijuana and increased use—a growing body of

scientific research provides a clearer understanding of pot's potential harms.

The aim of this paper is to review the brain-based harms of cannabis. Awareness of the supporting evidence of marijuana's downsides can help augment the risk-benefit discussions clinicians may have with patients in a motivational interviewing model, the preferred therapeutic frame for approaching substance-use discussions.[8] To facilitate this end, we introduce a mnemonic, DDUMB, to help remind us of the five brain-based harms associated with marijuana use: dependence, driving impairment, underachievement, mental illness, and bad to worse (i.e., marijuana serving as a "gateway" function for other more dangerous drugs of abuse). Before reviewing the science behind these five dangers, we will provide a brief summary of several important aspects of marijuana's history, politics, chemistry, and psychopharmacology.

THE HISTORY OF HEMP AND POLITICS OF POT

The terms *marijuana* and *cannabis* are often used interchangeably. Strictly speaking, however, *cannabis* is a botanical term for the hemp plant, while *marijuana* denotes the psychoactive drug derived from it. Though research on the central effects of cannabis is relatively new, its medicinal use can be traced back to the Chinese Han dynasty, circa AD 25 to AD 220, when it was used to treat rheumatic pain, constipation, malaria, and female reproductive disorders.[9] Medical cannabis was introduced to the Western world in the 1800s, and was used as such until the 1900s, when its popularity diminished with the rise of pharmaceuticals that could be used for the same conditions (e.g., aspirin, barbiturates).[10] Legislation enacted in 1937 (the Marijuana Tax Act) decreased accessibility and pushed the drug further out of the public eye. A sterling demonstration of the swings of public opinion toward marijuana use is the pulp-propaganda film "Reefer Madness,"[11] released shortly after the enactment of this legislation. Originally titled "Tell Your Children," this short film comically overdramatized marijuana's harms, describing cannabis as "the burning weed with its roots in Hell," and warning about the potential for pot-induced manslaughter, suicide, hallucinations, and "the ultimate end of the marijuana addict: hopeless insanity!"

In the present day, more tolerant state-based legislation has led to decriminalization, legalization, and medicalization of cannabis in many states and the likelihood for more cannabis use. In turn, more frequent use by current users and more new users may lead to a greater frequency of cannabis-related harms. Specifically, in December of 2012, Washington state and Colorado both legalized marijuana; Washington DC, Alaska, and Oregon followed suit, with at least 23 states now allowing for its medical use. Importantly, this large cultural and legal pro-pot shift has already been shown to increase a variety of cannabis-related collateral harms,[6] and likely has contributed to an increase of adolescent-onset use.[12] This trend is especially worrisome, since adolescent-onset use is associated with greater cumulative negative consequences than later-onset use.[13] Bachman et al[13] demonstrated an inverse relationship between perceived risks/social disapproval and the prevalence of marijuana use among youth.[13] Data from a 2010 national survey on drug use and health have shown a correlation between adolescent cannabis use and lower levels of parental disapproval.[14] Additionally, "vaping," a term used to describe a popular method of smoking via an electronic device such as an e-cigarette, may encourage more illicit and dangerous use of marijuana: Vaping produces less smoke than marijuana or tobacco cigarettes, making its use harder to detect by smell (e.g., in a school bathroom) and implies that the person is vaping nicotine-related products (not illicit substances).[15] These relationships suggest a continuing trend toward public approval and, possibly, risk-minimization of marijuana use, which may lead more at-risk youth and young adults to initiate use.

Unfettered by more permissive laws and attitudes, capitalism has embraced cannabis as the newest cash crop.[16,17] Commercialization of cannabis has been shown to increase the number of medical marijuana licenses purchased.[21] Therewith, powerful economic forces have and likely will continue to add to legal and attitudinal shifts that elevate the role of cannabis in public and individual health.[23] Market research suggests that widespread legalization of marijuana has the potential to create a 35-billion dollar marijuana market.[18] Comparatively, this would make the marijuana industry as big as the United States National Football League (NFL), 10 times more profitable than the opioid drug OxyContin, and about a fifth the size of the United States alcohol market.[18,19] As witnessed in recent years in the United States, where a surge in opiate-related mortality has been partly attributed to high-dollar opiate sales, the promise of profits in the burgeoning industry of marijuana production— the "green" industry— may inform how the drug is marketed and researched.[7,20] And as more states move to legalize marijuana, we may see an increase in both anticipated and unanticipated cannabis-related harms in those who use it, as was observed on a smaller scale in Colorado.[6,21]

As societal, legislative, and economic forces move toward the legalization of marijuana, there are three challenges that confront its scientific study. First, advances in cultivation techniques and grower knowledge have produced vastly more potent marijuana than was seen in previous decades. Tetrahydrocannabinol (THC), one of the main psychoactive components of marijuana (and the component associated with some of its brain-

based harms[74]) has increased in concentration from three percent in the 1980s to 12 percent in 2014, whereas the concentrations of cannabidiol (CBD), one of marijuana's calming components, has fallen.[7] This horticultural reality makes older literature on the effects of marijuana less applicable to current use, and is frequently cited as a reason for a relative increase in cannabis-related harms.[6,23]

Aside from differences in the chemical composition of the plant, a second, related challenge in marijuana research is that precise quantification of cannabis use (compared to a drug like nicotine found in tobacco) is difficult, due to differing potencies and variable delivery systems (e.g., smoking, ingestion). A third and final factor that creates challenges for cannabis research is its United States Drug Enforcement Agency (DEA) scheduling. Because marijuana is grouped with cocaine, heroin, and 3,4-Methylenedioxymethamphetamine (MDMA) in the most restrictive drug schedule (Schedule 1), access to the drug for scientific study is more difficult. From the perspective of advancing scientific knowledge, many researchers have suggested moving marijuana to a lower schedule to reduce barriers to research.[24,25]

CANNABIS CHEMISTRY AND PHARMACOLOGY

Unlike drugs that contain a single, specific, active chemical compound (e.g., lithium), different strains of the cannabis plant contain produce a variable array of centrally active substances. One of the main chemical groups in the several dozen constituents of marijuana are the cannabinoids, which become active by binding at cannabinoid receptors in the human brain. The three primary cannabinoids—found in varying ratios in different strains of cannabis—are cannabinol (CBN), cannabidiol (CBD), and Delta-9-tetrahydrocannabinol (THC). Importantly, CBD and THC often have opposing effects. CBD has anxiolytic and antipsychotic properties, and is often marketed as such, while THC has been shown to be anxiogenic and can induce transient psychosis.[5] From this chemical complexity follows the clinical reality discussed above: different strains of the cannabis plant, since they contain different ratios of centrally active chemicals, yield different central effects. This "blending"—rooted in the inherently variable chemistry of plant-based drugs—yields a compound that has different effects and potential harms in each of its permutations. These factors add additional challenge to the scientific study of marijuana, given that the actual drug one is studying may vary depending on the several variables (e.g., when it was grown, where it was grown).

Though marijuana has been around for millennia, our understanding of its mechanism of action in the brain is relatively recent. This understanding was propelled forward in the late 1980s by the discovery of central cannabinoid receptors, which bind both marijuana-derived cannabinoids as well as the brain-made substances called endogenous cannabinoids (or endocannabinoids).[5] Two sets of cannabinoid receptors, called CB1R and CB2R, exist. CB1R is located in widespread brain regions (i.e., hippocampus, cerebral cortex, limbic system, cerebellum), but is also found in the periphery (i.e., in liver, thyroid, uterus, bones, and testicular tissue). CB2R, on the other hand, is mainly peripheral, found mostly in immune cells, the spleen, and gastrointestinal system.[5]

Comparing endogenous and exogenous cannabinoids is informative. The primary endogenous endocannabinoid, anandamide, was named from the Sanskrit word for "supreme joy."[10] Unlike THC, which has a half-life that spans hours to days,[26] anandamide has a short half-life, being quickly removed from the synapse and degraded.[10] The difference in half-lives between anandamide and THC may contribute to some of the different central effects of these two molecules, including the potential for dependence.[27]

DEPENDENCE

The first cannabis-related harm captured in the DDUMB mnemonic is dependence. Substance dependence is a debilitating, brain-based disorder characterized by compulsive use, inability to desist in the face of negative consequences, and withdrawal symptoms upon cessation.[28] Although commonly believed to be nonaddictive, marijuana dependence has been clearly documented,[29] and a large percentage of global substance use admissions are related to cannabis.[30] Very recent prevalence data in the United States indicate that past-year prevalence of marijuana use doubled between the years 2001 and 2013 to nearly 10 percent, with a corresponding increase in marijuana use disorders to nearly three percent.[31] Though neurobiological responses are not yet used to validate substance dependence, THC has been shown to stimulate mesolimbic dopamine release, a brain phenomenon common to all addictive substances,[28] and many other experiments indicate that cannabis affects key parts of the brain's addiction centers.[32–34]

The misperception that cannabis is not addictive has at least three sources. First, the percentage of first-time cannabis users who develop dependence is relatively low compared to other commonly abused drugs. Specifically, nine percent of first-time cannabis users get hooked versus higher percentages of first-time stimulant (11%), alcohol (15%), cocaine (17%), heroin (23%), and nicotine (32%) users.[35] That said, though the percentage of first-time cannabis users who develop dependence is lowest among users of the other drugs mentioned, the overall number of people who will develop cannabis addiction is still large.

A second factor supporting the non-addiction myth is that although chronic cannabis users typically

"dose" multiple times a day, the long half-life of THC (25–57 hours)[26] means that the time intervals that mark its "compulsive use" can be spaced out longer than other shorter-acting drugs, such as nicotine, creating more of an illusion of control. The addicted marijuana user may only use pot at breakfast, lunch, and in the evening, whereas a person addicted to nicotine may need to smoke a cigarette every hour or two.

A third factor supporting the myth of non-addiction is that marijuana withdrawal is often relatively mild.[27,29] Moreover, marijuana withdrawal presents without clear, "signature" physical symptoms, at least compared to the often-dramatic physical symptoms of withdrawal from depressants like alcohol and benzodiazepines (i.e., tremors, seizures, agitation) and opiates (i.e., sweating, gooseflesh, diarrhea). Instead, marijuana withdrawal symptoms are more occult: anorexia, irritability, anxiety, anger, restlessness, and sleep disruption.[13] En toto, this delayed, nondramatic withdrawal syndrome adds support to the misperception that cannabis addiction does not exist.

For clinicians treating marijuana-addicted patients, it is important to be aware that cannabis withdrawal is both consequential and treatable.[2,37] In terms of its consequence, cannabis withdrawal symptoms clearly contribute to ongoing use, making cessation efforts aversive,[28,38,39] and to impairing both motivation and executive functions critical in decision making and treatment retention.[40,41] In terms of treatment, a seminal study by Mason et al[37] showed that in marijuana-dependent subjects, the commonly used calcium channel/GABA-modulating agent gabapentin—dosed 1200mg daily in divided doses—reduced both cannabis withdrawal symptoms and cannabis use. Though sustained recovery from cannabis addiction requires long-term, multimodal solutions, clinicians can help the process by utilizing available pharmacotherapies to attenuate withdrawal.

It is important to highlight that the risk of negative effects from marijuana use—including dependence—have been shown to be related to the age of first exposure.[42,43] Specifically, compared to people who start marijuana use in adulthood, adolescent initiators are 2 to 4 times more likely to exhibit dependence within two years of their first use.[42] This is not surprising, given that key stress, reward, and executive/regulatory circuits that underlie addiction continue to develop during the teenage and early adult years of human growth.[28,44] Moreover, studies indicate that early exposure to THC may 1) potentiate the future effects of THC, increasing risk of dependence; 2) cause impaired regional connectivity, decreasing the moderating influence of regulatory brain regions; and 3) lead to lower dopaminergic activity in addiction-related circuits.[23,35,46] Coming from the perspective of harm reduction, then, a tractable goal to reduce the risk of future marijuana dependence is to delay the age of onset of first use.

DRIVING

Standing alongside the misconception that marijuana is not addictive is the misconception that driving while under the influence of marijuana is safe. Several factors make this latter untruth more challenging to refute than the former. Until very recently, drivers involved in accidents or infractions were rarely tested for THC levels, whereas assessing blood alcohol content via the less invasive breathalyzer has been routine for years. This situation will likely change over time as marijuana use increases, allowing more THC-related auto morbidity studies to be conducted and compared with those in other countries. A second factor complicating the THC-driving research is that, based on studies from driving fatalities, drivers frequently use marijuana and alcohol simultaneously.[45] This combination makes assigning causality to a single drug complex, and their different mechanisms of action lead to additive impairments.[47]

Despite the abovementioned challenges to studying the topic, epidemiological and laboratory studies of the acute effects of marijuana on driving has demonstrated that drivers under the influence of marijuana are impaired. In fact, driving while under the influence of marijuana doubles or triples the risk of a crash.[47] Though people driving under the influence of marijuana tend to compensate by driving more slowly, as task intensity of driving increases, the person becomes more impaired.[48,49] Specifically, cannabis use increases lane weaving and impairs critical-tracking tasks, reaction time, and divided attention.[48,49]

Though a discussion of the ethical issues of driving while impaired is beyond the scope of this article, it bears mentioning that collateral damages result from individual choice—every time an impaired motorist decides to get behind the wheel, he or she extends the risk of potential harms to other drivers, passengers, pedestrians, and cyclists.

UNDERACHIEVEMENT

Despite marijuana's known risks, the scientific reality is that marijuana is in many ways the least deadly drug of abuse. In meteorological terms, if methamphetamine—with its capacity for brain damage and strokes[50]—is a tsunami, and opioids—with their morbid respiratory depressive effects[7]—are an earthquake, marijuana can be likened to a heavy fog. Disruptive, yes. Deadly, no. Partly due to the lack of activity in vital brainstem areas controlling respiration, there has never been a reported lethal overdose of marijuana in humans.[51] In animals, the deadly dose of cannabis is extremely high: about 12,500 times the amount needed to cause subjective effects.[52] Though risks of marijuana use are real and consequential, it is neither deadly nor overly dramatic. In the pot polemic, the lack of direct organ

toxicity, clearly consequent mortality, and extreme withdrawal symptoms likely contribute to the growing acceptance of marijuana use among the American population. And as argued in a recent editorial by a pediatrician in the *New York Times*, support for marijuana use may come from the perspective, "Since people are going to use something, why not the least toxic something?"[53]

From a wider social perspective of harm and risk reduction, this "low bar" argument has obvious merits: it is better to be alive and stoned than dead from a heroin or alprazolam overdose. That said, conscious of Weil's opening observation about our species' "innate drive to experience altered states of consciousness," we suggest that when considering effects on vulnerable future adults, professionals should focus not on what is the least toxic and not on merely accepting morbidity over mortality, but rather on the maximization and optimal development of human potential. From this vantage, the risk of cannabis promoting broad-spectrum underachievement (especially in teens) becomes more prominent. In point of fact, a large body of convergent data suggest that long-term use of marijuana may cause significant abridgement of one's potential.[33,44,54–59,60–67]

Underachievement may be the most well-supported correlate of regular marijuana use. Though direct causality is challenging to ascribe due to the correlative nature of this research (random assignment of daily cannabis use to adolescents is unethical), the association of daily marijuana use with the pruning of human potential appears across a breadth of contemporary research. For example, earlier studies have already demonstrated that marijuana use during adolescence is associated with low academic achievement and increased rates of school drop-out.[54,55] More recently, several very large examinations of the issue have reinforced not only these academic consequences, but a broader swath of negative outcomes. In one of these studies, Fergusson et al[56] performed a longitudinal study of over 1,000 New Zealanders from birth to age 25 years, and found that elevated marijuana use between ages 14 and 21 years was associated with the lower likelihood of getting a bachelor's degree, lower income, higher unemployment and welfare dependence, and lower levels of relationship and life satisfaction. These correlations survived adjustments for a number of important covariates, including family socioeconomic status, maltreatment, academic achievement, and comorbid mental disorders. In a similar study, Meier et al[57] followed a cohort of 1,037 subjects from birth until age 38 years, performing neuropsychological assessments at ages 13 and 38 years, as well as ascertaining cannabis use at ages 18, 21, 26, 32, and 38 years. In this cohort, persistent cannabis use was associated with a decline in neuropsychological performance across domains, which survived controlling for years of education. Importantly, these results were the most prominent among participants with adolescent-onset cannabis use, and showed a dose effect: more persistent use was associated with a more severe performance decline. Adolescent-onset cannabis use was correlated with a 10-point decrease in measured IQ. Moreover, people who had discontinued cannabis use did not achieve a full return to their baseline level of performance, a finding which suggests that heavy adolescent-onset cannabis use may have a cumulative neurotoxic effect. One group of detractors argued that certain brain-based personality traits that bias people toward marijuana use as well as school dropout may explain these results,[58] but the original authors' results survived a control for such personality factors.[59]

What are the putative mechanisms wherein adolescent cannabis use causes this pervasive underachievement and even cognitive decline? Adolescence, we know, is a neurodevelopmental stage of significant import in which neurobiological circuits critical to adult function develop, are pruned, and reinforced.[60] Moreover, adolescent brains have a stage-dependent hypersensitivity to rewards[23] and underdeveloped prefrontal inhibitory structures.[44] Chronic cannabis use through this sensitive window of development may cause persistent disruptions in these developing prefrontal and reward pathways, impacting important intellectual functions like working memory, sustained attention, verbal memory, and general intellectual functioning.[61–63] These disruptions may persist longer—and the person may not fully recover—when experienced in the developmental window of adolescence rather than in adulthood. Aside from prefrontal cortex disruptions, chronic marijuana use has also been correlated with changes in the hippocampus, a vital brain structure involved with short-term memory, long-term memory, and spatial navigation.[64]

Recent research on the effects of marijuana on brain function and structure (in both adolescents and adults) have shown other negative changes in the brain among chronic marijuana users.[65–67,35] In a study that compared chronic marijuana users with non-using adults (mean age 22–23 years), the chronic user group demonstrated poorer learning from errors, due in particular to lower levels of brain activity in the dorsal anterior cingulate cortex and hippocampus.[65] In another study, investigators found microscopic disturbances in the neural fibers that communicate between brain hemispheres (the corpus callosum) in heavy cannabis users (mean age 30 years) who started using at the age of 16 years.[66] In a 25-year follow-up study, investigators compared three domains of cognitive function (verbal memory, processing speed, and executive function) in three groups (aged 18–30 years at baseline): 1) current cannabis users, 2) individuals who used marijuana but stopped, and 3) individuals who never used marijuana. The researchers found that

current marijuana users demonstrated lower verbal memory and processing speed compared to the other groups, and even when current users were excluded, cumulative exposure was associated with worse verbal memory.[67] And in a study that examined brain functioning among chronic marijuana users (aged 21–33 years), investigators found impairments in dopamine release in the striatum that correlates with deficits in neurocognitive performance (memory, attention).[35.]

In summary, broad-spectrum, lasting underachievement—perhaps mediated by disruptions of critical developmental brain circuits—is a third potential harm from cannabis. Convergent evidence from several fields, including epidemiology and functional brain imaging, supports the idea that one of the more occult (but consequential) downsides of adolescent-onset marijuana use is a broad-spectrum abridgement of human potential.

MENTAL ILLNESS

Marijuana use has been associated with several specific brain-based illnesses. Much of this research has focused on the role of cannabis in psychotic illness. Though the details of this research arena are beyond the scope of this article (see references 64, 68, and 69 for more comprehensive treatment of this issue), the emerging theory follows a stress-diathesis model and posits that in genetically "at risk" individuals, marijuana use serves as a biological trigger that influences the full expression of what otherwise may have been a latent disorder. This body of research suffers the same shortcomings noted in the underachievement section: random assignment to the experimental condition—heavy cannabis use—is unethical. That said, a raft of studies have found strong support for a pot-psychosis link, indicating that cannabis use can increase the risk for the development of psychotic disorders[69] and worsen clinical outcomes in those at risk.[70] In a 35-year longitudinal study of more than 50,000 enlisted men, Manrique-Garcia et al[68] found that individuals who used cannabis frequently had an increased long-term risk for developing schizophrenia, whereas the risk declined for moderate users. Assessing the genetics of at-risk individuals, Caspi et al[71] reported that adolescent cannabis users carrying a permutation of the catechol-O-methyltransferase (COMT) gene were at highest risk of developing psychotic illness. Mechanistically, THC increases task-irrelevant neural "noise," which is associated with its psychosis-promoting effects[66] and has been implicated in brain maturation processes (marijuana users showed thinner cortices) in those at risk for schizophrenia.[72] Notable here is that the potential kindling effect of cannabis on psychotic illness is likely affected by the abovementioned changes in cannabis chemistry. As previously discussed, cannabidiol (CBD)—the component of marijuana that demonstrates antipsychotic properties—is found in smaller concentrations in many recent strains, whereas the percentage of the psychosis-prone component—THC—has increased.[73,74]

Not only can early, heavy cannabis use potentially contribute to the development and expression of psychotic illness, but ongoing exposure after developing a psychotic disorder can make it worse. In people already suffering with schizophrenia, exposure to THC may lead to an increase in latent psychotic symptoms or relapse back into a psychotic episode.[64,73] Specifically, patients with psychotic illness who use marijuana, compared to those who do not, tend to have 1) earlier onset of symptoms, 2) more severe and persistent psychotic symptoms, 3) higher relapse rates, and 4) a worse prognosis due to poor treatment adherence.[70,73] Summarizing the research, Hall et al[36] document that cannabis use doubles the risk of developing psychosis from 7 in 1,000 to 14 in 1,000. Therapeutically, however, cessation is salutary: young people with psychosis who desist from pot have better outcomes, including fewer psychotic symptoms and better social functioning.[36]

Although the bulk of research on the role of cannabis in severe mental illness is in psychotic disorders, recent research on patients with bipolar illness and posttraumatic stress disorder (PTSD) yields similar findings. Specifically, patients with bipolar disorder who used and then ceased use of marijuana have similar outcomes to those who never used, whereas continued use is associated with greater recurrence risk and functional impairments.[75] Veterans with PTSD who use marijuana have greater symptom severity of their disorder, use alcohol and other drugs more often, and exhibit more violent behavior than never-users.[76] Finally, growing evidence of the role of cannabis in other substance use disorders (SUDs) indicates that people with SUDs or who are at risk for developing them are uniquely vulnerable to developing negative effects of cannabis.

Overall, this research suggests that healthcare providers should have targeted risk discussions about cannabis use with adolescents, who are at a higher risk of developing dependence, and individuals at risk for (or suffering from) psychotic illness, bipolar disorder, PTSD, or SUDs.

What about the data on the role of cannabis in other common brain-based disorders (e.g., anxiety, depression), many of which are used by card-carrying medical marijuana users as the reason for their use? Here, unfortunately, research is limited. A few research groups have shown lower perceived quality of life among cannabis users, as well as finding a heightened occurrence of anxiety disorders among cannabis-dependent adults.[77–79] That said, these studies and others generally indicate that people who only use occasionally to moderately (i.e., who do not qualify for cannabis dependence, or as regular users) generally have the same mental health outcomes as non-users.[77,78,80]

BAD TO WORSE

Both Aldous Huxley and Jim Morrison famously opined that certain drugs open "the doors of perception." Does cannabis open the gates of addiction? In short, the "gateway drug" theory posits that the recreational use of "softer" drugs like alcohol, tobacco, and marijuana serves as an easy port of entry into later use of "harder" drugs such as cocaine, heroin, or methamphetamine. The empirical support for this theory largely rests on the observation that most people who develop problems with the latter first experimented with the former. An examination of dairy use, however, exposes this argument's logical flaw. That is, though many people with opiate dependence have used cannabis prior to developing their heroin habit, a significant majority also ingested milk prior to the onset of their addiction, and yet no one posits a causal connection in this latter case.

Rigorously proving that use of cannabis is consistently associated with a "bad to worse" progression-of-use phenomenon turns out to be methodologically challenging.[81] That said, efforts have been made to answer this question. For example, Olthius et al[82] looked at the actual circumstances under which people first experimented with a hard drug. This study showed that subjects tended to mix psychoactive substances the first time that they used a new drug. For example, people frequently reported that first-time use of cocaine, heroin, methamphetamine, or a hallucinogen like LSD was in conjunction with marijuana, alcohol, or tobacco, rather than experimenting with the hard drug by itself for the first time.

Additional evidence in support of bad-to-worse causality comes from Agrawal et al,[46] who performed a twin study examining early cannabis use and later illicit drug use. This study showed a strong association between early cannabis use and later abuse/dependence of other illicit drugs, and—though a large percentage of the variance in illicit drug use was due to genetic and environmental factors—there was also evidence of a causal influence of early cannabis use. Finally, in a very recent, prospective study (which overcomes methodological limitations inherent in other examinations of this issue), cannabis use during the first sampling period was significantly associated with substance use disorders in a second sampling period three years later.[83] In sum, though empirical validation of a direct, causal role of early cannabis use in later addiction to harder drugs is methodologically challenging, and though correlation does not equal causation, several lines of evidence support that the association between early cannabis use and later problems with harder drugs is at least partly due to a causal relationship.[36,83,84]

How would a gateway process actually work? At a behavioral and interpersonal level, cannabis use likely follows principles of the so-called social contagion seen with alcohol and tobacco,[85,86] creating "birds of a feather" networks of people with similar behaviors and greater likelihood of exposure to other drug use. At a neurobiological level, animal research points to THC's ability to change reward circuits in the brain.[32,33,86] Panlilio et al,[87] for example, found that exposing rats to THC increased likelihood of self-administration of the most highly addictive drug in humans: nicotine. This effect persisted even when the process to receive the nicotine became more arduous. Interestingly, this effect was not found when a similar experiment was performed with cocaine or heroin in place of nicotine. More recently, Volkow et al[32] examined 24 marijuana abusers using a methylphenidate challenge to probe the reactivity of the brain's dopamine system. They found that compared to normals, marijuana abusers (average 5 joints a day) displayed blunted dopamine responses in key brain areas associated with addiction (i.e., ventral striatum). In a very recent study using an amphetamine challenge, lower levels of dopamine release in key addiction areas (the striatum) were found in heavy cannabis users; these changes were correlated with inattention, negative symptoms, and poorer working memory.[35] These neurobiological differences, researchers hypothesize, may contribute to marijuana abusers' tendencies to negative emotionality (increased reactivity to stress and irritability) and addictive behaviors.[32] Research like this raises the possibility that part of the etiology of marijuana's bad-to-worse phenomenon is explained by its role in altering brain reward circuits in a way that increases the risk of future addiction.

CONCLUSION

Evaluating the potential harms of a commonly used drug—especially a complex substance like marijuana—is a challenging but vital task. Fully informed awareness of both the potential and proven benefits and the potential and proven harms of marijuana are necessary in order to have rational discussions with patients, teens, and decision makers regarding marijuana use. Based on a review of the current literature, we suggest the mnemonic DDUMB (dependence, driving, underachievement, mental illness, and "bad to worse") as a tool that captures several of the more well-supported, brain-based risks associated with marijuana. Using this mnemonic, we reviewed five research-supported harms related to marijuana use. First, cannabis dependence (addiction) is real. Second, driving while under the influence of marijuana is unsafe. Third, marijuana use has a strong association with global underachievement. Fourth, marijuana elevates the risk of developing a psychotic illness and worsens the course of several serious mental health conditions in certain individuals. Fifth, though proving causality is complex, evidence supports a "bad to worse" or "gateway" role of cannabis in the

development of other substance use disorders. Important to note, most of these harms are more likely to be present when marijuana use is frequent and starts early (i.e., in adolescence).

Though we don't always heed George Santayana's aphorism about learning from (and therefore being doomed to repeat) our past, a chapter of recent history informs the cannabis conversation. Like a string of white crosses on the shoulder of a dangerous stretch of road, deaths from the recent prescription opiate epidemic stand out as stark examples of the collateral damage from widespread availability of addicting substances and the powerful impact of market forces, medical culture, and societal mores on drug use. Though cannabis is less directly deadly than opiates, all of the factors that buoyed the recent opiate epidemic—availability, economic forces, changing cultural norms—inform the cannabis debate. Healthcare providers, educators, policy leaders, and parents will be well-served by keeping abreast of the burgeoning research on the potential harms of this version of "going green."

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