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Clinical Approach to the Heavy Cannabis User in the Age of Medical Marijuana

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ABSTRACT

This article begins with a case vignette exemplifying the common clinical problem of heavy marijuana users. The epidemiology and basic science underlying cannabis dependence is outlined, followed by clinical strategies for basing a therapeutic alliance on known research findings and using motivational interviewing to deal with typical patterns of denial.

A 28-year-old man complains of depression, anxiety, and sleep disorder since adolescence. He has been only intermittently employed for years and lives in an apartment provided by an alcoholic father with whom he has a contentious relationship. He openly acknowledges daily marijuana (MJ) use, claiming that it helps him cope with a disappointing world better than any medications prescribed by physicians. What approach should be taken?

Epidemiology of marijuana use

Every addiction treatment provider encounters patients today whose lives are compromised by marijuana, whether recognized by the patient or not. Forty-eight percent (48%) of American adults acknowledge lifetime marijuana use, with 12% of the general public having used it during the past year. Use rates among younger age groups are highest, with 27% of those under 30 acknowledging having used in the last year (Pew Research Center 2013).

However, complicating providers' task is the fact that past, or even present, marijuana use does not automatically mean problematic use. While use of any drug, whether by prescription, over-the-counter, or illicit, always entails some degree of risk, the majority of marijuana users manage this risk responsibly. The number of "current users" (i.e., past month) in 2007 was 14.5 million (5.8% of the population). This number rose to 18.9 million in 2012 (7.3%) (SAMHSA 2013). Monthly use is not generally considered heavy use, although it is frequent enough to have significant adverse consequences in selected populations; e.g.,

bipolar disorder, schizophrenia, addictive disease, or for those on probation.

Heavy marijuana use, defined as daily or almost daily use of marijuana (20 or more days in the past month) existed for 7.6 million persons in 2012, up from 5.1 million persons in 2007 (SAMHSA 2013). Perhaps most worrisome, due to the increased vulnerability of the developing brain, 6.5% of high school seniors reported smoking marijuana daily in 2012, up from 5.1% five years previously (Johnston et al. 2014).

Special attention needs to be paid to distinguishing lifetime dependence rates from current dependence rates. For example, although Horwood and Fergusson (personal communication, 2013) report that 43% of individuals with onset of MJ use at 13 years old exhibit a lifetime history of cannabis dependence by age 30, only 15% are dependent during the previous year at age 30. In other words, the majority of people who become dependent on MJ eventually spontaneously stop meeting the criteria for dependence. The National Commission on Marihuana and Drug Abuse (Nahas and Greenwood 1974) found that 71% of adults who had ever used MJ terminated use, with 61% of terminations being due to a loss of interest in the drug (Roffman and Stephens 2010). Unlike the rubric commonly recited regarding alcoholism, cannabis dependence is not necessarily a chronic, progressive disorder.

The impact of cannabis on the brain

Research over the past 25 years has made remarkable gains in understanding how cannabis affects the brain.
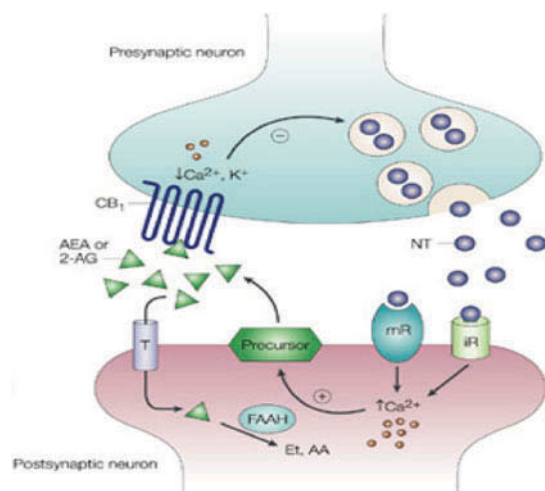
Figure 1. Endocannabinoids and Presynaptic CB1 Receptors -demonstrating the negative feedback function provided by the endocannabinoid system (Velasco et al. 2012). © Macmillan Publishers Ltd. Reprinted by permission from Macmillan Publishers Ltd. Permission to reuse must be obtained from the rightsholder.

Today, we understand how marijuana "works," along with important information about how it can also work to peoples' detriment. A fundamental understanding of the latest neuroscientific research on cannabis is necessary to form a therapeutic alliance and treatment plan for heavy marijuana users.

Marijuana research repeated the path that led to the discovery of endorphins. After extracting the psychoactive essence (primarily morphine) from the poppy's sticky exudate, scientists radioactively labeled opiate molecules to visualize where they go in the brain. In this way, they discovered opiate receptor sites, small protein complexes in the synaptic membranes of nerve cells that are specifically activated only by opiates. One year after discovering opiate receptors, the brain's own (endogenous) morphine-like neurochemistry was isolated in 1974. Combining parts of two words (endogenous and morphine), the word "endorphin" was born. Science had moved from botany to neuroscience, from the plant to the brain.

The same path of research was taken with marijuana, with similar results. The primary psychoactive chemical extracted from the cannabis plant is THC (delta-9-tetrahydrocannabinol). Labeling THC-like molecules led to the discovery of a high-affinity, stereospecific cannabinoid receptor in 1988, now labeled CB1 (Devane et al. 1988), and then to the first endogenous cannabinoid neurotransmitter, called anandamide, in 1992 (Devane et al. 1992). Together, these discoveries launched research around the world into the brain's endocannabinoid neurochemistry and physiology. While some researchers remained

interested in exploring the impact of THC, which works by mimicking anandamide, others pursued an understanding of the basic science of the newly discovered endocannabinoid system.

Mapping areas of high CB1 receptor densities provides clues to both the function of our endocannabinoid system and the neural mechanisms underlying the experience of marijuana intoxication (Herkenham et al. 1990). For example, when THC stimulates the high concentration of CB1 receptors in the hippocampus, memory and learning are affected (Riedel and Davies 2005; Ashtari et al. 2011). High concentrations in the amygdala lead to reduced anxiety (Viveros, Marco, and File 2005), increased appetite (Fride 2002), the sensation of novelty (Van Laere et al. 2009), forgetting aversive experiences (Marsicano et al. 2002; Chhatwal et al. 2005), and a sense of awe described by the young astronomer Carl Sagan (Grinspoon 1971). High concentrations in basal ganglia reduce spontaneous motor activity (Rodriguez De Fonseca et al. 1998; Sanudo-Pena et al. 2000; Darmani 2001). High concentrations in the frontal cortex alter executive functions, especially in adolescents (Medina et al. 2007; Hanson et al. 2010; Fontes et al. 2011), and bias the assessment of risk toward greater response to gains than to losses (Wesley, Hanlon, and Porrino 2011). In addition, high concentrations in the ventral tegmental area (VTA) contribute to marijuana dependence (Fattore et al. 2008).

The endocannabinoid system regulates activity of most other neurotransmitters. It is more of a neuromodulator system than a neurotransmitter system conveying detailed information. Unlike typical neurotransmitter systems, CB1 receptors are located presynaptically and endocannabinoid neurotransmitters are synthesized on demand from components of the postsynaptic membrane (e.g., arachidonic acid) rather than stored in vesicles (see Figure 1; Freund, Katona, and Piomelli 2003). This anatomy positions the endocannabinoid system perfectly to modulate other neurotransmitters. When action potentials release serotonin, dopamine, GABA, or glutamate, for example, these neurotransmitters activate their respective receptors on the postsynaptic neuron. This sets into motion the synthesis of anandamide, which travels back across the synapse to activate presynaptic CB1 receptors. Once activated, CB1 receptors reduce the outflow of whatever neurotransmitter initiated the process.

The endocannabinoid system is a negative feedback system. It acts as a circuit breaker when other neurotransmitters are activated above normal limits (Katona and Freund 2008). Endocannabinoids are an essential, tonically active homeostatic mechanism assuring that

other neurotransmitter systems are neither under- nor overactive. When a cloud of THC molecules, mimicking anandamide, hits hippocampal CB1 receptors, for example, the GABA's ability to produce post-synaptic inhibitory potentials (PSIPs) is markedly reduced, leading to difficulty forming effective memory traces (Hajos et al. 2000; Katona et al. 2000). When the same cloud of THC activates CB1 receptors in the amygdala, our normal level of habituation is decreased and attention is drawn to stimuli that had long been ignored. This enhanced experience of novelty is probably one of the most enjoyable aspects of being "high."

One very important consequence of excessively stimulating CB1 receptors is downregulation. The more CB1 receptors are stimulated, the fewer receptors remain. Rats exposed to a single dose of THC begin to down-regulate CB1 receptors in the hippocampus, and daily exposure for a week reduces CB1 activity as much as 30% (Romero et al. 1998). Ninety days of THC produces a 44% reduction in synapses as long as seven months later (Scallet et al. 1987). Two weeks of THC administration downregulates CB1 receptors in the amygdala as much as 24%. This reduction of cannabinoid receptors in the brain below their normal level can have subtle, but pervasive, impacts on brain function.

Not all cannabinoid molecules are created equal. For example, cannabidiol (CBD), the precursor to THC, has lower affinity for CB1 receptors and has a more sedating, less psychoactive, impact. Sophisticated heavy MJ users often choose their favorite strain of MJ based on the relative percentages of THC and CBD. A recent strain ("Charlotte's Web") (Wikipedia contributors 2015) has gained attention due to its documented antiepileptic effects. Different actions by different cannabinoid molecules are due to the recently discovered phenomenon called "functional selectivity." Functional selectivity posits that, contrary to our previously held belief that each distinct neuroreceptor is connected to one specific intracellular signaling cascade, different ligands can activate different signaling cascades through conformational changes in the same receptor. Functional selectivity has been demonstrated in the endocannabinoid system and almost certainly has clinical consequences still waiting to be clarified (Bosier et al. 2010).

Finally, recent research has demonstrated that the baseline level of CB1 availability in the amygdala is *inversely* related to degree of novelty seeking (Van Laere et al. 2009). A single nucleotide polymorphism in Caucasians has been shown to reduce FAAH, the enzyme that breaks down anandamide, by 25%, thus increasing endocannabinoid signaling, which leads to decreased threat-related amygdala reactivity (Hariri et al. 2009). We now understand how basic elements

of temperament (i.e., the degree of inhibition or attraction to novelty) are determined by the endocannabinoid tone in the amygdala. Since frequent enough use of MJ (i.e., daily for two weeks) can downregulate CB1 in the amygdala by 24%, heavy use is capable of altering temperament toward increased novelty seeking.

Clinical strategies

While adult heavy users usually establish therapeutic contact themselves (often in response to a partner's pressure), the parents of adolescents are more likely to make initial contact. I usually ask whether their child has expressed interest in speaking with a therapist. When the MJ user has expressed interest, I typically meet with him or her first and with the parents after a therapeutic alliance has been initiated. If the primary concern lies with the user's parents, I first meet with them. The goals are to evaluate their understanding of MJ, to provide missing information, to assess their own relationship to drugs and alcohol, and to guide them toward healthier strategies for dealing with a potentially active addict. In most cases, this involves making a referral to Al-Anon meetings that focus on parents of addicts. In cases where the adolescent is unwilling to enter any form of evaluation or treatment, therapists need to work through counseling parents on how best to set boundaries for their home.

The first step in initiating a discussion about marijuana is for the clinician to be careful not to add additional fuel to the patient's defenses. This requires not only a non-judgmental stance, but an approach that embodies genuine curiosity. Most heavy marijuana users are not reluctant to discuss their use if their defenses are initially honored rather than immediately attacked, no matter how gently.

The principles of motivational interviewing (MI) provide excellent guidelines for initiating dialogue about a patient's marijuana use (Miller and Rollnick 2002; Levensky et al. 2007). MI elicits behavior change by helping clients explore and resolve their ambivalence. It accepts that patients are at different levels of readiness to change their behavior and is non-judgmental, non-confrontational, and non-adversarial. The motivation to change arises from patients' recognition of the ambivalent feelings they tend to defend against.

Motivational interviewing techniques require clinicians to engage in active dialogue (McCambridge et al. 2003). Even single-session interventions have demonstrated significant declines in cannabis use at three months' follow-up in both adults and adolescents (McCambridge and Strang 2004).

Typical questions to open a discussion are "What do you enjoy the most about marijuana?" or "What is the most valuable thing marijuana has taught you?" When patients give one-dimensional or vague answers (e.g., "Makes me feel good"), the clinician should drill in deeper by saying that there are many different ways that people "feel good" and marijuana is not experienced exactly the same way by everyone. Use curiosity to inquire about the granular details of how the patient experiences marijuana.

After a patient begins helping the clinician understand what they like about marijuana, a two-step process can be initiated. First, ask about several specific experiences such as lessened anxiety, increased appetite, enhanced sensory pleasures, and sense of freshness/novelty. This direction of inquiry helps flesh out a wider range of marijuana's impact as well as establishing the clinician's bona fides as a marijuana expert. For example, when explaining what I mean by "novelty," I might describe the experience of noticing the small rainbow on the same place on every bubble in soapsuds, a perception that was habitual in preschool years until marijuana lowered the bar for sensing novelty. It is best not to take this direction until assured that you will not simply be putting words in the patient's mouth with your prompts.

The second step is to ask what the patient knows about how marijuana produces the experiences they most value. Most people know that THC is the active ingredient and an increasing number are beginning to know about marijuana receptors, but few have any deeper understanding. Focus on the experience each patient most values—relaxation/anxiolysis, novelty/pleasure, and sensory enhancement/munchies—to provide a deeper understanding of the endocannabinoid system. Most heavy smokers, though not all, can be fascinated by learning more about the drug with which they are in thrall. In the process, you will be moving the focus from the plant to their brain.

For example, I may explain how the brain's natural cannabinoid system is constantly regulating our sensitivity to novelty to fit different tasks. When hunting, we want to notice the subtlest new stimulus; when concentrating on a single task, we might want to filter out distractions, no matter how novel. The cloud of THC that marijuana provides lowers the bar for our brain's adding the sense of novelty to stimuli, which freshens our perceptions in a very enjoyable way. At this point, many patients are fully enthusiastic about the wonders marijuana brings into their life by heavily stimulating their natural receptors.

Another example that is easily understood is the modulation of short-term memory by our endocannabinoid tone. Increase tone and short-term memory shortens; decrease tone and it lengthens. Life presents varied tasks for which different amounts of short-term memory would be most useful. Attempting to remember a phone number until it can be recorded may benefit from being able to hold the number in memory for many seconds. However, holding what happened 15 seconds ago in memory is likely to make a basketball player less effective. Most people can understand the value of being able to modulate the parameters of their short-term memory, and most heavy MJ users have experienced such abbreviated shot-term memory when intoxicated by THC that they might forget the subject of a sentence by the time they have gotten to the predicate. The goal here is to flesh out the perspective that specific brain changes underlie the psychoactive properties of MJ.

Clinicians can now begin activating patients' ambivalence by introducing the phenomenon of receptor downregulation. Simply saying that "marijuana eventually dulls the mind," is too vague. Clinicians need to give a visual, a picture of what happens when the cloud of THC dissipates and fewer than normal CB1 receptors remain for our normal endocannabinoids to activate. Describing the endocytosis of receptors to reduce excessive stimulation fascinates some people. The result in the amygdala is that the bar for experiencing novelty rises above normal, and everything becomes more boring—unless marijuana is reused. A roller coaster develops in which sensations are freshened with using MJ and boredom returns when the cloud of MJ recedes.

Once the concept of cannabinoid deficiency, on the basis of downregulated CB1 receptors, has been established, it is safer to begin approaching the question of dependence—addiction. These two words—"dependence" and "addiction"—are much more difficult for people to identify with than "cannabinoid deficiency."

Alan Budney has developed criteria for marijuana withdrawal symptoms with both reliability and validity (Budney et al. 2004) (Figure 2). In truth, however, the intensity of withdrawal has been shown to resemble no more or less than that from tobacco (Budney et al. 2008). Not a life and death matter. On the other hand, as with tobacco, relapse most often occurs to quell the symptoms of withdrawal. Sometimes patients readily acknowledge addiction; other times, defensive barricades are erected.

After exploring whether a patient can identify any experience of cannabinoid deficiency (boredom, lack of motivation, increased anxiety, insomnia, restlessness), the question of addiction/dependence can be approached. At this point, patients can be asked

Common
 Anger, aggression, irritability
 Anxiety/nervousness
 Decreased appetite or weight loss
 Restlessness
 Sleep difficulties including strange dreams

Less Frequent
 Chills
 Depressed mood
 Stomach pain/physical discomfort
 Shakiness
 Sweating

Figure 2. Cannabis Withdrawal Syndrome (Budney et al. 2004). © *American Journal of Psychiatry*. Reproduced by permission of the *American Journal of Psychiatry*. Permission to reuse must be obtained from rightsholder.

directly if they believe marijuana can be addictive, or if they have become dependent to any degree?

Marijuana dependence

Before marijuana dependence can be discussed with patients, it is paramount for clinicians to explore whether they themselves believe the drug is addictive. If clinicians do not hold this belief, or do not understand the brain mechanisms underlying dependence, they are not in the best position to help someone find recovery.

There are four lines of research supporting the conclusion that marijuana is addictive for a minority of those who ever use it. First, THC stimulates CB1 receptors in the midbrain (ventral tegmental area), leading to an outflow of dopamine in the nucleus accumbens (Lupica, Riegel, and Hoffman 2004). This is the hallmark and *sine qua non* for all drugs of addiction—direct action on the brain's reward circuitry—and is thought to play an important role in sustaining the self-administration of marijuana in humans.

Second, the use of cannabinoid blockers in animals pretreated for at least seven days with THC produces the same pattern of withdrawal symptoms, including restlessness, sleep disturbance with typical EEG changes, "wet dog" shakes, and increased aggressiveness. Similar symptoms are seen in rats, cats, dogs, and monkeys (Tanda and Goldberg 2003). Third, reports from humans in treatment for heavy marijuana use parallel those seen in other species, including the same sleep-related EEG changes.

Fourth, epidemiologic studies in several countries (Australia, Canada, Great Britain, the U.S.) all find roughly the same rate of marijuana users satisfying the criteria for dependence at some point in their lifetime—9%. The caveat regarding rates of dependence is that adolescents are far more vulnerable to becoming

dependent, and becoming dependent more rapidly. For example, 16.4% of 15-year-olds who started using marijuana sometime in the past two years already meet criteria for dependence (Winters and Lee 2008).

Marijuana dependence resembles all other drug dependencies. In Hamlet's words, speaking of his widowed mother's too-soon sexual consorting with his uncle, "As if increase of appetite had grown by what it fed on...."

Dealing with typical patterns of denial

Several common themes run through patients' denial that marijuana can cause problems, almost as if the clinician's patients are talking to one another. This is because they are, at least indirectly, talking to each other through the ethos and mores binding stoner culture together, aided by the Internet (see Erowid. org). It is helpful to be armed ahead of time with responses to these typical patterns of denial to provoke cognitive dissonance, and thereby increase ambivalence. The following examples will inevitably be encountered when treating marijuana users:

(1) "But, doc, everyone uses weed." Wrong; even among the highest-use age group, non-use is as normal as use (56.6% of 26- to 29-year-olds).
(2) "It can't be harmful—it's natural and organic." So are death cap mushrooms. And with no quality control, it is impossible to know what chemicals have been used in marijuana's cultivation unless you have grown it yourself.
(3) "No one ever died from a marijuana overdose." Probably true, if restricted to direct overdose and not auto accidents. But death is a very low bar to achieve.
(4) "It makes me feel better." So does cocaine, but that does not make it a good medication.
(5) "I feel more present." Research shows that the brains of marijuana users respond less to subtle emotional cues than non-users (Gruber, Rogowska, and Yurgelun-Todd 2009). Perceptions are not always accurate measures of reality.
(6) "Marijuana doesn't do any harm." Marijuana alters the assessment of risk (Wesley, Hanlon, and Porrino 2011), diminishes executive functions (higher-order cognitive abilities), especially in early onset users (Fontes et al. 2011), and is associated with significantly lower income by age 25 in heavy MJ smokers (Fergusson and Boden 2008).
(7) "But, doc, it's my medicine and I have a right to have my medicine." Patients have a right to receive

effective medication, and physicians have the responsibility to make objective decisions that weigh benefits and side-effects of each medication in light of each individual's disease condition.

Remember that the goal is not to prove patients wrong, but rather to create cognitive dissonance and stimulate dialogue regarding their reasoning. By failing to understand how to reconcile a patient's contentions with equally logical but incompatible facts and perspectives, the clinician provides an opportunity for a patient's ambivalence to rise into the discussion.

"Medical" marijuana

The phenomenon of "medical" marijuana presents two distinct facets. One facet involves pharmacotherapy; the other, complex politics. Familiarity with both facets is clinically important, as the majority of heavy cannabis users will have deeply integrated information from both areas into their system of rationalization.

There is absolutely no doubt that manipulations of the endocannabinoid system hold considerable promise for relieving human disease and suffering. Folk medicine has been using cannabis for over 5,000 years. Today, we have the ability to increase the endocannabinoid system's production of either cannabinoid agonist or antagonist actions as well as to administer direct cannabinoid agonists and antagonists. For example, AM404 inhibits endocannabinoid reuptake; URB597 increases endocannabinoids by inhibiting its enzymatic breakdown by FAAH (fatty acid amide hydrolase); and AM1241 selectively stimulates CB2 receptors that are found primarily outside the central nervous system. Together, and with other potential medications under development, evidence already exists that cannabinoid medications could be used for a wide variety of clinical indications, all based on endocannabinoid modulation (see Figure 3).

- Diseases of Metabolism and Appetite
  - Obesity
  - Anorexia / Wasting Syndromes
  - Nausea & Emesis
- Pain
  - Somatosensory Pain
  - Neuropathic Pain
- Inflammation
- CNS Disorders
  - Head and Spinal Cord Injury
  - Stroke
  - Multiple Sclerosis
  - Neurodegenerative Disease
  - Epilepsy
  - Mood Disorders
  - Insomnia
  - Post-Traumatic Stress Disorder
  - Drug & Alcohol Addiction
- Cardiovascular & Respiratory
  - Hyper- and Hypotension
  - Myocardial Reperfusion Injury
  - Atherosclerosis
- Cancer
  - Cancer Cell Proliferation
  - Colorectal Cancer
- GI and Liver Disorders
  - Inflammatory Bowel Disease
  - Ulcerative Colitis
  - Hepatitis
  - Cirrhosis
- Musculoskeletal Disorders
  - Arthritis
  - Osteoporosis
  - Post-Fracture Bone Healing
- Reproductive Disorders

Modified from slides by Eliot L. Gardner, PhD, Senior NIDA Investigator
April 16, 2011
ASAM Medical-Scientific Conference, Washington, D.C. Where Does ASAM Stand?"

Figure 3. Potential Cannabinoid Medication Clinical Targets.

While most medical organizations have acknowledged that useful cannabinoid medications will be developed, few have embraced the current concept of "medical" marijuana, generally citing the inappropriateness of administering unknown quantities of active pharmacologic agents via inhalation of smoked material. However, politics have gradually been trumping medicine for reasons that the medical community has been slow to grasp. Mainstream medicine has fallen behind the curve being created by a political groundswell. The forces promoting "medical" marijuana are highly heterogeneous, with a wide variety of goals. The coalition favoring legal use of marijuana for medical purposes includes seriously ill cancer patients for whom marijuana has been a balm for pain, anorexia, and the distress of chemotherapy. It also includes strict libertarians, marijuana users, drug policy reformers, and a public that has tired of the heavy and generally ineffective hand of enforcement relied upon for over 40 years in America's War on Drugs. A significant international movement has begun to reject policies that have often devolved into a war on drug users in favor of promoting treatment rather than incarceration (Briones et al. 2013), recognition of nuances that exist between "hard" and "soft" drugs (Nutt et al. 2007), and legalization of drugs in amounts for personal use (Hughes and Stevens 2010).

Today, 23 states and the District of Columbia have legalized medical marijuana (ProCon.org 2015). Four states—Colorado, Washington, Oregon, and Alaska—have legalized the recreational use industry. Data on the impact of these liberalized policies is scarce and often lost under a pile of opinion, fear, and fantasy. On the one hand, state-by-state comparison of adolescent use of marijuana prior to legalization of "medical marijuana" with most recent data does not show a significant impact (see Figure 4; Ammerman 2011).

On the other hand, recent research reports that 10% of non-using high school students intend to initiate use if marijuana is legalized. This would be a 5.6% absolute increase in lifetime prevalence of cannabis use in this age group from 45.6% to 51.2% (Palamar, Ompad, and Petkova 2014). On the other hand, more liberal marijuana policies in the Netherlands than the U.S. have not led to greater use by adolescents. Use in the past 12 months was 33.0% for boys and 26.0% for girls in the U.S. and 28.6% for boys and 19.8% of girls in the Netherlands. Similarly, use in the past 30 days in the U.S. was 21.4% for boys and 15.8% for girls, and 18.8% for Dutch boys and 10.6% for girls (Simons-Morton et al. 2010).

Many medical societies have conflated the issue of "medical marijuana" with the issue of decriminalization/legalization (American Society of Addiction Medicine 2012). While many physicians feel that medicine's forced involvement with providing legal cover for marijuana users has had a corrupting influence, this is not the same issue as whether enforcement-oriented or public-health-oriented policy would be most beneficial for marijuana users and society as a whole.

Individual patients, especially those harmfully involved with marijuana, often adopt a libertarian political stance, adamantly asserting their "right" to put whatever they choose into their bodies. As with most resistance, it is usually important to "roll" with this argument. I freely acknowledge this "right" while comparing it to every adult's right to put as much alcohol into their bodies as they wish. From a medical perspective, however, the only issue is the safety and effectiveness of chemicals, not political liberties. This strategy usually disarms patients by refusing to engage in important, but medically irrelevant, issues.

When patients argue from the perspective of "medical" marijuana being legal, it is again best not to oppose, but rather to expose them to wider perspectives. For example, "medical" marijuana simply means that law enforcement is not able to arrest people with recommendations by a physician to use marijuana for medical purposes. It does not permit physicians to prescribe, or pharmacies to dispense, marijuana. In fact, there are many fine medications that are illegal for people to possess without a prescription; e.g., morphine. The rationale for requiring physician prescription is that many medications are capable of doing as much harm as good, and psychoactive medications, in particular, are often difficult for individuals to assess accurately whether their illness is being treated or they are merely led to "feel better," even as the illness goes untreated. While the chemistry in marijuana is absolutely going to yield many

State	MM Legalized	Recent Data
California	1996	11th grade 25.9 to 23.9
Alaska	1998	12th grade 30.9 to 23.9
Oregon	1998	11th grade 21.0 to 21.8
Washington	1998	12th grade 28.7 to 23.4
Maine	1999	12th grade 30.4 to 25.4
Hawaii	2000	12th grade 22.7 to 20.5
Nevada	2000	12th grade 27.5 to 22.7
Montana	2004	12th grade 29.1 to 27.7
Vermont	2004	12th grade 37.2 to 32.9
Rhode Island	2006	12th grade 34.3 to 31.7
New Mexico	2007	12th grade 25.4 to 29.5
Michigan	2008	12th grade 19.0 to 27.4

Figure 4. Percent Adolescent Marijuana Use Before and After Passage of Medical Marijuana Law (Ammerman 2011).

useful medications, "medical" marijuana is more of a legal than a medical concept at this point.

The goal should be to turn discussions toward the medical aspects of marijuana use and away from legal and policy issues. No matter what public policies govern marijuana, its impact on the brain is the same, and this impact is what lies within the purview of medicine.

Evidence-based treatment of marijuana dependence

The standard psycho-educational approaches to treating substance abuse have also been proven to be useful with cannabis dependence (Dennis et al. 2004). The Cannabis Youth Treatment Study summarized outcomes from randomized trials conducted to evaluate the effectiveness of five short-term outpatient interventions for adolescents with cannabis use disorders. Clinical outcomes were very similar for five sessions of Motivational Enhancement Therapy plus Cognitive Behavioral Therapy (MET/CBT), 12-session regimen of MET and CBT (MET/CBT12), Adolescent Community Reinforcement Approach (ACRA), Multidimensional Family Therapy (MDFT), and Family Support Network (FSN). All five interventions demonstrated significant pre- and post-treatment improvements over 12 months as measured by days of abstinence and the percent of adolescents in recovery (no use or abuse/dependence problems and living in the community).

In Thomas McLellan's framework of addiction as a chronic medical illness requiring ongoing management, treatment of cannabis dependence works (McLellan et al. 2000). Indeed, the Cannabis Youth Treatment Study confirms that, while the initial intervention was effective, half of the adolescents experienced intermittent relapse one or more times after discharge. Two-thirds still reported substance use or related problems at 12-month follow-up. The study's authors concluded that the conceptualization of drug problems as a chronic condition suggests the need to focus more on long-term monitoring and care.

Two medications have been reported of value in treating cannabis dependence, both when administered in the context of structured psychosocial treatment. N-acetylcysteine (NAC), at 1200 mg BID, more than doubled the odds of having negative urine cannabinoid tests as compared with placebo, with benefits detectable within a week of treatment initiation (Gray et al. 2012).

For cannabis-dependent patients who have discontinued use (again, within structured treatment programs), titrating gabapentin up to 300 mg Q AM, 300 mg Q mid-day, and 600 mg Q evening substantially reduced withdrawal symptoms (Mason et al. 2012). Sleep and mood disturbances are reduced, as is craving.

Most importantly, executive functions are improved within the first week, an extremely important factor in patients' ability to make effective use of treatment.

Conclusions

Marijuana, a potentially addictive drug, modifies brain chemistry by strongly stimulating endogenous cannabinoid receptors. Regular use downregulates cannabinoid receptors sufficiently to produce structural changes in the brain, functional changes in the mind, and changes in temperament. Among adults, approximately 9% of marijuana users exhibit lifetime dependence. Children and adolescents are the age group most vulnerable to the harmful effects of marijuana, including dependence, in part because the unnaturally strong cannabinoid stimulation occurs during ongoing and uncompleted brain development.

Treatment depends on developing a non-confrontational therapeutic relationship, beginning with eliciting the patient's experience with marijuana. Providing factual information about marijuana and the brain that is directly related to patients' experience can evoke cognitive dissonance. The principles of motivational interviewing respect patients' ambivalence and encourage them to wrestle with uncomfortable new information. Physicians need detailed understanding of the science of marijuana and the brain's endogenous cannabinoid system in order to help patients see through their rationalizations. In addition, physicians must create a safe arena for discourse by a deeply non-judgmental attitude. Genuine curiosity about patients' subjective experience is the most effective avenue for developing a therapeutic alliance.

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