THE JOURNAL OF GLOBAL DRUG POLICY AND PRACTICE

VOLUME 3, ISSUE 2 - Summer 2009

Focus on Marijuana: Science and Policy

The controversy surrounding marijuana, especially in light of its approval by states for medicinal use, continues to swirl. This issue surveys current research and discusses the drug's documented harms in the scientific literature.

For those states within the US that have allowed marijuana use, the laws and regulations concerning marijuana dispensaries are confusing at best. Our two part article analyzes the status of dispensaries and recommends appropriate actions for the federal government.

The Journal of Global Drug Policy and Practice, a joint effort of the Institute on Global Drug Policy and the International Scientific and Medical Forum on Drug Abuse, is an international, open access, peer-reviewed, online journal with the goal of bridging the information gap on drug policy issues between the medical/scientific community, policymakers and the concerned lay public.

Edited by Eric A. Voth, MD, FACP and David A. Gross, MD, DFAPA, our intended readership includes clinicians, clinical researchers, policymakers, prevention specialists and the interested public.

IN THIS ISSUE

Marijuana Dispensaries and the Federal Government: Recommendations to the Obama Administration 2009: Part 1

Marijuana Dispensaries and the Federal Government: Recommendations to the Obama Administration 2009: Part 2

A Review of the Research on the Risks and Harms Associated to the Use of MarijuanaBarack Obama on Medical Marijuana

THE JOURNAL OF
GLOBAL DRUG POLICY AND PRACTICE

Marijuana Dispensaries and the Federal Government: Recommendations to the Obama Administration 2009: Part 1

Andrea G. Barthwell, M.D.

Abstract

Cannabis dispensaries are proliferating at a rapid rate — a cause for concern, given the potential for such operations to take advantage of desperate patients and put seriously ill patients at affirmative risk. Local jurisdictions do not have sufficient resources to deal with these abuses. Requiring the DEA unequivocally to take a "hands-off" approach, no matter how egregious the dispensary's practices, will not serve the best interests of patients.

Definitions

The terms "cannabis" and "marijuana" are used interchangeably in this paper to refer to the psychoactive material, in either herbal or resinous form, from the *Cannabis* genus of flowering plants.

The use of the terms "medical marijuana" and "medical marijuana dispensaries" in this paper should not be taken as conferring or acknowledging any validity to the use or distribution of cannabis for medical purposes.

I. Introduction

In the early weeks of his administration, President Barack Obama has voiced a number of laudable goals. He has stressed that "Science and the scientific process must inform and guide decisions of my Administration on a wide range of issues..."(1)He has expressed compassion for seriously ill patients and their families.(2) With regard to the use of marijuana for medical purposes, the president is said to believe that "federal resources should not be used to circumvent state laws."(3) Prior to his election, then-Senator Obama noted that any use of marijuana for medical circumstances should take place "under strict guidelines... in the same way that other [pain relievers] or palliative drugs would be prescribed."(4) These aspirations are not necessarily inconsistent. As this paper will show, each of these goals can be met without allowing marijuana dispensaries to multiply free of federal control and intervention.

The Administration need not fear that Drug Enforcement Administration (DEA) intervention into cannabis dispensaries will conflict with state law; indeed, dispensaries are, in almost all instances, not permitted by state medical marijuana laws. Nevertheless, cannabis dispensaries are proliferating at a rapid rate — a cause for concern, given the potential for such operations to take advantage of desperate patients and put seriously ill patients at affirmative risk. Local jurisdictions do not have sufficient resources to deal with these abuses. Requiring the DEA unequivocally to take a "hands-off" approach, no matter how egregious the dispensary's practices, will not serve the best interests of patients.

Uncontrolled proliferation of these dispensaries will seriously undercut our Food and Drug Administration (FDA) drug approval system and deprive patients of important regulatory protections. Such a result will defeat the Administration's avowed desire to support and follow the results of sound science. As President Obama has stressed, medical marijuana should be controlled "the same ...as other drugs prescribed by doctors." Other prescription medications, such as morphine, are subject to a host of quality, safety, and efficacy requirements. Without such requirements, vulnerable patients can be exposed to harmful or ineffective products.

The Food, Drug, and Cosmetic Act (FDCA) and the Controlled Substances Act (CSA) are carefully integrated to ensure that patients' access to medications is determined by good medical science, not politics. The FDA approves specific medical products for marketing and, thereafter, for distribution to patients, based on a determination of those products' safety and effectiveness. Through the scheduling process, the DEA -- after a scientific and medical evaluation by the Department of Health and Human Services (the FDA, in particular) -- determines whether and which restrictions should be placed on basic classes of substances that may have abuse liability. Under this coordinated system, only individual products that have undergone rigorous scientific testing can be made available for medical use; crude botanical substances, such as opium, coca, and cannabis, cannot be sold to patients. Cannabis dispensaries, by distributing herbal cannabis and unapproved cannabis preparations directly to patients, significantly undermine this system.

In addition to maintaining the integrity of our domestic drug approval system, the United States must uphold its international treaty obligations. Under the Single Convention on Narcotic Drugs, which governs the cultivation, distribution, and use of marijuana, the U.S. must prohibit or strictly regulate such activities. When Congress enacted the CSA -- which is enforced by the DEA -- it expressly recognized our obligation to adhere to this and other drug control treaties. Again, the scientific process should guide our path as we

fulfill our global responsibilities. The Administration should therefore allow the DEA to determine when, and to what extent, federal intervention is required to meet our commitments in this area.

The legal status and common practices of cannabis dispensaries

Most Cannabis Dispensaries are Illegal Under State Medical Marijuana Laws.

The DEA's intervention into the practices of marijuana dispensaries does not circumvent state law or violate the concept of "states' rights." First, state legislation relating to the use of cannabis for medical purposes is generally quite limited in scope. These laws merely qualify the reach of the state's existing criminal legislation prohibiting the use, possession, cultivation, etc., of cannabis.(5) California's medical marijuana law -- the oldest in the nation -- clearly illustrates this fact. Proposition 215, the California Compassionate Use Act of 1996 (CCUA),(6) was enacted by the voters in 1996. The Act renders possession and cultivation of cannabis noncriminal under specified conditions; that is, it creates a potential defense against criminal prosecution and conviction.(7) The California Supreme Court has specifically ruled that the Act confers only a limited immunity which "operates by decriminalizing conduct that otherwise would be criminal."(8) Such enactments do not fall within the realm of classic "states' rights."(9)

Second, in most cases, cannabis dispensaries are not actually authorized under these state medical marijuana laws. In California, for example, the original CCUA decriminalized the cultivation and possession of cannabis by a patient, or by that patient's "primary caregiver," if the use of cannabis was recommended by the patient's physician. A primary caregiver was defined as the individual designated by the patient who has consistently assumed responsibility for the patient's housing, health, or safety. The California Supreme Court has ruled that a person whose responsibilities consist principally of supplying cannabis and instructing on its use, and who otherwise only sporadically takes a patient to medical appointments, cannot qualify as a primary caregiver under the CCUA.(10) The Court concluded that a primary caregiver must prove at a minimum that he or she consistently provided caregiving, independent of any assistance in taking medical marijuana, at or before the time he or she assumed responsibility for assisting with medical marijuana. A primary caregiver must be the principal, lead, or central person responsible for rendering assistance in the provision of daily life necessities.

In 2003, the California state legislature enacted the Medical Marijuana Program (MMP).(11) The MMP clarified, but did not modify or expand, the reach of the CCUA.(12) The MMP acknowledges that patients and their primary caregivers may "associate" in order to cultivate cannabis "cooperatively or collectively" for medical purposes, without becoming subject to criminal sanctions solely because of that fact.

This language does not establish a "green light" for cannabis dispensaries. The California Attorney General has recognized that this provision was intended to be quite narrow. In August 2008, the State Attorney General issued guidelines to identify legitimate cooperatives and collectives.(13) The guidelines stressed that neither cooperatives nor collectives should purchase cannabis from, or sell to, non-members; instead, "they should only provide a means for facilitating or coordinating transactions between members." Both types of entities must carefully monitor their members, and both should document "each member's contribution of labor, resources, or money,"(14) as well as tracking and recording the source of the cannabis. Neither type of entity should profit from the sale or distribution of cannabis.

These guidelines allow for small groups of patients and primary caregivers to share the labor, expenses, and other responsibilities of cultivation on a common piece of land or other facility. This description does not apply to the vast majority of cannabis dispensaries in California, which have hundreds or even thousands of members.

In California, dispensaries have had 13 years to flourish, and it is in California that their abuses have become evident. Most dispensaries are merely retail storefronts that distribute cannabis to customers. The California Attorney General has made clear that such dispensaries are operating outside the boundaries of state law: "dispensaries that merely require a patient to complete a form summarily designating the business owner as their primary caregiver -- and then offering cannabis in exchange for cash "donation" -- are likely unlawful."(15) Nevertheless, dispensaries have proliferated across California.(16)

It is the current system and practices of medical marijuana dispensaries in California, and not the DEA's disruption of their merchandising operations, that circumvent state law: both medical marijuana laws, and laws prohibiting the sale or possession of cannabis for non-medical purposes.

The Operation of Cannabis Dispensaries Will Not Generate Scientific Data Leading to a Meaningful Assessment of Cannabis-based Medications.

The practices of cannabis dispensaries will not enable this country to answer the pivotal question: what are the scientific data which demonstrate the risks and benefits of cannabis or cannabis-derived medications? Without such data, no new medical product can gain acceptance by the medical profession, policymakers, and an informed public. California's cannabis dispensaries offer a broad menu of cannabis products to a wide and shifting range of customers. Different strains of herbal materials, as well as capsules, highly concentrated extracts, and edibles are available. Herbal material may be smoked or otherwise inhaled by means of a wide variety of devices. Patients may try one product (or one dispensary), then another. Some patients will have adverse reactions, or will obtain no benefit. Those individuals will simply not make further purchases; their experiences will not be recorded or otherwise captured for medical benefit/risk analysis.

Such practices cannot generate reliable, controlled data that could lead to a meaningful assessment of the future of cannabis or cannabis-based medical products—certainly not data on the myriad different cannabinoid preparations and dosage forms. Acceptable and usable scientific data can be generated only by transforming crude herbal material into standardized formulations of known and reproducible composition and dose, incorporating those into appropriate delivery forms, and testing such combinations through the modern regulatory system.

Cannabis Dispensaries May Put Seriously-Ill Patients at Risk.

State medical marijuana laws themselves recognize that cannabis is not a "harmless herb," akin to a dietary supplement or a home remedy. These laws treat cannabis more like a prescription medication, making a licensed physician the gatekeeper to a patient's access to cannabis(17) (the physician, however, is not required to be federally registered, despite the fact that cannabis holds Schedule I status under the CSA). Despite this "quasi-prescription" status, there is little assurance of quality, consistency, safety, or efficacy. Cannabis in herbal form, or contained in crude preparations, is not a homogeneous substance.(18) Depending on the concentration of various cannabinoids and other plant components, use of inert excipients, and delivery system or dosage form, patients may be exposed to a variety of active ingredients with quite different pharmacological effects. Increasingly, cannabis cultivated in North America and Europe is being bred to express very high concentrations of tetrahydrocannabinol (THC).(19) By contrast, cannabidiol (CBD), a non-psychoactive cannabinoid that dampens down the effects (including the psychoactive effects) of THC, and which was present in significant amounts in cannabis used centuries ago, has been bred out of modern cannabis.(20)

The delivery system also enormously affects the impact that a cannabinoid product has on a patient. If inhaled (as in smoking or vaporizing), THC blood levels rise rapidly and then fall dramatically, which is likely to cause undesirable psychoactive side effects. Indeed, when smoked cannabis is compared with standardized cannabis-derived product (containing equal amounts of THC and CBD and delivered by a sublingual method), the patients using smoked cannabis report more significant adverse events.(21) In addition, in a recent small study examining the effects of cannabis delivered in a (non-FDA-approved) vaporizer,(22) the subjects experienced notable intoxication; they found the cannabis with an intermediate THC concentration (3.4%) more tolerable than the higher THC concentration (6.8%) material.(23) Oral consumption has delayed and unpredictable effects.(24) This variability and unreliability of effect may be particularly harmful to seriously ill patients, who are often debilitated and likely to be taking a range of other prescription medications.

Cannabis distributed by dispensaries also poses other, even more serious risks for patients. It may be contaminated by pesticides,(25) heavy metals, or fungus. For example, in the Netherlands , cannabis is grown for medical use by two cultivators who are licensed by the government's Office of Medicinal Cannabis. The cannabis has such high microbial content that it must be irradiated before it can be distributed to patients.(26)

In a U.S. cannabis dispensary, however, there is no such quality control. If seriously ill patients suffer harm from such contamination,(27) they will receive no compensation, there will be no product recall or governmental investigation, and there is no tool to deter future malfeasance. In short, none of the federal and state regulatory protections are in place, and the cannabis distributed by dispensaries is not subject to reliable oversight.(28)

Cannabis Dispensaries May Take Advantage of Desperate Patients.

Reverend Scott Imler, one of the early California proponents of "medical marijuana," co-author of Proposition 215 and a founder of one of the original dispensaries, has voiced concern that dispensaries can be predatory, taking economic advantage of desperate and vulnerable patients:

We created Prop. 215 so that patients would not have to deal with black market profiteers. But today it is all about the money. Most of the dispensaries operating in California are little more than dope dealers with store fronts.(29)

There is little doubt as to why cannabis dispensaries are multiplying at such a rate. The price of cannabis in dispensaries ranges from $12.50 to $25 per gram (28 grams per ounce).30) The average "medical" user with a chronic medical condition may consume from 1.5 to 3.0 grams per day.(31) Therefore, the monthly cost to patients ranges from $562 (1.5 grams/day at $12.50/gm) to $2,250 (3 grams/day at $25/gm). Since the herbal cannabis, which is of varying strains and quality, has not received FDA approval, none of this expense is covered by a patient's health insurance,(32) and there is no assurance of quality control or accurate dosage information.

This system actually impedes access by patients to cannabis-derived medications. If a medication has gone through the FDA process, there is at least an opportunity for it to be covered by public or private health insurance. Given its exclusion from health insurance plans, its cost exceeds that which most seriously ill patients, many of whom may not be working, can afford to purchase. This cost in turn implies that the majority of purchasers are not, in fact, patients who require cannabis for medical purposes. In the meantime, cannabis dispensaries are profiting; some dispensaries take in over $20,000 per day.(33)

The need for regulatory protections

Allowing a Proliferation of Cannabis Dispensaries Will Seriously Undercut the FDA Drug Approval System and Deprive Patients of Important Regulatory Protections.

President Obama has expressed his desire to ensure that the U.S. provides "continued global leadership in scientific discoveries and technological breakthroughs." He has assured the public that modern scientific developments will "guide" the Administration's policy decisions.(34) A proliferation of cannabis dispensaries in states across the country would have the opposite effect, seriously undermining the FDA approval system. The federal Food, Drug, and Cosmetic Act (FDCA)(35) and the federal Controlled Substances Act (CSA)(36) work in synergy to form this impressive regulatory fabric. The FDCA requires that rigorous scientific data determine which medications may enter the marketplace and, thereafter, be prescribed and distributed to patients. The CSA establishes a process (scheduling) through which those scientific data can be used to ensure that controlled substances are made available for -- and limited to -- appropriate medical and scientific use, through a closed system of distribution that includes proper registration, security, recordkeeping, reporting, quota, and other requirements.

The Requirements of the Food, Drug, and Cosmetic Act Reduce the Likelihood that Patients Will be Exposed to Harmful or Ineffective Products.

The FDCA has been developed over more than a century to protect the health and safety of vulnerable patients. It enforces rigorous standards at all stages in the development of a new medicine.(37)

Before a medical product may be approved by the FDA and be released for marketing, it must be assessed in various nonclinical and preclinical laboratory tests, including drug-drug and drug-food interaction tests. Its final formulation must be analyzed for batch consistency, stability, and absence of dangerous contaminants. Its manufacturing process must be validated and quality-controlled.

Even after extensive preclinical studies have demonstrated the likely safety of the product for human use, several phases of clinical (human) research must be conducted. If a product is intended to be used for a chronic condition, carcinogenicity and reproductive toxicity tests must be performed. Adverse events must be reported and described in the product label. The research is published in peer-reviewed journals, enabling physicians to judge the quality of the research, as well as the relative safety and efficacy of the product.

The FDA also inspects and supervises the pharmaceutical manufacturer's facility. If a flaw exists in the manufacturing process, the FDA can withhold marketing approval. Subsequent to approval, if the FDA receives reports of serious, unrecognized side effects, a product's label can be amended to include heightened warnings, or the product can be removed from the market entirely.

This thorough and dynamic process reduces the likelihood that patients will be exposed to dangerous or ineffective products, and provides important data to allow physicians to conduct meaningful dialogues with, and give informed advice to, patients regarding treatment options.

The Controlled Substances Act Plays a Critical Role in Ensuring that Properly-Tested Medications are Made Available for Appropriate Medical Use.

The CSA and the Drug Enforcement Administration (DEA) play important roles in this system of medication development. When medications contain controlled substances, and therefore pose a potential risk of abuse or addiction, the regulatory system is even more cautious. Mere FDA approval of such a medication is not sufficient; the product must also undergo review through an administrative process under the CSA (the scheduling process).

Cannabis proponents often contend that herbal cannabis should be moved from Schedule I to Schedule II in order to increase its availability to patients through cannabis dispensaries. This argument, however, reflects a misunderstanding of the scheduling process as it relates to the ultimate FDA approval and marketing of a medication. That process must be viewed in the context of the larger FDA/DEA regulatory scheme.

When Congress enacted the CSA, it established five categories, known as schedules, to which different levels of requirements, restrictions, and prohibitions are attached.(38) A drug's classification in a specific schedule is determined by its abuse and dependence potentials on the one hand, and by the evidence of its safety and therapeutic effectiveness on the other. The scheduling process involves independent but complementary roles for the DEA, Department of Health and Human Services, the FDA, and the National Institute on Drug Abuse (NIDA) in particular.

Substances in both Schedules I(39) and II are subject to the greatest restrictions because they have a "high potential for abuse."(40) For the most part, these restrictions are similar: for example, bulk manufacturers of Schedule I or II substances are subject to production quotas;(41) manufacturers of finished dosage forms (products) containing Schedule I or II substances are subject to procurement quotas.(42) Because they have no "accepted medical use," Schedule I substances are subject to some additional restrictions and may only be used in FDA-approved research programs.(43)

Under the CSA, Schedule II Placement Does Not Make a Substance Available for Direct Use By Patients.

The CSA schedules contain basic types or "classes" of substances (such as oxycodone), not specific

products (such as OxyContin® or Fentora®), although each new "branded" medication undergoes a scheduling analysis as part of the FDA approval process. Placement of a substance in Schedule II is not sufficient to allow a specific product containing the substance to be marketed and distributed directly to patients. The latter requires FDA approval.

In order for a substance to move from Schedule I to Schedule II, the DEA must determine that it has an "accepted medical use." In order for a substance to have an "accepted medical use," the following criteria must be met:

> Its chemistry must be known and reproducible;
>
> There must be adequate safety studies;
>
> There must be adequate and well-controlled studies proving efficacy;
>
> It must be accepted by qualified experts; and
>
> The scientific evidence must be widely available.(44)

These criteria can only be met by data of very high scientific quality, essentially equivalent to the data that must be generated in order for a specific finished product to achieve FDA approval.(45) As a practical matter, therefore, the scheduling of new controlled substances generally occurs only after, or simultaneously with, FDA approval of products containing those substances.(46,47)

FDA Approval is Required in Order for a Specific, Finished Medication to be Marketed and Distributed to Patients.

By contrast to the CSA's scheduling of substances rather than individual products, the FDA approves only specific products for marketing and distribution to patients. The FDA does not approve pure active pharmaceutical ingredients (APIs), nor crude herbal substances, such as narcotic raw materials (NRM). Only a finished dosage form containing a specific type of controlled substance can obtain FDA approval and become a prescription medication.

This applies to cannabis as well as to other controlled substance plant materials. In 1970, at the time it enacted the CSA, Congress placed opium and coca leaves in Schedule II of the CSA because modern, standardized, and refined medical products derived from these substances were already on the market. Such schedule II placement did not put crude opium or coca leaves on the pharmacy shelves. Opium and concentrate of poppy straw (CPS)(48) contain different concentrations of alkaloids, such as morphine, thebaine, and oripavine. These alkaloids are themselves considered Schedule II substances, from which final pharmaceutical products are developed.(49) If a dispensary were to attempt to cultivate and distribute crude opium or coca leaves, it is beyond doubt that the DEA would have both the authority and the obligation to take action against such conduct, whether or not that activity was decriminalized under state law.

Author Information

Andrea G. Barthwell, M.D.

Dr. Barthwell is a member of EMGlobal LLC, a firm that advises on public health policy. In the past, she has worked in an advisory capacity for GW Pharmaceuticals Limited and King Pharmaceuticals, Inc., on issues of a public health nature.

Bio: Andrea Barthwell, M.D., F.A.S.A.M., is the former Chief Executive Officer of Human Resources Development Institute, Inc. (HRDI), a community-based behavioral health and human services organization. Dr. Barthwell served from 2002 to 2004 as Deputy Director for Demand Reduction of the Office of National Drug Control Policy, a President-appointed and Senate-confirmed position. She is a former president of the American Society of Addiction Medicine. Dr. Barthwell also is a former member of the National Institute on Drug Abuse and Center for Substance Abuse Treatment National Advisory Councils, as well as the U.S. Food and Drug Administration's Drug Abuse Advisory Committee. She earned her undergraduate degree in Psychology from Wesleyan University in Connecticut and received her M.D. from the University of Michigan. Dr. Barthwell is a member of the global health care and consulting firm EMGlobal LLC.

Michael C. Barnes, Esq.
DCBA Law & Policy

Mr. Barnes is a member of DCBA Law & Policy, a firm that advises on public health policy. In the past, he has worked in an advisory capacity for Alpharma Inc. on issues of a public health nature.

Bio: Mr. Barnes is responsible for strategic growth, business development, and client satisfaction for DCBA Law & Policy and its Center for Lawful Access and Abuse Deterrence (CLAAD). Prior to establishing DCBA in 2004, Mr. Barnes served as confidential counsel in the Office of National Drug Control Policy, where he provided direction on policy and program matters aimed at reducing the demand for illicit drugs. Leading up to his presidential appointment, Mr. Barnes worked for The Perles Law Firm.

Mr. Barnes obtained his Juris Doctor degree from George Mason University School of Law. He earned a master's degree in international economic policy from La Universidad de Belgrano in Buenos Aires,

Argentina, where he lived and studied as a Rotary Foundation International Ambassadorial Scholar. He received his bachelor's degree *summa cum laude* from Flagler College.

Reprinted with permission of the authors.

References

1. Office of the Press Secretary, The White House, "Memorandum for the Heads of Executive Departments and Agencies," (March 9, 2009) (hereinafter "Memorandum") at p. 1. http://www.whitehouse.gov/the_press_office/Memorandum-for-the-Heads-of-Executive-Departments-and-Agencies-3-9-09.

2. Montopoli, B., "Obama Announces Stem Cell Decision," CBS News Political Hotsheet (March 9, 2009) (President Obama remarks in full) at p. 2.

3. Egelko, B., "Feds Hint No More Raids on Pot Clubs in State," San Francisco Chronicle A1 (Feb. 27, 2009).

4. Town hall meeting in Audubon, Iowa, Nov. 24, 2007. "Medical Marijuana ProCon.org", http://medicalmarijuana.procon.org/viewsource.asp?ID=002447.

5. See National Organization for the Reform of Marijuana Laws (NORML), "Active State Medical Marijuana Programs," http://norml.com/index.cfm?Group_ID=3391. In 2004, Oregon voters rejected an initiative that would have authorized dispensaries in that state. At present, under SB 1085 (effective Jan. 1, 2006), Oregon permits a patient to register a "marijuana grow site," which can cultivate cannabis for no more than four patients. In March 2009, New Mexico granted the first license for a cannabis dispensary, the name and location of which are undisclosed. See Major Holmes, S., "First medical marijuana producer in NM approved," The Associated Press (March 19, 2009). In Michigan, dispensaries are springing up, even though the recently-enacted medical marijuana law does not authorize them. http://www.mlive.com/news/flint/index.ssf/2009/03/group_to_offer_marijuana_advic.html.

6. Calif. Health & Safety Code §11362.5.

7. People v. Mower 28 Cal.4th 457, 472; 122 Cal.Rptr.2d 326 (2002). It is not uncommon for a state to render certain conduct noncriminal that otherwise would be criminal under its laws. See, e.g., Calif. Penal Code sec. 602(n) (the crime of trespass on another's property is not applicable to persons engaged in lawful labor union activities); Calif. Insurance Code sec. 12924(b) ("no individual shall be prosecuted or be subjected to punishment for any crime concerning which he/she is compelled by the Insurance Commissioner to testify or produce other evidence").

8. People v. Mower, supra, at p. 473. This limited immunity entitles a defendant to raise a defense at trial and to bring a motion to set aside an indictment or information prior to trial. Id. at p. 470. It does not confer complete immunity from arrest and prosecution. Id. at p. 474.

9. Neither the CCUA nor, subsequently, its clarifying legislation, created other, affirmative "rights." For example, there is no requirement for any accommodation of the use of cannabis on the property or premises of any place of employment or during the hours of employment. See Calif. Health & Safety Code §11362.785(a). Furthermore, nothing precludes an employer from discharging an employee who fails a drug test as a result of his/her use of cannabis for medical purposes (even outside of working hours or the workplace). See Calif. Health & Safety Code §11362.785(a); Ross v. Ragingwire Telecommunications (2008) 442 Cal.4th 920, 70 Cal.Rptr.3d 382 (pre-employment drug testing). These provisions demonstrate that no robust "rights" are created by the limited grant of immunity.

10. People v. Mentch (2008) 45 Cal.4th 274, 85 Cal.Rptr.3d 480.

11. Calif. Health & Safety Code §§11362.7-11362.83.

12. Under California law, the legislature cannot amend an initiative, such as the CCUA, unless the initiative grants the legislature authority to do so, Calif. Const., art. II, §10, subd.(c). The CCUA does not give the legislature authority to amend it without voter approval.

13. California Department of Justice, "Guidelines for the Security and Non-diversion of Marijuana Grown for Medical Use," (Aug. 2008) (hereinafter Attorney General Guidelines). http://ag.ca.gov/cms_attachments/press/pdfs/n1601_medicalmarijuanaguidelines.pdf.

14. "Members also may reimburse the collective or cooperative for marijuana that has been allocated to them. Any monetary reimbursement that members provide to the collective or cooperative should only be an amount necessary to cover overhead costs and operating expenses." Id.

15. Attorney General Guidelines at p. 11.

16. See the partial listing of publicly-advertised dispensaries at http://www.canorml.org/prop/cbclist.html.

17. For example, patients cannot "self-diagnose," as they do when purchasing dietary supplements, nor can patients seek a physician's approval only after their use of cannabis, in an effort retroactively to "validate" such self-diagnosis. See, e.g., People v. Rigo (1999) 69 Cal.App.4th 409.

18. This is also true of opium. Different strains of the opium poppy may be rich in morphine, thebaine, or oripavine. These substances, in turn, are used to prepare very different medications. See DEA, "Authorized Sources of Narcotic Raw Materials," 73 Fed. Reg. 6843 (Feb. 6, 2008).

19. Potter D.J., Clark P., Brown M.B., "Potency of Delta 9-THC and Other Cannabinoids in Cannabis in England in 2005: Implications for Psychoactivity and Pharmacology," Journal of Forensic Sciences (2008 Jan) 53(1):90-4; Mehmedic Z., Martin J., Foster S., ElSohly M.A., editors, "Delta-9-THC and Other Cannabinoids Content of Confiscated Marijuana: Potency Trends, 1993-2003," International Association of Cannabis as Medicine (2005 September 10) Leiden, Netherlands: International Association of Cannabis as Medicine; ElSohly M.A., Ross S.A., Mehmedic Z., Arafat R., Yi B., Banahan B.F., 3rd. Potency Trends of Delta9-THC and Other Cannabinoids in Confiscated Marijuana from 1980-1997," Journal of Forensic Sciences (2000) 45(1):24-30. A complete description of the adverse health effects of high-potency, inhaled herbal cannabis is beyond the scope of this document.

20. Russo E.B., "History of Cannabis and its Preparations in Saga, Science and Sobriquet," Chemistry & Biodiversity (2007) 4(8):2624-48; Pertwee RG, "Cannbidiol as a Potential Medicine," 47-65, in: Mechoulam R., ed. Cannabinoids as Therapeutics, (Basel, Switzerland ; Birkhauser Verlag) (2005).

21. Russo, E.B., "The Solution to the Medicinal Cannabis Problem," in: Schatman, M.E. and Gant, B.L. eds, Ethical Issues in Chronic Pain Management 165, 176-181(Boca Raton, FL; Taylor & Francis).

22. The Volcano® is produced by Storz & Bickel GmbH & Co. in Germany . A description and drawing can be found in Abrams, D., infra. It has limited portability. In use outside the clinical trial setting, the dose of cannabinoids, and the extent of pyrolytic products, will vary with the temperature setting and the patient's inhalation practices.

23. Abrams, D., et al., "Vaporization as a Smokeless Cannabis Delivery System: A Pilot Study," Clinical Pharmacology & Therapeutics (April 2007) at p. 4. http://www.nature.com/cpt.

24. Joy, J., Watson, S.J., Benson, J.A., Jr., Marijuana and Medicine: Assessing the Science Base (Washington DC; Institute of Medicine) (1999) at p. 203 ("Variation in individual responses is highest for oral THC and bioavailability is lowest.").

25. There is no requirement in local legislation that cannabis sold in dispensaries must be organic. Indeed, one dispensary in San Francisco advertises itself as the "only" dispensary offering organic cannabis in the City. http://www.sanfranciscocannabisclubs.com/directory/san-francisco-alternative-patient-caregivers.htm.

26. Scholten, W., "Therapeutic Cannabis in the Netherlands ," Drug Information Association Annual Meeting (June 17, 2004) (presentation); Hazekamp, A., "An Evaluation of the Quality of Medicinal Grade Cannabis in the Netherlands ," Cannabinoids 2006; 1(1):1-9. Canada also has a small government-sponsored and licensed cultivation program. There, too, the cannabis must be irradiated before it is distributed to patients. See Health Canada , "Product Information Sheet on Dried Marihuana." http://www.hc-sc.gc.ca/dhp-mps/marihuana/supply-approvis/dried-information-sechee-eng.php. Certain high-technology cultivation practices, e.g., a computer-controlled greenhouse operated by a pharmaceutical company under strict standard operating procedures, can prevent such fungal growth. http://www.gwpharm.com.

27. One scientist has stressed that certain pathogens, such as aflatoxins, are not destroyed by heat (as in smoking or vaporizing) and are increasingly being recognized as an "underestimated source of neurological toxicity or infections such as aspergillosis." Individuals who are using anti-inflammatory steroids or have compromised immune systems are especially vulnerable to such infections. See Hazekamp, supra, at p. 6.

28. Smoking also produces harmful pyrolytic products that can impair a patient's pulmonary function and cause other harm. Tashkin DP, "Smoked Marijuana as a Cause of Lung Injury," Monaldi Arch Chest Dis. (2005 June) 63(2):93-100. In addition, many dispensaries permit cannabis consumption on the premises However, if cannabis joints or vaporizers are shared, dangerous pathogens can be spread amongst seriously ill patients. Zanocco V, "Meningococcal Cases Linked by Sharing Joints," Vancouver, BC, Canada : Vancouver Coastal Health; 2005 [April 8]. http://www.vch.ca/news/docs/2005_04_07_mening_joints.pdf.

29. Office of National Drug Control Policy, "Medical Marijuana Reality Check." http://www.whitehousedrugpolicy.gov/drugfact/factsht/medical_marijuana.html. Accessed Feb. 27, 2009. Alternatives Magazine, Fall 2006 Issue 39.

30. CNBC, "A Gallery of Medical Marijuana." http://www.cnbc.com/id/28561896. Accessed March 1, 2009.

31. People v. Mentch (2008) 45 Cal.4th 274, 85 Cal.Rptr.3d 480 (patient using 3 grams per day).

32. In California, for example, state law does not require a government, private, or any other health insurance provider or health care service plan to be liable for any claim for reimbursement for the use of medicinal cannabis. Calif. Health & Safety Code §11362.785(d).

33. CNBC, "A Gallery of Medical Marijuana," http://www.cnbc.com/id/28561896. Accessed March 1, 2009. CNBC, "Inside America's Pot Industry," (Jan. 22, 2009).

34. Montopoli, B., "Obama Announces Stem Cell Decision," CBS News Political Hotsheet (March 9, 2009) (President Obama remarks in full) at p. 3.

35. 21 U.S.C. §§ 301-399a.

36. 21 U.S.C. §§ 801-971.

37. Even at the research stage, an investigational product may be tested in actual patients only if the physician-investigator has preliminary evidence of safety and a protocol approved by the FDA. The protocol must undergo careful scrutiny from an Institutional Review Board (IRB).

38. Congress placed most of these substances in their respective schedules as part of the CSA's enactment in 1970, but new substances are continually scheduled and existing substances are moved between schedules as new scientific data become available. DEA, "Controlled Substance Schedules," (Chronological Order). http://www.deadiversion.usdoj.gov/schedules/schedules.htm.

39. Examples of Schedule I botanical materials classified as "hallucinogens" are marijuana (cannabis), psilocybin, and ibogaine. Pure synthetic THC is also in Schedule I. 21 C.F.R. §1308.11.

40. A drug's potential for abuse is a threshold issue in determining the schedule into which the drug may be placed. The term is not defined in the CSA, but the legislative history demonstrates that the following factors are indicators that a drug or other substance has a potential for abuse:

> There is evidence that individuals are taking the drug or other substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community;
>
> There is significant diversion of the drug or other substance from legitimate drugs channels;
>
> Individuals are taking the drug or other substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs; or
>
> The drug is a new drug so related in its action to a drug or other substance already listed as having a potential for abuse to make it likely that the drug will have the same potential for abuse as such drugs, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.

Of course, evidence of actual abuse of a substance is indicative that a drug has a potential for abuse.

H. R. Rep. No. 1444, 91st Cong., 2d Sess. (1970), reprinted in 1970 U.S. Code Cong. & Ad. News 4566, 4601.

41. 21 C.F.R. §1303.21; the registration application of a bulk manufacturer must pass through a notice (publication in the Federal Register) and comment procedure. 21 CF.R. §1301.33.

42. 21 C.F.R. §1303.12.

43. Substances in Schedule II-V have an accepted medical use. Substances in schedules III-V also have lower abuse potential and are subject to fewer restrictions. Interestingly, in California, cannabis remains in Schedule I of the state controlled substances law, despite the fact that it has been decriminalized for limited medical use. Calif. Health & Safety Code §11054(d)(13).

44. See 57 Fed.Reg. 10499, 10506 (March 26, 1992). See Alliance for Cannabis Therapeutics v. DEA, 15 F.3d 1131 (D.C. Cir. 1994). The DEA originally developed these criteria during the scheduling of MDMA. 53 Fed. Reg. 5156 (Feb. 22, 1988); Grinspoon v. Drug Enforcement Administration, 828 F.2d 881 (1st Cir. 1987).

45. Hence, FDA approval of a specific finished product is generally sufficient to establish an "accepted medical use" for the substance contained therein. There are rare exceptions. See, e.g., "dronabinol (synthetic) in sesame oil and encapsulated in a soft gelatin capsule in a U.S. Food and Drug Administration approved product" is in Schedule III and has a Drug Code of 7369, 21 C.F.R. §1308.13(g), whereas pure synthetic THC remains in Schedule I, with a Drug Code of 7370. 21 C.F.R. §1308.11(d).

See, 51 Fed. Reg. 1746 (May 13, 1986; 64 Fed. Reg. 35928 (July 2, 1999) (dronabinol product). FDA-approved products containing GHB are in Schedule III while "street" GHB is in Schedule I. 65 Fed. Reg. 13235 (March 13, 2000), Pub. L. 106-172 (GHB). Hence, a formulated cannabis-derived product could be placed in Schedule II or III after FDA approval, while crude herbal cannabis could remain in Schedule I.

46. FDA approval is not technically a legal precondition to rescheduling. Grinspoon, supra, at p. 8991.

47. See, e.g., tapentadol. The finished pharmaceutical product, manufactured by Johnson & Johnson, was approved by the FDA in November 2008. DEA has issued a proposed rule placing tapentadol into Schedule II. 74 Fed. Reg. 7386 (Feb. 17, 2009). The finished product does not yet have a trade, i.e., "branded," name.

48. Under the CPS method (used by all cultivating countries except India), the plant is allowed to go to seed; portions of the plant are then processed into a concentrate. It is generally believed that CPS is less divertible than opium. CPS may be rich in morphine, thebaine, or oripavine. See DEA, "Authorized Sources of Narcotic Raw Materials," 73 Fed. Reg. 6843 (Feb. 6, 2008).

49. Thebaine is used to manufacture oxycodone, which in turn can be used to manufacture hydromorphone; oripavine is used to make buprenorphine, as well as naloxone (an opioid antagonist). Id. See 72 Fed. Reg. 54208 (Sept. 24, 2007) (oripavine scheduled separately in Schedule II -- rather than as a derivative of thebaine -- to comply with the U.S. 's obligations under the Single Convention).

THE JOURNAL OF
GLOBAL DRUG POLICY AND PRACTICE

Marijuana Dispensaries and the Federal Government: Recommendations to the Obama Administration 2009: Part 2

Andrea G. Barthwell, M.D.

The Scientific Process

Crude Herbal Cannabis and Unstandardized Cannabis Preparations Do Not Meet the Standards of Modern Medicine.

The Institute of Medicine (IOM) has recognized that crude herbal cannabis has little future as a true medication:

Although marijuana smoked delivers THC and other cannanbinoids to the body, it also delivers harmful substances, including most of those found in tobacco smoke. In addition, plants contain a variable mixture of biologically active compounds and cannot be expected to provide a precisely defined drug effect. For those reasons there is little future in smoked marijuana as a medically approved medication. If there is any future in cannabinoid drugs, it lies with agents of more certain, not less certain, composition.(50)

The IOM stressed that "the purpose of clinical trials of smoked marijuana would not be to develop marijuana as a licensed drug but rather to serve as a first step toward the development of nonsmoked rapid-onset cannabinoid delivery systems."(51)

The FDA agrees that crude herbal cannabis is not a medication.(52) The California Medical Association recently announced its intention to "re-examine the need for continued research on smoked herbal cannabis in light of recent research on its benefits and harm and the long-term prospect of smoked herbal cannabis as a medicine."(53) The DEA also acknowledges the need for standardized product:

[H]erbal cannabis should comprise only the starting material from which a bona fide medical product is ultimately derived… [S]tandardizing herbal starting material represents only the first of many steps necessary to create a modern medicine that is safe and effective for use in specific medical conditions… [A] final medical product… must also be delivered in a dosage form that is consistent in composition and that allows the patient to obtain an identifiable and reliable amount of medication.(54)

Only Recently Has Technology Made Possible the Development of Modern Cannabis-derived and Cannabinoid Medications.

There are good reasons why the development of cannabis-derived medications has lagged far behind that of synthetic and naturally-derived opioids and other modern medications. Given that the active ingredients (morphine, codeine) of opium are water soluble, it was relatively simple in the 19th and early 20th centuries to isolate them and develop standardized and purified medications with the technologies that existed at that time.(55)

The story of cannabis is quite different. Cannabinoids (especially THC) are lipophilic (i.e., not water soluble) and unstable, making it difficult for early scientists to identify and isolate the active ingredients. Consequently, potentially therapeutic applications were limited to oral preparation of cannabis (tinctures and extracts),(56) which could not be adequately standardized. Patient response was variable and unpredictable. As more modern medicines became available, these unreliable extracts and tinctures fell out of favor with the medical profession.(57)

The modern era of cannabinoid research was in its infancy in 1964, when the primary psychoactive ingredient of cannabis, THC, was isolated and then synthesized.(58) Beginning in 1989, a robust body of cannabinoid research began to develop, following scientists' discovery of the human cannabinoid receptor system.(59) This delay in the development of modern cannabinoid and cannabis-derived medications has, therefore, been caused more by past technological limitations, than by governmental obstructionism. That development gap is now slowly closing, and there is no justification for affording a non-scientific acceleration, i.e., a "free pass," to herbal cannabis:

This evolution has followed the same principles as the evolution of drug therapy in general. The direction has been away from crude substances of variable composition, stability, and potency, toward the development of progressively more specific or selectively active pure compounds that permit more precise dosage and reduced risk of unwanted side effects.(60)

This is not to say that complex botanically-derived preparations cannot pass FDA muster. There is strong evidence that some properly tested and standardized plant preparations, including those derived from

89. See, e.g., "California Law Enforcement Investigating 'Pot Docs'" (July 8, 2008). http://www.officer.com/web/online/Top-News-Stories/California-Law-Enforcement-Investigating-Pot-Docs/1$31450. The Medical Board of California has promulgated guidelines for physicians who recommend cannabis; however, there has been very limited enforcement. http://www.medbd.ca.gov/Medical_Marijuana.html. Physicians who recommend cannabis can avoid the need for a DEA registration if they do not prescribe other controlled substances.

90. Salmonella and E. coli are common bacterial contaminants that can be transmitted to botanical material through improper handling techniques.

91. San Francisco regulations state that dispensary operators must require employees only to "wash hands" and "use sanitary utensils" when handling cannabis, rather than use sterile gloves and instruments. Sec. 3312(b)(3).

92. As one dispensary advertises: "We are also experienced and knowledgeable about the various medications and how they work for various ailments, so we can steer you toward an answer, not just another dead end." http://greendragoncoop.com/default.htm?gclid=CKWtgr6wj5kCFRBbagodxhFTZg. http://www.mlive.com/news/flint/index.ssf/2009/03/group_to_offer_marijuana_advic.html. http://www.sanfranciscocannabisclubs.com/directory/san-francisco-green-door.htm (patients can expect to deal with "knowledgeable" staff members).

93. Downs, D., "The Manhattan Project of Marijuana," East Bay Express (Mar. 4, 2009) http://www.eastbayexpress.com/ebx/PrintFriendly?oid=936926. Hereinafter " Manhattan Project."

94. Many cities have no regulations and, indeed, have issued bans or moratoria. http://www.scribd.com/doc/294869/Medical-Marijuana-moratorium-map.

95. Medical Cannabis Act revisions, Official San Francisco Website. http://www.sfgov.org/site/uploadedfiles/bdsupvrs/ordinances09/o0025-09.pdf.

96. Cannabis is a highly abuseable substance and, if determined to have an accepted medical use in treatment in the U.S. , would remain subject to the closed system of distribution required by the CSA. State regulation does not fulfill this requirement.

97. Manhattan Project, supra.

98. Of course, this "laboratory" is a far cry from currently-acceptable scientific standards ("looks like a bachelor pad with a locked room in the back"). Id.

99. Id.

100. For example, bills are pending in Illinois, Minnesota, New Hampshire, and New York, among others to decriminalize cannabis for medical use. http://www.mpp.org/legislation.

101. For example, a bill is currently pending in the Rhode Island legislature to amend the existing "medical marijuana" law to authorize cannabis dispensaries. This bill has gained more force following Attorney General Eric Holder's remarks, although it failed in the state House of Representatives last year. Members of the House have stated that the Attorney General's comments have caused them to view the proposal "much more favorably" than last year. Needham, C., "Bill Would License Dispensaries to Sell Medical Marijuana" (Mar. 5, 2009). http://www.projo.com/news/content/MARIJUANA_BILL_03-05-09_UNDHM3N_v17.37894c1.html.

102. Single Convention on Narcotic Drugs, March 30, 1961, 18 U.S.T. 1407.

103. Single Convention, preamble, Art. 4c.

104. The need for the practice of medicine to be "evidence-based" had become well-established, particularly in the Western world. For several decades, scientists had been conducting randomized, placebo-controlled clinical trials to investigate the safety and efficacy of investigational medical products. Chow, S. and Liu, J., Design and Analysis of Clinical Trials, p. 4 (1998). Then, as now, the results of such clinical trials formed the basis both of governmental regulators' marketing approvals and physicians' prescribing practices. See Guyatt, G. et al., "Evidence Based Medicine: Principles for Applying the Users' Guides to Patient Care," 284 Journal of the American Medical Association 1290 (Sept. 13, 2000).

105. Cannabis and cannabis resin were placed in Schedule IV, the treaty's most restrictive schedule, whereas oral cannabis preparations, i.e., tinctures and extracts, were placed in Schedule I, along with most other narcotic drugs. The Single Convention's schedule structure does not parallel that of the Controlled Substances Act, in which Schedule I is the most restrictive.

106. See Secretary General of the United Nations, Commentary on the Single Convention on Narcotic Drugs, 1961, (1973), para. 12, p. 111 ("legitimate" existing systems of indigenous medicine may be taken into account) (hereafter Commentary).

107. The INCB is the United Nations organ created by the Single Convention to implement, and monitor compliance with, the Convention. See Single Convention, arts. 5, 9-15, 19-20.

108. INCB, Report 2002, at p. 21 (2003).

109. The treaty imposes other, very specific restrictions on the cultivation of cannabis, opium, and coca. Article 22 requires a Party to prohibit cultivation, if the Party concludes in good faith that the "prevailing conditions" in the country make such prohibition the most suitable measure of protecting the public health and safety. Furthermore, a Party that prohibits such cultivation must "take appropriate measures" to seize and destroy any plants that are illegally cultivated, except for small quantities that the Party itself may need for scientific or research purposes.

110. The Commentary also indicates that, under the Single Convention, all licensed cultivators "should to the greatest extent possible, be located in the same part of the country, and be contiguous, in order to facilitate more effective control." Commentary at p. 280. This provision would not permit the establishment of cannabis cultivation sites in numerous locations all over the U.S.

111. Preparations of cannabis, such as pharmaceutical-grade extracts and tinctures, are exempt from the government monopoly on wholesale distribution. Single Convention, art. 23, para. 1(e). The treaty also does not extend the government's exclusive rights to "medicinal opium and opium preparations." Id. at art. 23, para. 2(e). "Medicinal opium" is a form of opium powder to which lactose has been added to reduce the morphine content to the standard of about 10 percent." Commentary at p. 21-22. In other words, the term "referred to a product which had not only been extracted from the opium poppy but had also undergone several further processes ... to prepare it for use in other drugs and to obtain a specific and standardized content of morphine, its primary active ingredient." DEA, "Lyle E. Craker; Denial of Application," 74 Fed. Reg. 2101, 2104 (Jan. 14, 2009) at p. 2116. "[T]here were recognized standards for the substance's manufacture and composition and ... the drug had an accepted medical use in humans." Id. By contrast, "there are no recognized standards with respect to herbal marijuana." Id. Therefore, cannabis, even if intended for medical use, d

cannabis, may offer different -- and better -- pharmacological effects than a pure, synthesized cannabinoid alone.(61)

The FDA has recognized that there is burgeoning scientific and public interest in botanically-based products, and that modern technology makes it possible to develop medications of botanical origin. In order to guide the development of such products, the agency has set forth the criteria that must be met to achieve FDA approval.(62) While allowing some flexibility at the early stages of medication development, the guidance specifically states that, by the time of Phase 3 clinical studies,(63) the requirements for a botanical drug product are virtually the same as to those that apply to a new chemical entity (NCE). Botanical Raw Material (BRM), such as herbal cannabis, has not been formulated, incorporated into a specific dosage form, and tested through this demanding NCE process. The FDA guidelines make it quite clear that, even if crude herbal cannabis were moved to Schedule II, it could not thereby be marketed and distributed directly to patients.

The Administration Should Respect and Support the Proper Workings of the Scientific Process.

As a result of modern technologies, and as demonstrated by the receptor research mentioned above, there is significant interest within the scientific and medical communities in cannabinoid research. Scientists are moving as expeditiously as possible to bring new cannabinoid products to market. Time is required, however, for such research to be conducted in accordance with modern medical standards. In keeping with its commitment to science, this Administration should do nothing to discourage these efforts. As President Obama has stated:

Medical miracles do not happen simply by accident. They result from painstaking and costly research, from years of lonely trial and error, much of which never bears fruit, and from a government willing to support that work.(64)

The United States is, indeed, supporting such work in this area. For example, the FDA has allowed a cannabis-derived product to enter into advanced clinical trials in the U.S. For the past ten years, research has been underway in the United Kingdom by GW Pharmaceuticals to develop a range of prescription medications derived from the components of the cannabis plant.(65) GW cultivates particular strains of cannabis that have been bred to express specific ratios of cannabinoids. In order to maintain the consistency of the plants' chemical composition, they are grown by clones (cuttings) under highly-standardized and computer-controlled conditions in secure glasshouses. GW extracts the pharmacologically-active components of the plant, removes waxes and other unwanted constituents, and formulates the resulting botanical drug substance into a final dosage form of specified composition, which is characterized by various standard chromatographic techniques.

The company's lead product, Sativex®, is an oromucosal (inside of the mouth) spray composed primarily of THC and CBD. It is believed that this combination has distinct and important pharmacological activity. The product has already been approved in Canada for neuropathic pain in multiple sclerosis and for cancer pain. The DEA has licensed the importer(66) and the research sites.

A number of other companies, including Alexa Pharmaceuticals, Inc. (THC aerosol product); Aphios (naturally-derived THC product); and Insys Therapeutics, Inc., are also developing cannabinoid products in the U.S.(67) All of these research programs are moving through the conventional domestic regulatory process.(68) None is attempting to distribute crude herbal cannabis, or non-standardized botanical preparations, to pharmacies and patients.(69) These research programs indicate that cannabis-derived medications can, and therefore should, be developed within the parameters of modern regulatory oversight. Allowing a proliferation of cannabis dispensaries would undermine these efforts to bring properly tested medications to market, a result at odds with this Administration's position that its policies should be based on sound science.(70)

Developing properly standardized and tested cannabis-derived or cannabinoid medications is not an easy matter; it requires patience, perseverance, and a commitment of substantial resources. But numerous medical tragedies(71) have proven that shortcuts to the FDA process do a disservice to patient safety and well-being. The FDA drug approval process is not perfect, as demonstrated by recent news about previously-unknown dangers of marketed medications, such as Vioxx®.(72) The lesson of these experiences, however, is not that we should do less testing, or lower our current standards, for prescription medicines. Indeed, those incidents have led to demands for greater oversight by the FDA and, recently, for the establishment of an independent institute to examine the comparative safety and effectiveness of medications.(73)

The FDA Has Limited Power to Protect Patients Who Seek Medical Treatment and Advice From Cannabis Dispensaries.

The FDA has limited jurisdiction to address the dangers posed by cannabis dispensaries. The provisions of the FDCA govern only products that have been introduced into interstate commerce. Therefore, it can be argued that the activities of intra-state cannabis dispensary operations are beyond the reach of the FDA. Ironically, the FDA has greater power over dietary supplements (which have generally passed through interstate commerce) and over health food stores than it does over cannabis dispensaries and their operators.(74) Indeed, the manufacturers of herbs and other dietary supplements (and the retail establishments that sell them) are prohibited by federal law from making claims regarding the product's

medical usefulness or specific health effects.(75) Cannabis dispensaries, however, do give out advice, and provide books and pamphlets, containing such medical claims.(76)

The DEA, therefore, plays a critical part in protecting patients from dangerous, ineffective, and federally unapproved cannabis products. The CSA, and therefore the DEA's authority, extends to products containing controlled substances and activities that may affect interstate commerce, even if the specific products have been manufactured and distributed solely within the state.(77) If this Administration ties the DEA's hands with regard to dispensaries, patients will lose altogether any avenue of federal protection.

States Laws and Regulatory Bodies Should Enhance, Rather Than Undermine, the Protections Provided by the FDA System.

In cases other than medical marijuana, the FDA and DEA are able to rely to a large extent on state regulatory and law enforcement systems to support and augment the federal structures. States have generally accepted this responsibility, enacting their own food and drug laws to fill the gap in the FDA's jurisdiction. These state laws are, for the most part, modeled after the federal FDCA. In California, for example, the Sherman Food, Drug, and Cosmetic Law ("Sherman Law") establishes rigorous scientific standards that must be met before a new drug may be marketed for medical use. The Sherman Law states that a new drug generally may not be sold, delivered, or given away unless a new drug application has been filed with, and approved by, the state or federal government.(78)

State regulatory boards and agencies similarly enhance the effectiveness of the FDA and DEA. State boards of medicine, nursing, pharmacy, etc., supervise the education, training, and practices of all health care providers who examine or advise patients, or dispense or distribute medications. Health care providers who do not adhere to accepted standards of medical practice may incur sanctions from these boards, as well as risk potential civil liability for inappropriate prescribing or other conduct falling below the standard of care.(79) Health care facilities are monitored and licensed by state departments of health services. State tort systems allow patients who have suffered injury from a medication to seek damages from the manufacturer, even if that medication has been FDA-approved.(80) These state mechanisms, when they operate effectively, provide patients with additional or greater avenues of redress and protection and, thereby, complement federal food and drug provisions.

By contrast, when states utilize their food and drug laws (or enact other state legislation) for the purpose of circumventing the FDCA, patient health and safety is jeopardized. In many ways, the current cannabis controversy parallels the Laetrile controversy of the 1970s. At that time, Laetrile (amygdalin) was vigorously promoted as a cancer treatment and preventative. Despite efforts by its supporters to characterize it as a dietary supplement ("Vitamin B17"), the FDA determined that Laetrile was a new drug (since it was intended for medical use) and was subject to premarketing approval.(81) Since it had not been proven safe and effective for medical use, the FDCA precluded Laetrile's shipment in interstate commerce. Desperate cancer patients, spurred on by anecdotal reports of efficacy, contended that they had a right to use Laetrile, despite evidence of cyanide toxicity. Laetrile advocates claimed that the FDA, the American Medical Association, the American Cancer Society, the pharmaceutical companies, and others were conspiring against Laetrile.(82) This political pressure, rather than scientific evidence, caused twenty-seven state legislatures to pass laws allowing the sale and use of Laetrile within their borders. These state laws had little effect, since it was not feasible to manufacture Laetrile within each state. "Proponents hoped, however, that if enough states legalized its use within the states, Congress would change the federal law as well."(83) Ultimately, the National Cancer Institute conducted clinical testing and determined that Laetrile was not effective as a cancer treatment.(84) The lesson of Laetrile is that state legislation should only be used to enhance, rather than undermine, the protections of the federal regulatory system.

The same is true with regard to controlled substances. Many states have adopted the Uniform Controlled Substances Act,(85) the provisions of which parallel those of the federal CSA. States can serve as an early warning system, and have the flexibility to respond more quickly to abuses of controlled substances -- or of uncontrolled substances with abuse potential -- within their borders.(86) For example, as an added layer of protection, states may require that individuals who conduct research into controlled substances must be independently inspected, licensed, and/or approved by state agencies, in addition to obtaining DEA registrations.(87) States may enact prescription monitoring programs to track physicians who prescribe controlled substances, in order to identify and stop inappropriate prescribing practices by physicians, as well as "doctor shopping" by patients (obtaining prescriptions from multiple doctors simultaneously).(88) States also have greater flexibility in their scheduling actions. If a state believes that a new substance has abuse potential and poses a threat to patient safety or public health, the state need not wait on the DEA; it may schedule that substance more restrictively, or prohibit its sale and use altogether.

Cannabis Dispensaries Are Not Subject to State Laws and Regulations Applicable to Entities Operating in the Health Care Area.

Cannabis dispensaries starkly conflict with this robust state system of patient-oriented controls. "Pot docs," for cash payments of several hundred dollars, provide recommendations to patients (including minors), with whom they have virtually no physician-patient relationship, to enable them to use cannabis for a wide variety of medical conditions.(89) Patients purchase cannabis from dispensaries with which they have only a retailer-consumer relationship. Dispensary personnel need not be licensed as health care providers, nor are they required to follow proper sterile techniques to protect against on-site bacterial(90) or other contamination of the herbal material, although it is intended for consumption directly by patients.(91)

Despite their lack of training and accreditation, such personnel freely offer medical information and advice to patients(92) about the panoply of cannabis products, including extracts, capsules, tablets, and various types of edibles. Some of these products can reach THC concentrations as high as 80%, which could produce significant side effects, especially in seriously ill patients or those who have not used cannabis before.(93)

At best, cannabis dispensaries are regulated at the local level.(94) Where they are permitted by local legislation (as in San Francisco),(95) such dispensaries are not regulated as if they were health care facilities (e.g., clinics or pharmacies) answerable to the state department of health services. Nor are the employees who provide direct patient service (e.g., distributing medical marijuana or medical advice) subject to the scope of practice restrictions and requirements supervised by the state boards of pharmacy, nursing, and medicine. Rather, dispensaries are regulated as if they were retail establishments, subject only to the Building, Planning, Housing, Police, Fire, and Health codes of the local jurisdiction.(96)

Cannabis and Cannabis-Derived Products Should be Governed by the Quality Control and Other Testing Procedures Applicable to All Modern Medications.

Gradually, even some cannabis dispensaries have begun to voice concern that these unregulated distribution practices may be placing patients in danger. One operator has acknowledged that, if cannabis "is going to become an accepted mainstream medicine," there must be quality assurance and dosage information:

[A] dog walks in the grow room, and wags its tail—anything can be coming off that dog's tail. It's gross. Fertilizers with E. coli. Compost ... that they don't make right, anaerobic tea that has elevated levels of E. coli and salmonella. It has to come. There's no way that this is sustainable. All it takes is one story of immune-compromised people dying from Aspergillus infection.(97)

This operator has affiliated with an informal laboratory, and envisions a testing program using such instruments as a gas chromatograph and mass spectrometer.(98) He also notes, however, that "It's expensive to test every single thing that comes through the door—that's the price you pay with a decentralized supply system... five pounds coming from here and two from there."(99) It is far from certain whether other dispensaries would voluntarily join such an effort.

These rudimentary laboratory-testing efforts merely confirm the importance of adhering to the existing body of technological tools and methodologies mandated by state and federal regulatory agencies. There is no need to "recreate the wheel" for cannabis or cannabis-derived preparations. Drug manufacturers are already required to institute extensive testing procedures to ensure that their products are quality-controlled during manufacture, and that their formulations and dosage forms are standardized and reproducible. Testing procedures must be validated, instruments must be calibrated, equipment operators must be appropriately educated and trained, careful records must be kept, and practices must be sterile. Finished medical products must be analyzed for batch-to-batch consistency, and any degradants and minor contaminants must be identified and strictly limited.

Should a system of cannabis-testing laboratories ultimately develop at all, it is hard to imagine that it would be allowed to operate at a different or inferior level to the current U.S. medication-development system. If cannabis dispensaries are allowed to proliferate across the country, our current regulatory system, to which the American Medical Association and all other major U.S. medical associations give their unwavering support, may be seriously undermined.

If there were only a single state with a few dispensaries, the risk might not be as significant. At present, however, 13 states have laws decriminalizing the use of cannabis for medical purposes, and bills are pending in many more states.(100) If such cultivation and distribution activities are deemed to be beyond the reach of the DEA, dispensaries are likely to emerge all over the country.(101)

The United States' International Obligations

Good Science Should Also Guide Decisions Implementing Our Obligations Under International Drug Control Treaties.

President Obama has announced his intention to trust science and research when designing our international, as well as domestic, policies. Sound science should inform and guide this Administration as it implements our international responsibilities in the field of drug control policy. The U.S. -- and thereby the Department of Justice -- has an obligation under our international drug control treaties to control strictly the manufacture and distribution of controlled substances, including the cultivation and distribution of cannabis, within our borders.

In particular, if the U.S. permits the cultivation of cannabis plants for medical use, it must apply the same provisions as are imposed for the cultivation of the opium poppy for medical use. This rigorous system of controls must be maintained by a single government agency. States, therefore, cannot have sole jurisdiction over the proliferation of cannabis dispensaries.

The United States is a signatory to the Single Convention on Narcotic Drugs 1961 ("Single Convention").(102) This treaty was intended to ensure that the production and use of narcotic substances are limited exclusively to bona fide medical and scientific purposes.(103) Accordingly, the Single Convention requires

a party to impose strict controls, not merely on international trade, but also on domestic manufacture, distribution, import, export, and possession of botanically-derived controlled substances (such as coca, opium, and cannabis).

The phrase "medical and scientific purposes" has a clear meaning. The treaty was promulgated at a time when governments around the world were developing regulatory procedures to ensure the quality and safety of medical products.(104) Crude narcotic plant material was not considered suitable for direct medical use. For example, under the treaty, opium smoking was not an accepted method for delivering the therapeutically useful components contained within the herbal material.(105)

The Single Convention recognized that different countries may have different regulatory systems.(106) However, the treaty expected that each party would in good faith adhere to modern scientific standards: that is, employ conventional regulatory standards when determining whether, when, and which, narcotic substances and products could be made available for medical use. Nowhere in the treaty is there any suggestion that a Party may allow a diluted or informal medical system solely for a specific controlled substance such as cannabis.

In response to the activities of medical cannabis proponents, the International Narcotics Control Board (INCB)(107) stressed that a party may not allow cannabis to be cultivated, manufactured, and used for medical purposes unless such products have satisfied the rigorous regulatory standards that apply to other medical products. Such use must be supported by objective scientific data from properly-conducted research studies, and must otherwise accord with principles of modern medicine.(108)

The Single Convention places particularly severe restrictions on the cultivation of cannabis, opium, and coca bush. Article 23 requires that, if a party permits(109) cultivation of opium poppies within its borders, the Party must establish and maintain a national Agency to carry out the Party's obligations. Articles 26 and 28 apply those requirements to the cultivation of the coca bush and the cannabis plant, respectively. Article 23 requires that only nationally-licensed cultivators, whose license specifically identifies the precise extent and location of the land that they are authorized to cultivate, may grow such narcotic plants.(110) They must deliver their total crops to the Agency, and only the national Agency may deal with such crops. The Agency must have the exclusive right of importing, exporting, wholesale trading, and maintaining stocks.(111)

The National Institute on Drug Abuse (NIDA) serves as the U.S. national Agency under the Single Convention.(112) Under the auspices of NIDA, the U.S. maintains a domestic cultivation facility, in which research-grade cannabis is cultivated by the National Center for Natural Products Research at the University of Mississippi under contract with NIDA.(113) This cannabis is supplied to investigators who have research protocols that have been approved by the FDA and by an expert committee of the Public Health Service, and who have obtained research registrations from the DEA.(114) As of April 2004, the University of Mississippi, with the approval of NIDA and the PHS committee,(115) had provided cannabis to more than 17 clinical and preclinical studies funded by the Center of Medicinal Cannabis Research (CMCR) at the University of California San Diego.(116)

If, in the future, cannabis-derived medications were to be developed and approved for marketing, it would not be necessary for the cannabis cultivation (production of starting materials) to take place in the United States. The herbal material, or the Botanical Drug Substance (extracts) could be imported into the U.S. for further formulation. For over 85 years, it has been the policy of the U.S. not to cultivate or produce narcotic raw material (NRM), such as opium, poppy straw, and concentrate of poppy straw (CPS).(117) By long-standing international policy, the U.S. is a country that imports and consumes, rather than one that produces and supplies, NRM.(118) The U.S. relies on a specific list of countries authorized to import NRM into the U.S. in order to meet the legitimate medical needs of the U.S.(119) This list is deliberately kept very short, in order to prevent a proliferation of NRM-producing countries.

Furthermore, the treaty imposes additional controls on all manufacture and distribution of cannabis-derived and other controlled substances. Such activities must be conducted by federally-licensed and regulated entities that are producing standardized products for medical or research purposes.(120) Therefore, were the U.S. to permit dispensaries in various states across the country to distribute(121) or cultivate cannabis for medical use, the U.S. would be in violation of these unmistakably clear treaty obligations. The INCB has confirmed this position:

The control measures applied in California for the cultivation, production and use of cannabis do not meet the control standards set in the 1961 Convention to prevent diversion of narcotic drugs for illicit use. Such standards require, inter alia, the control of cultivation and production of cannabis by a national cannabis agency, and detailed record keeping and reporting on the activities with cannabis, including reporting to INCB.(122)

The Controlled Substances Act Was Enacted in Part to Fulfill Our Obligations Under the Single Convention, and the Proliferation of Cannabis Dispensaries Cannot be Left Solely to State Control.

The federal CSA was enacted, in part, to fulfill the United States ' obligations under the Single Convention (123) The CSA and its implementing regulations have two prongs. They are designed:

1) to ensure that there is a sufficient supply of controlled substances for legitimate medical, scientific, research, and industrial purposes; and

2) to prohibit, deter, and punish the sale and use of controlled substances to illegal purposes.

These goals parallel those of the Single Convention: to ensure that narcotic and other psychoactive substances are manufactured, traded, and used only for legitimate (i.e., evidence-based) medical and scientific purposes. If the DEA were prohibited from shuttering cannabis dispensaries and seizing the materials purveyed therein, the U.S. would have failed to comply with its international responsibilities. If the U.S. does not abide by its treaty obligations, other countries will be unlikely to adhere to theirs. As in other arenas, the U.S. should seek to be a leader with respect to modern medical science and its responsibilities under international agreements.

The CSA achieves its purposes by:

1) establishing a process (scheduling) through which scientific and other data may be used to ensure appropriate levels of control of abuseable substances, and the adequate availability of medications containing them;(124) and

2) creating a "closed" system, in which every importer, exporter, manufacturer, distributor, dispenser, and researcher handling a controlled substance must meet strict licensing, recordkeeping, and security requirements, which are consistent with those required by the Single Convention.

Cannabis dispensaries operate entirely outside of this system of controls. It is hard to see the logic or merit of any position that would relieve cannabis dispensaries from federal oversight, despite the fact that cannabis is a Schedule I substance, while requiring manufacturers and distributors of Schedule II substances to secure DEA registrations, adhere to quotas, keep accurate records, and institute strict security measures. The DEA has both the power(125) and the obligation to curb the proliferation of cannabis dispensaries. It cannot abdicate this responsibility in the name of deferring to states' rights.(126)

Under the Single Convention, the United States must in good faith strive to prevent the non-medical sale and use of controlled substances. A decision by the Administration to prevent the DEA from intervening in cannabis dispensaries, if they are "authorized" under state law, will effectively prevent the agency from enforcing the CSA against cannabis retail storefronts that are merely subterfuges for non-medical distribution of cannabis.

State and local law enforcement do not alone possess adequate resources to stem the proliferation of dispensaries that distribute cannabis for non-medical use. Moreover, local law enforcement needs the assistance of the DEA in combating these operations. These entities do not have access to the highly efficient law enforcement tools that the DEA has at its disposal. For example, local law enforcement cannot utilize federal asset forfeiture laws to deter landlords from permitting cannabis distribution activities to take place on their property.(127) Indeed, attempting to require the DEA selectively to halt only non-medical distribution centers will require the DEA to dissipate its limited resources in a futile line-drawing exercise.

The process of identifying cannabis dispensaries that distribute cannabis for non-medical use would be extremely onerous for a federal agency. In order to fulfill its unquestioned obligation to enforce the CSA's and Single Convention's prohibitions against non-medical distribution, the DEA would be required to examine the records of dispensaries to make the following assessments: the true non-profit nature of the entity; the means by which physician recommendations are verified; the bona fides of members and the relative labor, monetary, or other resource contributions of those members to the non-profit enterprise; the source of the cannabis; and whether it can be determined to have been cultivated in all cases by legitimate members, etc.(128)

Moreover, the DEA's resource-intensive struggle to distinguish between legitimate (under state law) and unlawful (under state law) dispensaries would be compounded by the fact that, increasingly, cannabis dispensaries have delivery services.(129) Such delivery services would make it even more difficult for the DEA to track and evaluate cannabis distribution activities for compliance with state law.

Even for local jurisdictions, detailed state guidelines, such as those issued by the California Attorney General, are difficult enough to interpret and enforce. To require the DEA to take a hands-off approach to any dispensary that may be operating in accordance with such state guidelines would effectively ban the DEA from any significant cannabis interdiction, leading to a free-for-all of cannabis dispensaries across the state and, potentially, across the nation. As a result, cannabis would become readily available for any use—both medical and recreational.(130)

Conclusion

For the reasons stated above, the Obama Administration must take a measured approach in addressing marijuana dispensaries, maintaining the commitment to enforcing the CSA that the Department of Justice has recently reiterated. This commitment must be met even in states that authorize "medical" use of marijuana, and especially where illegal distributors attempt to use state medical marijuana laws as a pretext. We recognize that the Department of Justice and the DEA have limited resources, and those resources must be spent wisely. The United States , however, also has both domestic and international responsibilities to protect the health and safety of patients and to promote the responsible development of modern medications. A fixed Administration ruling against DEA intervention into the operations of

cannabis dispensaries would allow informal, quasi-medical networks to spring up across the nation, thereby putting at risk the critical protections so carefully crafted under the national food and drug legislation of the 20th and 21st centuries.

Author Information

Andrea G. Barthwell, M.D.

Dr. Barthwell is a member of EMGlobal LLC, a firm that advises on public health policy. In the past, she has worked in an advisory capacity for GW Pharmaceuticals Limited and King Pharmaceuticals, Inc., on issues of a public health nature.

Bio: Andrea Barthwell, M.D., F.A.S.A.M., is the former Chief Executive Officer of Human Resources Development Institute, Inc. (HRDI), a community-based behavioral health and human services organization. Dr. Barthwell served from 2002 to 2004 as Deputy Director for Demand Reduction of the Office of National Drug Control Policy, a President-appointed and Senate-confirmed position. She is a former president of the American Society of Addiction Medicine. Dr. Barthwell also is a former member of the National Institute on Drug Abuse and Center for Substance Abuse Treatment National Advisory Councils, as well as the U.S. Food and Drug Administration's Drug Abuse Advisory Committee. She earned her undergraduate degree in Psychology from Wesleyan University in Connecticut and received her M.D. from the University of Michigan. Dr. Barthwell is a member of the global health care and consulting firm EMGlobal LLC.

Michael C. Barnes, Esq.
DCBA Law & Policy

Mr. Barnes is a member of DCBA Law & Policy, a firm that advises on public health policy. In the past, he has worked in an advisory capacity for Alpharma Inc. on issues of a public health nature.

Bio: Mr. Barnes is responsible for strategic growth, business development, and client satisfaction for DCBA Law & Policy and its Center for Lawful Access and Abuse Deterrence (CLAAD). Prior to establishing DCBA in 2004, Mr. Barnes served as confidential counsel in the Office of National Drug Control Policy, where he provided direction on policy and program matters aimed at reducing the demand for illicit drugs. Leading up to his presidential appointment, Mr. Barnes worked for The Perles Law Firm.

Mr. Barnes obtained his Juris Doctor degree from George Mason University School of Law. He earned a master's degree in international economic policy from La Universidad de Belgrano in Buenos Aires, Argentina, where he lived and studied as a Rotary Foundation International Ambassadorial Scholar. He received his bachelor's degree *summa cum laude* from Flagler College.

References

50. Joy, JE, Watson, SJ, Benson JA, Jr. (eds), Marijuana and Medicine: Assessing the Science Base (Washington DC; Institute of Medicine)(1999) at pp.177-78 (hereafter Marijuana and Medicine).

51. Currently popular "vaporizers" eliminate some, but not all, potentially harmful polyaromatic hydrocarbons. Gieringer D, St. Laurent J, Goodrich S. "Cannabis Vaporizer Combines Efficient Delivery of THC with Effective Suppression of Pyrolytic Compounds," Journal of Cannabis Therapeutics. 2004; 4(1):7-27. Vaporizers are also not efficient as a delivery device. Hazekamp A, Ruhaak R, Zuurman L, van Gerven J, Verpoorte R., "Evaluation of a Vaporizing Device (Volcano) for the Pulmonary Administration of Tetrahydrocannabinol," Journal of Pharm. Sci. 2006 June; 95(6):1308-17. See also, McCarberg, W., "Cannabinoids: Their Role in Pain and Palliation," Journal of Pain & Palliative Care Pharmacotherapy, 2007; 21(3): 19-28 (vaporization provides no assurance of consistency of dose or quality with unstandardized plant material). Id. at p. 11.

52. In 2001, in rejecting a petition for the rescheduling of marijuana , the FDA stressed:

The agency cannot conclude that marijuana has an acceptable level of safety without assurance of a consistent and predictable potency and without proof that the substance is free of contamination. If marijuana is to be investigated more widely for medical use, information and data regarding the chemistry, manufacturing and specifications of marijuana must be developed.

DEA, Notice of Denial of Petition, 66. Fed. Reg. 20038, 20045 (April 18, 2001). The agency more recently confirmed its position. FDA, Interagency Advisory Regarding Claims That Smoked Marijuana is a Medicine (April 2004). http://www.fda.gov/bbs/topics/news/2006/new01362.html.

53. California Medical Association, ON-CALL document #1315 (Jan. 2009). http://www.cmanet.org.

54. DEA, Lyle E. Craker; Denial of Application, 74 Fed. Reg. 2101, 2105 (Jan. 14, 2009), citing Letter from Alice P. Mead, GW Pharmaceuticals, PLC, to Christine V. Beato, Acting Asst. Sec. for Health, HHS (Apr. 12, 2005).

55. As technologies advanced, synthetic medicines appeared, necessitating the promulgation of a subsequent treaty, the Psychotropic Convention of 1971.

56. Cannabis was generally not smoked at that time for medical purposes.

57. "Unlike cannabis, the medicinal and recreational forms of opium were clearly distinct. Had medical technology been advanced enough at that time to allow cannabinoids to be identified, formulated, and delivered, the "medical marijuana" movement would probably not have occurred. As with the opium poppy, prescription cannabinoid medications and crude herbal cannabis would have been used in very different venues." McCarberg, WH and Barkin RL, "The Future of Cannabinoids as Analgesic Agents: A Pharmacologic, Pharmacokinetic, and Pharmacodynamic Overview," (2007) American Journal of Therapeutics 14(5); 475-483,476 (emphasis added).

58. Gaoni Y, Mechoulam R, "Isolation, Structure and Partial Synthesis of an Active Constituent of Hashish," Journal Am Chem Soc, 1964; 86:1646-7.

59. Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, et al. "Isolation and Structure of a Brain Constituent that Binds to the Cannabinoid Receptor," Science 1992; 258(5090):1946-9; Howlett AC, Johnson MR, Melvin LS, Milne GM, "Nonclassical Cannabinoid Analgetics Inhibit Adenylate Cyclase: Development of a Cannabinoid Receptor Model," Molecular Pharmacology (1988 Mar) 33(3):297-302.

60. Kalant, H, "Smoked Marijuana as Medicine: Not Much Future," Clinical Pharmacology & Therapeutics, (April 2008) 83:4; 517-519, 517.

61. McPartland JM, Russo EB, "Cannabis and Cannabis Extracts: Greater Than the sum of Their Parts?" Journal of Cannabis Therapeutics. 2001; 1(3-4):103-132.

62. FDA, Guidance for Industry: Botanical Drug Products, 2004, http://www.fda.gov/cder/guidance/4592fnl.pdf (hereinafter Botanical Guidance) at p. 34. ("A botanical product submitted for marketing approval as a drug will be treated like any other new drug under development... [P]revious human experience may be insufficient to demonstrate the safety of a botanical product, especially when it is indicated for chronic therapy.")

63. This is the last stage of human research before the submission of a marketing application or NDA.

64. Montopoli, B., "Obama Announces Stem Cell Decision," CBS News Political Hotsheet (Mar. 9, 2009) (President Obama remarks in full) at p. 2.

65. GW Pharmaceuticals, Research & Development / Cannabis Cultivation. http://www.gwpharm.com/research_cultivation.asp.

66. The original registration was originally granted in 2006, 71 Fed. Reg. 64298 (Nov. 1, 2006), and was recently renewed. 73 Fed. Reg. 9589 (Feb. 21, 2008). Clinical trials began in November 2007. http://www.gwpharm.com/states.asp.

67. Such efforts are not confined to the U.S. ; see, e.g., Echo Pharmaceuticals (the Netherlands) (Namisol, a naturally-derived THC in sublingual tablet form). The U.S. (through NIDA) has also provided research-grade cannabis to a number of researchers whose studies have been funded by grants from the Center of Medicinal Cannabis Research, which is based at the University of California San Diego. The results of a number of these studies have been published (www.cmcr.ucsd.edu/geninfo/marijuana.htm) and respond to the IOM's statements that such clinical trials serve "as a first step toward the development of nonsmoked rapid-onset cannabinoid delivery systems." Marijuana and Medicine, supra, at p. 11.

68. Indeed, even the staunchest herbal cannabis advocates are recognizing the need to develop standardized cannabis pharmaceutical products with "innovative formulations." http://www.phytiva.com.

69. The path of Cannasat is instructive. Cannasat, the only firm in Canada devoted to the development of cannabinoid medications, initially extolled the benefits of herbal cannabis plant material. Recently, it sold off its ownership interests in the cannabis cultivation program operated under contract from Health Canada and is developing synthetic cannabinoids with "proprietary formulations and drug delivery technologies." http://www.cannasat.com/news-5.html. http://www.cannasat.com/.

70. The Institute of Medicine has described the many financial and other challenges that would be faced by a developer of legitimate cannabis-derived pharmaceutical products, even if a parallel, "informal" system of dispensaries did not exist. To allow such dispensaries would increase these disincentives and potentially prevent the U.S. from responding to the IOM's call for the development of rapid-onset, alternative delivery systems for cannabis- or cannabinoid-based products. Marijuana and Medicine, supra, at pp. 193-219.

71. For example, the Elixir Sulfanilamide disaster led to the enactment of the 1938 Food, Drug & Cosmetic Act (FDCA), June 25, 1938, c.675, 52 Stat. 1040, which required, among other things, that new drugs be tested for safety before marketing. The thalidomide tragedy in Europe led to the passage of the Drug Amendments of 1962, Pub. L. 87-781, sec. 1, Oct. 10, 1962, 76 Stat. 780 (also known as the Kefauver-Harris Amendments), which required that products be proved to be both safe and effective before marketing.

72. http://www.fda.gov/cder/drug/infopage/COX2/default.htm. "FDA Estimates Vioxx Caused 27,785 Deaths," (Nov. 4, 2004). http://www.consumeraffairs.com/news04/vioxx_estimates.html.

73. Walker, EP, "Stimulus Bill Gives $1.1 Billion for Comparative Effectiveness Research," MedPage Today (Feb. 19, 2009).

74. Dietary supplements are already subject to a lower standard of regulatory scrutiny because they are presumed to be less dangerous than prescription medications and because they are not intended -- and cannot be labeled or advertised as -- for use in diagnosing, mitigating, treating, or curing disease. See, the Dietary Supplement Health and Education Act of 1994 (DSHEA), 21 U.S.C. §321(ff). Dietary supplements are orally ingested. FDA Botanical Guidance at p. 3.

75. See The Dietary Supplement Health and Education Act of 1994 (DSHEA), Pub. L. 103-417. http://www.fda.gov/opacom/laws/DSHEA.html. Whether a product is a drug under the FDCA turns on its "intended use." "Intended use," in turn, is created by claims made by or on behalf of a manufacturer or distributor of the item to prospective purchasers, such as in advertising, labeling, or oral statements. 21 U.S.C. §321(g)(1)(B); Botanical Guidance at p. 2. Dietary supplement manufacturers, distributors, or retailers cannot make specific health claims. See, e.g., U.S. v. 24 Bottles "Sterling Vinegar and Honey Aged in Wood Cider Blended With Finest Honey Contents 1 Pint Product of Sterling Cider Col, Inc., Sterling, Mass.," 338 F.2d 157 (2nd Cir. 1964); Kordel v. U.S., 335 U.S. 345 (1948).

76. See, e.g., "California Law Enforcement Investigating 'Pot Docs'" (July 8, 2008). http://www.officer.com/web/online/Top-News-Stories/California-Law-Enforcement-Investigating-Pot-Docs/1$31450.

77. Gonzales v. Raich, 545 U.S. 1 (2005).

78. Calif. Health & Safety Code §111550.

79. If physicians prescribe unapproved medications (those that are not approved by the state or federal regulatory agency), and a patient suffers harm as a result, the physician's professional liability policy may not cover a claim for damages. See, Educating Voices "The Potential Medical Liability for Physicians Recommending Marijuana as a Medicine," (white paper). http://www.educatingvoices.org/EVI_WhitePaper1.pdf.

80. Wyeth v. Levine, 555 U.S. ___ (Mar. 4, 2009).

81. 42 Fed. Reg. 39,768-39,795 (1977).

82. Bone, M., MD, "Laetrile Drug Never Proved to be Effective Cancer Treatment," The Palm Beach Post (Mar. 20, 2008).

83. Wilson, B., MD, "The Rise and Fall of Laetrile." http://www.quackwatch.org/01QuackeryRelatedTopics/Cancer/laetrile.html.

84. Moertel CG et al., "A Clinical Trial of Amygdalin (Laetrile) in the Treatment of Human Cancer," New England Journal of Medicine 1982; 306(4):201-6. Nevertheless, even at present, companies continue to promote and sell Laetrile as a cancer treatment through internet web sites. See, e.g., FDA Talk Paper, "FDA Takes Action Against Firms Marketing Unapproved Drugs," (Sept. 6, 2000). http://www.fda.gov/bbs/topics/ANSWERS/ANS01032.html.

85. See, National Conference of Commissioners on Uniform State Laws. http://www.nccusl.org/nccusl/uniformact_summaries/uniformacts-s-ucsa90.asp. Calif. Health & Safety Code §§11000-11651.

86. For example, Salvia divinorum (whose active constituent is salvinorin A) is an herb that is increasingly used by the public for its hallucinogenic effects. Salvia is not currently controlled under the CSA, although the DEA is observing it closely. As of November 2008, thirteen states had enacted legislation placing regulatory controls on Salvia divinorum and/or salvinorin A; a number of those states placed the substances in schedule I of state law. Proposed legislation is pending in a number of other states. DEA, "Drugs and Chemicals of Concern," Nov. 2008. http://www.deadiversion.usdoj.gov/drugs_concern/index.html.

87. The Research Advisory Panel (RAP) of the California Attorney General's office must approve all Schedule I and II research projects and protocols. Calif. Health & Safety Code §§11480-81. http://caag.state.ca.us/research.

88. DEA, State Prescription Drug Monitoring Programs. http://www.deadiversion.usdoj.gov/faq/rx_monitor.htm. When controlled substances are at issue, the federal government also has authority to regulate directly some aspects of a physician's medical practice. Under the CSA, physicians who prescribe or dispense controlled substances must hold a registration from the DEA, and such controlled substances must be prescribed for a legitimate medical purpose and in the course of regular professional practice. 21 C.F.R. §1306.04(a); U.S. v. Moore, 423 U.S. 122, 137, 140-42 (1975). Although states bear the primary responsibility for preventing and punishing the diversion of (prescription) controlled drugs by health care providers, the DEA in egregious cases may investigate and revoke the registration of (and even criminally prosecute) a physician or other health care provider who facilitates and/or promotes drug abuse and addiction.

THE JOURNAL OF
GLOBAL DRUG POLICY AND PRACTICE

A Review of the Research on the Risks and Harms Associated to the Use of Marijuana

Jordan Diplock, Irwin Cohen, and Darryl Plecas

Abstract

The truth about the risks and harms associated to personal marijuana use is rarely a feature of the ongoing debate over the legal status of the drug, with advocates on both sides at fault. Some consensus over the potential harms needs to be reached before any meaningful discussion can occur on this issue. This article reviews research published between 2000 and 2007 and suggests that there are many risks associated to marijuana use with regards to impairment, academic and social development, general and mental health, and continued drug use. Although some findings highlight very serious concerns for users, the numbers that become adversely affected by marijuana use do not represent the majority of users. A debate on the legal status of marijuana based on the facts about the risks and harms of this drug will greatly aid in determining the appropriate actions to address personal marijuana use around the world.

Keywords: Academic Performance; Gateway; Harms; Health; Impairment; Marijuana; Mental Health; Risks

Introduction

The debate over the personal use of marijuana in North America and around the world is extremely contentious with supporters for decriminalization and legalization, and others who assert the importance of strict prohibition. The exceptionally adversarial nature of this debate is likely one of the main obstacles to determining the most appropriate way to address marijuana use within society. As a result of interested parties remaining resolute in their particular positions, the marijuana debate often becomes characterized by selective reporting or the misuse or misinterpretation of the available information. In addition, the popular debate rarely transcends ideological arguments on marijuana's potential harms. With proponents of legalization championing marijuana as a benign drug and prohibitionists stressing its dangerousness, the debate often fails to consider the totality of the empirical research evidence. The purpose of this review is to discuss the harms associated with marijuana use from an objective viewpoint to provide a basis for the development of further research on how to best address the issues of marijuana use.

As research on marijuana use and its effects is constantly providing additional information, the full extent of the effects of marijuana on users will likely not be known conclusively in the near future. This should not be regarded negatively, as it is the nature of research that future studies improve upon the methodologies and results of previous research. For example, in 1997, *The Independent*, a popular British newspaper, was a strong supporter of the decriminalization of marijuana in the United Kingdom . In part, this support led to a pro-cannabis march that pressured the government to downgrade the classification of marijuana (1). Ten years later, that newspaper printed a public apology for its leadership role in the legalization campaign with a headline stating "If only we had known then what we can reveal today" (1). This example demonstrates the importance of considering new evidence and being willing to refine one's position based on the best available information. By reviewing the current research on the potential harms associated with marijuana use, this review intends to synthesize the best evidence to inform the debate.

Ensuring that one considers the most current research on marijuana use is not only important because of the changing nature of academic research, but also because the drug under study has changed over the years. In other words, marijuana does not refer to cannabis with a particular level of Δ^9-Tetrahydrocannabinol (THC). Over time, the level of THC in marijuana has changed; typically, it has increased. However, because there have been very few studies on the changes in potency of marijuana over the years, it cannot be confirmed conclusively that marijuana users in the 1970s were typically consuming a different drug than today's users. The information that does exist suggests that, on average, marijuana users today are exposed to higher levels of THC than in past decades. Research on potency trends of seized marijuana between 1980 and 1997 concluded that average THC levels of marijuana seized in the United States increased from less the 1.5% in 1980 to approximately 3% in the early 1990s, to over 4% in 1997 (2). Moreover, in an article published by the Drug Enforcement Administration (DEA), Newell (3) reported that average THC concentrations in marijuana from 36 samples seized in the state of Florida in 2002 were over 6%. These levels were determined to be at par with the averages reported by the Marijuana Potency Monitoring Project (3). In Canada , the Royal Canadian Mounted Police [RCMP] (4) reported that on average seizures of marijuana in Canada had THC concentrations over 10%. Seizures in Europe of imported marijuana typically had THC levels between 2% and 8%, but the potency of hydroponically-grown "skunk" may be as high as double that of the imported marijuana (5). However, it must be kept in mind that the nature of marijuana production and distribution is such that a regular user would likely be exposed to marijuana of various different concentration levels of THC. As the majority of marijuana production remains the industry of criminals, many of whom use hydroponic operations and

Irwin Cohen is a professor in the School of Criminology and Criminal Justice and the Director of the BC Centre for Social Responsibility.

Darryl Plecas

Darryl Plecas is the RCMP Research Chair and Director, Centre for Criminal Justice Research in the School of Criminology and Criminal Justice at the University of the Fraser Valley.

References

1. Owen, J. Cannabis: An apology. The Independent. 2007 Mar 18 [cited 2008 Mar 19]. Available from http://news.independent.co.uk/health/article2368994.ece

2. ElSohly MA, Ross SA, Mehmedic Z, Arafat R, Yi B, Banahan BF. Potency trends of 9-THC and other cannabinoids in confiscated marijuana from 1980 – 1997. J Forensic Sci. 2000;45(1):24–30.

3. Newell, CJ. Potency of cannabis seized in central Florida during June 2002. Microgram Journal. 2003 [cited 2007 Nov 20];1:37-39. Available from http://www.usdoj.gov/dea/index.htm

4. Royal Canadian Mounted Police. Drug situation in Canada – 2006 [Internet]. Ottawa: RCMP; 2007 [cited 2009 May 26]. Available from http://www.rcmp-grc.gc.ca/drugs-drogues/drg-2006-eng.htm

5. King LA, Carpentier C, Griffiths, P. Cannabis potency in Europe. Addiction. 2005;100(7):884 – 886.

6. ElSohly MA, Slade, D. Chemical constituents of marijuana: the complex mixture of natural cannabinoids. Life Sci. 2005;78:539-548.

7. United Nations Office on Drugs and Crime. World Drug Report. 2007 [cited 2008 Feb 21]. Available from http://www.unodc.org/unodc/en/data-and-analysis/WDR-2007.html

8. Copeland J, Gerber S, Swift W. Evidence-based answers to cannabis questions: a review of the literature. Canberra: Australian National Council on Drugs; 2007.

9. Voth EA. Marijuana and cannabinoid research: current status and future potential. The Journal of Global Drug Policy And Practice. 2006[cited 2008 May 1];1(1):[about 5 p.]. Available from http://www.globaldrugpolicy.org/previous.php

10. Palys T S. Research Decisions: Quantitative and Qualitative Perspectives, 2nd ed. Toronto: Harcourt Brace & Company; 1997.

11. Howard RC, Menkes DB. Changes in brain function during acute cannabis intoxication: preliminary findings suggest a mechanism for cannabis-induced violence. Crim Behav and Ment Health. 2007;17:113–117.

12. Ilan AB, Smith ME, Gevins A. Effects of marijuana on neurophysiological signals of working and episodic memory. Psychopharmacology . 2004;176:214–222.

13. Kanayama G, Rogowska J, Pope HG, Gruber SA, Yurgelun-Todd DA. Spatial working memory in heavy cannabis users: a functional magnetic resonance imaging study. Psychopharmacology. 2004;176:239–247.

14. O'Leary DS, Block RI, Koeppel JA, Schultz SK, Magnotta VA, Laura BP, et al. Effects of smoking marijuana on focal attention and brain blood flow. Human Psychopharmacology: Clinical and Experimental. 2007;22:135–48.

15. Ramaekers JG, Kauert G, Van Ruitenbeek P, Theunissen EL, Schneider E, Moeller MR. High-potency marijuana impairs executive function and inhibitory motor control. Neuropsychopharmacology. 2006;31:2296–2303.

16. Bedard M, Dubois S, Weaver B. The impact of cannabis on driving. Can J Public Health: 2007;98(1):6–11.

17. Blows S, Ivers RQ, Connor J, Ameratunga S, Woodward M, Norton R. Marijuana use and car crash injury. Addiction. 2005l;100:605–611.

18. Kalant H. Adverse effects of cannabis on health: an update of the literature since 1996. Prog Neuropsychopharmacol Biol Psychiatry. 2004;28:849–863.

19. Khiabani HZ, Bramness JG, Bjornboe A, Morland J. Relationship between THC concentration in blood impairment in apprehended drivers. Traffic Inj Prev. 2006;7(2):111–116.

20. Laumon B, Gadegbeku B, Martin J, Biecheler M. Cannabis intoxication and fatal road crashes in France : population based case-control study. Br Med J. 2005;331:1371–1376.

21. Papafotiou K, Carter JD, Stough C. An evaluation of the sensitivity of the Standardised Field Sobriety Tests (SFST) to detect impairment due to marijuana intoxication. Psychopharmacology. 2005;180:107-114.

22. Ramaekers JG, Robbe HWJ, O'Hanlon JF. Marijuana, alcohol and actual driving performance. Hum Psychopharmacol: Clin Exp. 2000;15:551–558.

23. Pope HG, Gruber AJ, Hudson JI, Cohane G, Huestis MA, Yurgelun-Todd D. Early-onset cannabis use and cognitive deficits: What is the nature of the association? Drug Alcohol Depend. 2003;69:303–310.

24. Tapert SF, Schweinsburg AD, Drummond SPA, Paulus MP, Brown SA, Yang TT, et al. Functional MRI of inhibitory processing in abstinent adolescent marijuana users. Pyschopharmacology. 2007;194:173–183.

25. Pope, HG, Gruber, AJ, Hudson, JI, Huestis, MA, & Yurgelun-Todd, D. Neuropsychological performance in long-term cannabis users. Arch Gen Psychiatry. 2001;58:909–915.

26. Schneider JT, Pope HG, Silveri MM, Simpson NS, Gruber SA, Yurgelun-Todd, DA. Altered regional blood volume in chronic cannabis smokers. Exp Clin Psychopharmacol. 2006;14:422–428.

27. Bovet P, Viswanathan B, Faeh D, Warren W. Comparison of smoking, drinking, and marijuana use between students present or absent on the day of a school-based survey. J Sch Health. 2006;76(4):133–137.

28. Lynskey M, Hall W. The effects of adolescent cannabis use on educational attainment: a review. Addiction. 2000;95:1621-1630.

29. Fried P, Watkinson B, James D, Gray R. Current and former marijuana use: preliminary findings of a longitudinal study of effects on IQ in young adults. Can Med Assoc J. 2002;166:887–891.

30. Diego MA, Field TM, Sanders CE. Academic performance, popularity, and depression predict adolescent substance use. Adolescence. 2003;38:37–42.

31. Jeynes WH. The relation between the consumption of various drugs by adolescents and their academic achievement. Am J Drug Alcohol Abuse. 2002;28(1):15–35.

32. Eisen SA, Chantarujikapong S, Xian H, Lyons MJ, Toomey R, True WR, et al. Does marijuana use have residual adverse effects on self-reported health measures, socio-demographics and quality of life? a monozygotic co-twin control study in men. Addiction. 2001;97:1137–1144.

33. Green KM, Ensminger ME. Adult social behavioural effects of heavy adolescent marijuana use among African Americans. Dev Psychol. 2006;42:1168–1178.

34. Schuster C, O'Malley PM, Bachman JG, Johnston LD, Schulenberg J. Adolescent marijuana use and adult occupational attainment: A longitudinal study from age 18 – 28. Subst Use Misuse. 2001;36:997–1014.

35. Aldington S, Williams M, Nowitz M, Weatherall M, Pritchard A, McNaughton, A, et al. Effects of cannabis on pulmonary structure, function and symptoms. Thorax. 2007;62:1058–1063.

36. Earleywine M, Barnwell SS. Decreased respiratory symptoms in cannabis users who vaporize. Harm Reduct J. 2007[2007 Nov 21];4(11):[about 4 p.]. Available from http://www.harmreductionjournal.com/

37. Hazekamp A, Ruhaak R, Zuurman L, Van Gerven J, Verpoorte R. Evaluation of a vaporizing devince (Volcano) for the pulmonary administration of tetrahydrocannabinol. J Pharm Sci. 2006;95:1308–1317.

38. Moore BA, Augustson EM, Moser RP, Budney AJ. Respiratory effects of marijuana and tobacco use in a U.S. sample. J Gen Intern Med. 2004;20:33–37.

39. Sarafian TA, Habib N, Mao JT, Tsu I, Yamamoto ML, Hsu E, et al. Gene expression changes in human small airway epithelial cells exposed to 9-tetrahydrocannabinol. Toxicol Lett. 2005;158:95–107.

40. Sarafian TA, Habib N, Oldham M, Seeram N, Lee R, Lin L, et al. Inhaled marijuana smoke disrupts mitochondrial energetics in pulmonary epithelial cells in vivo. American Am J Physiol Lung Cell Mol Physiol. 2006;290:1202–1209.

41. Tashkin DR, Baldwin GC, Sarafian T, Dubinett S, Roth MD. Respiratory and immunological consequences of marijuana smoking. J Clin Pharmacol. 2002;42:71–81.

42. Taylor DR, Hall W. Respiratory health effects of cannabis: position statement of the Thoracic Society of Austra

compete with each other to produce the most and the 'best' marijuana, there is no reason to believe that the quality of street marijuana has remained consistent over time.

In addition to levels of THC, the understanding of the number of different constituents of marijuana and their potential to interact with each other changes over time. ElSohly and Slade (6) reported that the number of known natural compounds in marijuana increased from 423 to 489 between 1980 and 2005. Of those numerous chemicals, 70 were Cannabinoids, 9 of which were discovered since 1980 (6). The changes in knowledge about the complex chemical makeup of marijuana further complicate the study of the potential dangers of its use.

Because marijuana is used around the world by approximately 160 million people, there has been a great deal of research conducted on its effects on users (7). The use of marijuana results in a variety of changes within the user's body that can have a range of effects (8). Given this, the focus of this review is limited to the research evidence on potential harms associated with marijuana use in the areas of: impairment; academic and social development; general physical health; mental health; and continuing drug use. Although there is also a substantial body of research on the medical use of marijuana for particular patients, a review and discussion of the research on medical marijuana is not included in this study. This exclusion is not meant to suggest that marijuana is universally accepted as a safe or effective treatment for any illness, as Voth (9) has clearly demonstrated that the wider debate over the use of marijuana extends into the issue of the drug's medical use. The discussion presented in this review will concentrate on the use of marijuana within the general population and the empirical evidence for how marijuana use effects the general population in the five previously listed areas.

Methodology

To ensure that this review considered the most current research, information was collected from articles published from 2000 to 2007. Articles were identified by searching a number of databases, including Medline, PubMed, PsychINFO, and Google Scholar. To ensure a more complete search, a variety of keywords were combined with 'marijuana' to search the databases. In particular, these keywords related to the five aforementioned areas. An extremely partial list of keywords included 'impairment', 'academics', 'heart disease', 'respiratory', 'cancer', 'psychosis', and 'gateway'.

Once an article was identified, it was assessed for appropriateness based on a review of the article's title and abstract. One potential limitation of this review was that only full-text-available articles written in English were considered for this review. However, in order to expand the number of articles considered, both original research studies and articles that reviewed topics related to the harms of marijuana use were included. In order to ensure objectivity in the selection process, the inclusion or rejection of articles occurred without consideration of authorship or the conclusions or recommendations made by the authors. Given this, the articles considered in this review represented the continuum of current research on the harms that may be associated with marijuana use. Because of the scope of this topic and the amount of literature on marijuana use, the articles included in this review do not represent all available research on the effects of marijuana use. However, because many of the articles included in this review included extensive reviews of previous literature, the areas of focus for this review were well represented.

Finally, when considering the evidence presented in this review, it is critical to keep in mind that many of the studies based their results and conclusions on self-reported effects of marijuana use by the users themselves. While self-report studies are extremely valuable, they are susceptible to a variety of methodological problems, such as social desirability effects, errors in memory, exaggeration, and deception, which must be considered when evaluating results or conclusions (10). In addition, it is also extremely difficult to link or establish a direct causal relationship between drug use and other specific behaviours as it is likely that behaviours or outcomes are the result of multiple factors, rather than exclusively one factor, such as drug use.

Marijuana Related Impairment

One of the important debates in the research literature is the effect of marijuana use on cognitive and motor skills. Several studies have focused on determining whether there are any negative effects on cognitive or motor skills within hours of marijuana use (11 - 15). A number of studies have more specifically focused on the effect of marijuana use on abilities related to operating a motor vehicle (16 - 22). In addition to studies of short-term impairment, research has been conducted on long-term impairments associated with prolonged marijuana use (23 - 25).

Short-term Impairment

Impairment immediately after the consumption of marijuana may be a concern for users and the community at large. Short-term impairment has generally been assessed anywhere from 5 – 10 minutes to several hours after use. Testing the effects of marijuana on working and episodic memory (12) determined that focusing attention and response accuracy were impaired immediately after smoking marijuana, even marijuana with less than 4% THC. The authors (12) concluded that the marijuana resulted in difficulty maintaining a coherent train of thought and disruptions to selective filtering processes, both of which impaired memory. Similarly, another study (11) reported that acute marijuana intoxication was accompanied by impairment of brain function related to goal-oriented activities. Further, it was suggested that marijuana consumption inhibited impulse and anger control in some users implying a possible link between marijuana use and violent or antisocial behaviour in some individuals (11). However, impaired attention was not found in a study of marijuana's effects on auditory focused attention tasks (14) where participants responded to a tone by pressing a button as quickly as possible. Results of an examination of brain functioning hours after using marijuana (13) found that heavy marijuana users did not present

impaired abilities on simple spatial working memory tasks, as deficits were compensated for by employing regions of the brain not commonly used during such tasks.

Although the research reported that short-term cognitive impairment could occur among marijuana users, the level of impairment and its seriousness was not significant. However, this does not suggest that there are no or few short-term risks of impairment. Instead, this conclusion may be due to the small sample sizes of only 10 to 12 participants in the studies examined (12 - 14). In effect, the sample sizes in these studies limited the ability to draw any firm conclusions about the range or seriousness of short-term cognitive impairments associated with marijuana consumption.

Researchers also examined the relationship between marijuana induced cognitive impairment and common abilities, activities, or behaviours, such as operating a motor vehicle. Ramaekers and coworkers (15) concluded that decision-making, planning, tracking, reaction time, and impulse control were impaired by high-potency marijuana. Although the 20 subjects were considered only light users, substantial impairment of executive and motor functioning for a period of at least six hours was found. Although the 13% THC level in the marijuana used in this study (15) was higher than the averages reported by the DEA (3) and RCMP (4), this study demonstrated that serious impairment lasting for many hours was common when consuming high potency forms of marijuana.

Operating a motor vehicle can be dangerous at any time. However, doing so while impaired by marijuana significantly increases the risks of accident. Although some studies revealed that recent marijuana use was a causal factor for only a small proportion of accidents(89), short-term marijuana impairment does contribute to serious motor vehicle accidents (16, 17, 20). To better determine marijuana impairment among drivers, standardized field sobriety tests have been designed to detect impairment by marijuana in a manner similar to alcohol. Research on field tests concluded that, as expected, impairment increases with the level of THC (19, 21). Even low levels of THC can moderately impair driving abilities, but driving is severely impaired when either higher levels of THC marijuana is consumed or marijuana with lower levels of THC is consumed with even small amounts of alcohol (22). Considering the research examined for this review on the relationship between marijuana consumption and impairment, there appears to be a strong consensus that marijuana use has a negative and potentially harmful effect on driving.

Long-term Impairment

There are few studies on the long-term impairment of chronic marijuana consumption compared to the acute effects of marijuana use. Still, some researchers examined the potential for impairment as a result of long-term use, even during periods of abstinence (23-25). From the results of one study of older participants (33-50 years old), it appeared that, although heavy marijuana users showed impaired cognitive abilities after a week of abstinence, there were no noticeable impairments after twenty-eight days of abstinence (23). When compared to a control group, long-term marijuana using teens (aged 16 – 18) had equivalent task performance on a go/no-go task after twenty-eight days of abstinence (24). However, marijuana users committed more errors on cognitive tests and showed increased brain processing effort during the inhibition task (24). When comparing early-onset users to late-onset users, even after twenty-eight days of abstinence, early-onset frequent marijuana users had a greater likelihood of suffering a range of cognitive functioning impairments, in particular verbal IQ, compared to late-onset and non-users (25).

One interesting finding about long-term marijuana users was that there was an increase in brain activity in more regions of the brain when performing a variety of cognitive tests when compared to non-users. The researchers concluded that this finding was the result of the brain working harder and differently to overcome the deficits resulting from the marijuana use (13,24). In addition to working harder and differently, significantly increased blood volumes in various regions of the brain have been discovered (26), even after a period of abstinence of six to thirty-six hours. The researchers (26) indicated that it remained unknown how these changes affected brain functioning and whether these changes were permanent, long-lasting, or temporary. However, these findings do suggest that there is a potential for some type of long-term brain impairment. Nonetheless, with the exception of impairments caused by psychosis and other mental illnesses discussed later in this review, when considering the totality of the research literature on the relationship between marijuana use and long-term cognitive or motor impairment, there appears to be little evidence to support the assertion that serious impairment is a likely result from long-term marijuana use, especially after a period of abstinence.

The Effects of Marijuana Use on Academic and Social Development

As marijuana is the drug of choice for many young people, it is necessary to understand whether marijuana has any negative effects on academic performance and the transition from adolescence to adulthood. The evidence for both immediate impairment and the possibility of longer-term impairment supports the notion that marijuana use may have negative consequences on the development of young users. In a consideration of academic performance and graduation, a number of studies have focused on the relationship between marijuana use and absenteeism (27, 28), I.Q. (29), and academic achievement (28, 30, 31). By examining the lifestyles of adults who reported being heavy marijuana users in their youth, other researchers have attempted to assess the effects of marijuana use on social development (32 - 34) The following section provides a discussion of the literature in these areas.

Marijuana and School Performance

There are many factors that contribute to academic achievement, such as general intelligence,

interest/curiosity, motivation, lifestyle, and social relationships/networks. Since the adolescent human brain is still developing, it is possible that recreational marijuana use may disrupt 'normal' development, which may manifest in, among other things, poorer school performance. Survey research (27) revealed that students who were absent(90) on the day of a school-based survey were more likely to use marijuana, alcohol, and cigarettes than students who were present. Although it is unsupportable to conclude that one specific day of absence from school was caused by or related to marijuana use, this study provides some small support for the more impressive findings of Lynskey and Hall's review (28) of cross-sectional studies on marijuana and school-related issues. Their review of over 50 research studies concluded that marijuana appeared to have a strong relationship with absenteeism, lack of retention, and not graduating.

An examination of the relationship between academic achievement and drug use in a diverse sample of 18,726 students (31) concluded that marijuana use, when examined alone, was statistically significantly related to lower standardized test scores in math, science, reading, and social studies. Average scores on the math comprehension test for marijuana users were further below the mean than on any other test, while reading comprehension appeared to be affected the least. However, when marijuana was combined with alcohol or cigarettes, the results were much less robust. In effect, both regular smoking and alcohol intoxication explained much more of the variance, thus reducing the influence of marijuana on test scores. (91) The explanation provided for this finding was the relatively small number of students who reported ever being under the influence of marijuana at school compared to the number of students who regularly used alcohol and/or cigarettes at school (31). Similarly, a study by Diego and colleagues (30) found that grade point averages decreased as the reported frequency of marijuana use increased. Marijuana use had a larger negative correlation with grade point average as frequency of use increased than alcohol or cigarettes(92) (30). While these findings suggested a link between marijuana use and academic achievement, the research could not establish a direct causal relationship or the direction of the relationship. Nonetheless, for the most part, social scientists agree that marijuana use is detrimental to school performance (28, 31).

Since marijuana has been linked to short-term impairment and a decrease in school performance, some researchers have studied the effects of marijuana on IQ (29). However, measuring the direct effects of marijuana use on IQ has been difficult as there is rarely a baseline measure of a subject's IQ prior to their initiation into marijuana use (8). One longitudinal study that had baseline measures of IQ prior to the subject ever using marijuana (29) reported a statistically significant decrease in IQ score among individuals who smoked five or more marijuana cigarettes per week. On average, a 4.1 point decrease was measured between the time the subject was 9 – 12 years old (no prior use) and 17 – 20 years old (current and/or past use). However, when considering the degree of marijuana use for the sample of 70 marijuana users, only those characterised as heavy users showed any decreases in IQ compared to slight users, former users, and non-users who demonstrated increases in IQ (29). These results suggested that marijuana use has an effect on general intelligence but is more severe for regular and chronic marijuana users.

Marijuana Use and Later Social Development

Success in adulthood is related to a wide range of developmental and social variables throughout childhood and adolescence. It has been hypothesised that many of these contributing dynamics could be negatively affected by the use of marijuana. For example, some people contend that one of the possible outcomes of marijuana use is chronic low motivation. In effect, the hypothesis is that marijuana use among young people contributed to the development of low motivation which has long-term effects on school and employment performance. In their research, however, Lynskey and Hall (28) concluded that there was little evidence to support the low motivational syndrome hypothesis because the majority of supportive evidence was based on older uncontrolled studies of case histories and observational reports, while controlled field or laboratory studies did not find compelling evidence of such a syndrome. Moreover, long-term (over 20 years), regular marijuana use among males was not associated with any specific negative socio-demographic effects such as alcohol or nicotine abuse or dependence, hospitalizations, and health-related quality of life (32).

However, other researchers have found several adverse associations between marijuana use and social development. A study of the relationship between marijuana use in 2,842 high school students and later occupational attainment concluded that marijuana had some differential negative associations with occupational attainment for males and females (34). Specifically, for males, self-reported abstinence or low frequency use of marijuana had no effect on occupational attainment, although high prestige jobs(93) typically had a greater percentage of non-users or former low frequency users. However, for male users, after a certain threshold level was passed, success in occupational attainment decreased with increased early marijuana use. The threshold for this relationship in this study was ambiguous as the linear relationship began with the category associated to between 3 and 39 occasions of marijuana use in one year. Among females, early marijuana use was found to have strong negative outcomes on occupational attainment, but the pattern was different from that of males, lacking the easily identifiable threshold and negative linear relationship (34).

Green and Ensminger (33) examined the effects of marijuana use on a variety of social variables among a cohort of 530 African Americans. Frequent adolescent marijuana use was associated with poorer academic achievement, a lack of stable employment, and family dysfunction. These results suggested that using marijuana 20 or more times during adolescence was associated with being unemployed, unmarried,

and becoming a parent while unmarried. Early marijuana use was also linked to dropping out of school and continued marijuana use as an adult (33). Although this study was specific to African Americans, when considered with other studies on occupational attainment and school performance, these results contribute to the body of literature indicating that marijuana use among young people can have a detrimental outcome on their future. However, these findings do not confirm a causal relationship between marijuana use and poor performance in school or life. Still, the evidence does suggest that, even in the absence of a direct causal link, the use of marijuana during adolescence, for many young people, is often accompanied by other factors, such as the development of delinquent peer associations or a general lack of commitment to pro-social activities and institutions, which can lead to problems with social development.

General Health Consequences of Marijuana Use

The use of marijuana introduces foreign substances into the body and produces a number of chemical changes in the user's brain and body. Given this, there is a large amount of literature focusing on the physical effects of marijuana. To begin, there is little evidence to suggest that marijuana use poses a serious risk for an overdose death or its infrequent use is related to the development of long-term health problems (8). Given this research, the majority of health-related studies focused on the potential harmful health outcomes associated with long-term and heavy marijuana use. One of the most widely studied issues is the relationship between smoking marijuana and the development of respiratory ailments (18, 35 - 44).

In addition, the short-term and long-term effects of marijuana use on the circulatory system have also been extensively studied (45 - 49). Other researchers have focused on potential reproductive harms (50 - 57), the effects of marijuana use on the immune system (41, 58), and the risks for cancers (18, 59 - 66). There is also a burgeoning research literature on the degree to which marijuana users can develop a dependency and experience withdrawal symptoms (67, 68). The following section will review the research literature on these important issues.

Respiratory Ailments Related to Marijuana Use

The most common way of using marijuana is by smoking it. A direct consequence of this method of consumption is that smoke must enter the airways and lungs of the user. As a result, researchers are interested in the amount and type of harm that smoking marijuana has on the respiratory system of users. This is particularly important because marijuana smoke contains many of the same poisons found in tobacco smoke. Given this, research has focused on determining whether the respiratory outcomes of smoking marijuana are similar or worse than those associated with smoking tobacco (8). Taylor et al. (43) reported that respiratory symptoms were significantly more prominent in marijuana-dependent users than in non-users. The sample consisted of 21 year old subjects from the 1970s who self-reported short histories of smoking marijuana (43). The associated self-reported respiratory problems included wheezing, shortness of breath after exercise, nocturnal chest tightness, and early morning phlegm and mucus. These symptoms, which are typically indicative of chronic bronchitis, were also found to be associated with smoking marijuana in other research (38).

In their review of the research literature, Taylor and Hall (42) argued that marijuana should be considered as damaging to the airways as tobacco and that there was a strong possibility that smoking marijuana was a contributing factor to the development of chronic lung disease. Further research (44) concluded that long -term marijuana smoking was also associated with an increase in airflow obstruction and obstructive lung disease. A comparison of the effects of marijuana cigarettes to tobacco cigarettes (35) concluded that one marijuana cigarette can have the obstructing effects on the lungs equal to that of two to five tobacco cigarettes. Lower lung density and increased total lung capacity were also recorded for marijuana smokers, but macroscopic emphysema was not found to be a common symptom (35). These findings suggested that serious negative respiratory outcomes should be expected for regular marijuana smokers, regardless of the marijuana's THC levels, even among youth or young adults.

Since many of the detrimental effects on the respiratory system are the direct result of smoking, there have been several studies examining whether vaporizers provide a less harmful way to consume marijuana (36, 37). Based on self-reported respiratory symptoms after using vaporizers to inhale marijuana cannabinoids, Earleywine and Barnwell (36) concluded that vaporizers did provide some measure of safety, especially as the amount of marijuana inhaled increased. Hazekamp et al. (37) reached a similar conclusion.

While the use of vaporizers may reduce or eliminate some of the respiratory ailments for users, the THC in marijuana may pose a respiratory risk. In response to the presence of THC, human airways experience cellular changes, especially to mitochondrial energetics, which are responsible, in part, for the health of cells and their energy production (39, 40). Sarafina et al. (39) described these changes as deleterious effects, as changes to the mitochondria of lung cells affects the viability and functioning of those cells. These changes were more significant with higher concentrations of THC and longer exposure times (39) In effect, as a result of THC in the lungs and airways, the risk of adverse pulmonary conditions is substantially increased by the potential for damage to the airway epithelial cells (39, 40).

Potential Harms of Marijuana Use on the Heart and Circulatory System

One direct outcome from using marijuana is an immediate increase in heart rate. It is estimated that marijuana use increases the heart rate 20% to 50% immediately following consumption (8). This has led researchers to examine the short and long-term implications of marijuana use on the heart and the circulatory system. The majority of research in this area relies on case studies (46, 47, 49). Although the conditions documented in the research literature may be serious, it must be kept in mind that there is little evidence to suggest that the outcomes discussed in the case studies are typical or the norm for marijuana users.

Based on their case study of a 34-year-old man who reported heart fluttering and near syncope after marijuana use, Rezkalla and coworkers (49) suggested that marijuana was a likely contributor to the decrease in coronary blood flow and ventricular tachycardia experienced by their subject. Another study (47) described two cases; one in which a man with a history of heart problems suffered arrhythmia precipitated by marijuana use, the second described a young patient who suffered an onset of myocardial infarction. The researchers (47) concluded that marijuana was a serious concern for those who may be predisposed to heart-related illnesses. Similarly, Caldicott et al. (46) documented the case of a young patient who suffered a heart attack after marijuana use, despite having no other identifiable risk factors for a cardiac event.

Findings may be more informative when referring to larger samples that identify cardiac risks associated with marijuana use. One study concluded that, although it was less common than other stressors, marijuana use was a trigger for myocardial infarction (48)(94). In this study (48), the risk of onset of myocardial infarction increased approximately five-fold in the first hour after use.(95)

The conclusion of existing research is that marijuana use may, in rare instances, trigger a heart attack. However, it is important to recognise that the evidence in support of this conclusion may be confounded by the subject's participation in a wide range of other unhealthy habits that may also contribute to a greater or lesser degree to a heart attack. Still, there is some evidence to conclude that marijuana is harmful to the heart and researchers, such as Aryana and Williams (45), have stated a belief that heart problems related to marijuana use may be more common than is currently recognized. In addition, they warned that as the population of marijuana users aged, continued use may increase the risk for a number of adverse cardiovascular issues, such as tachyarrhythmia, acute coronary syndrome, vascular complication, and congenital heart defects (45).

Consequences of Marijuana Use on Reproduction and Pregnancy

There is a growing body of literature on the effects of drug use on sperm and egg development and the short and long-term outcomes for the foetus. This literature focuses on the relationship between drug use and implications for fertility and healthy, successful pregnancy. For example, several studies have investigated the effects of marijuana use on male sperm fertility (55, 57) and female hormones (52, 54). Scheul et al. (55) found that the presence of THC in the reproductive fluids of both males and females could inhibit the ability of sperm to complete fertilization. Other research (57) reported that THC inhibited male fertility by binding to sperm cells and impairing sperm functions. In females, marijuana was found to disrupt the endocrine system and produce an estrogenic effect, which can have detrimental effects on specific elements of the female reproductive system (54). It should be noted, however, that the effects were more the result of the contaminants of smoking the drug than the psychoactive chemicals (54). In addition, marijuana use negatively affected female reproductive hormones which could lead to delayed ovulation (52). In considering these studies, the conclusion is that marijuana use may have some negative effects on human reproduction and that these outcomes are increased for those already at risk for infertility or other reproductive conditions.

Research also examined the degree to which marijuana use by pregnant mothers affected the unborn foetus and whether maternal marijuana use led to negative outcomes for the child (50, 51, 53, 56). Kuczkowski (53) reported that THC crosses the placental barrier, but that there was no confirmation that it had a teratogenic effect. In other words, there is no evidence that marijuana use by a pregnant mother contributes or causes birth defects or malformations. However, research by Wang et al. (56) determined that some impairment was present in foetuses exposed to marijuana. This finding led the researchers to conclude that some long-term emotional and behavioural implications existed for children exposed to marijuana while in the womb.

Fried and Smith's review of literature (51) concluded that the effects of prenatal exposure to marijuana were subtle, with little evidence supporting growth or behavioural effects prior to age three. Others (50) concluded that there was a statistically significant association between prenatal exposure to marijuana and later use; however, they concluded that there were many other potential factors that could have contributed to later marijuana use among those exposed to the drug while in the womb. One common theme among the research conducted to date was that they all called for more study on this issue. Although further research is needed in this area, to date, no substantial dangers have been confirmed to be associated to smoking marijuana while pregnant. However, marijuana smoke contains hazardous chemicals and materials, many of which exist in tobacco smoke. Therefore, just as health providers caution that tobacco should not be used by pregnant mothers, the caution should extend to marijuana use.

Marijuana Use as a Potential Threat to the Immune System

THC from marijuana may act upon the immune system similarly to the way it does on cells in the reproductive system (55). If the immune system is compromised by the use of marijuana, there may be significant implications for health care systems around the world (8). The relationship between marijuana use and deficiencies of the immune system is based, in part, on the findings that THC inhibits the ability of T-cells and alveolar macrophages to protect the body from foreign pathogens (41, 58). Alveolar macrophages are a main defence against infections in the lungs. A review of the research literature in this area by Copeland et al. (8) suggested, however, that it might require high doses of THC to substantially impair immune system functioning. Still, when considering the number of respiratory problems associated with smoking marijuana, and the possibility of serious carcinogenic properties in the drug, compromising the immune system may further compound the harms of marijuana use, especially among those already suffering from weakened immune systems.

Cancer Causing Effects of Marijuana

Because marijuana smoke contains many of the same harmful carcinogens as tobacco smoke, there is a possibility that marijuana use may be associated with the onset of various types of cancers, especially lung cancer as the most common method of consuming marijuana is by smoking it (41). To date, however, the research does not support the association between marijuana use and cancer. In their study, Hashibe and colleagues (62) failed to find substantial evidence for an association between marijuana use and lung or upper areodigestive tract cancers. A review of research on lung cancer and marijuana use by Mehra et al. (63) revealed many of the methodological difficulties in attributing outcomes specifically to smoking marijuana. For example, in many instances, marijuana users also smoke tobacco, there is the challenge of determining proper thresholds for marijuana use, and the research has typically included only small sample sizes. Mehra et al. (63) suggested that because the plausibility of an association between marijuana smoking and cancer is so apparent, improved studies are required to test this possible link. Other research has reached similar conclusions about the link between marijuana use and cancer (59, 64, 65). Although a 1999 study by Zhang and colleagues (66) reported a potential for marijuana use to increase the risk of squamous cell carcinoma of the head and neck, the evidence for a link between marijuana use and head and neck cancers has been limited and conflicting (59 - 62). In a recent study, marijuana was not found to increase the risk of head and neck cancer, although the duration of use under study might have been too limited to rule out the possibility of a longer-term effect (59). Another large-sample study (64) concluded that marijuana was not associated to oral squamous cell carcinoma. There was also no link between maternal or paternal marijuana use and risk of childhood acute myeloid leukaemia (65).

Although there is currently no evidence to confirm that marijuana use increases the risk for any type of cancer, there will likely be continued research. Already, there are many researchers who believe that the changes to a variety of cells in the body caused by marijuana use may contribute to the development of cancers including lung cancer, oral cancers, and breast cancer (41, 54, 60, 63).

Marijuana Dependency and Withdrawal

Despite the commonly held belief that marijuana use does not lead to addiction, existing research has often referred to a dependency on the drug (8). Although many people use marijuana on a regular basis, Looby and Earleywine (68) reported that fewer than half of all daily users exhibited the behaviours necessary to meet the established criteria for being classified as drug dependent. These criteria include tolerance, withdrawal, taking the drug for longer periods of time or larger doses than intended, inability to stop or reduce use, increasing the time spent obtaining the drug and recovering from its effects, ignoring other important activities, and continuing use despite undesirable consequences. The authors (68) argued that frequent use does not necessarily result in dependence, but that it may be a contributing factor. Their research suggested that negative effects of marijuana use, such as dissatisfaction with life, low motivation, and unhappiness, were more related to dependence on the drug than regular use (68). When considering the results of this research with findings from Copersino et al. (67) on withdrawal symptoms, strong support is established for the idea that a proportion of frequent marijuana users suffer negative effects resulting from a dependency.

In terms of factors that most likely contribute to the development of a marijuana dependency, Hall (69) reported that initiation to drug use at an early age was the most significant. However, in terms of public policy, if THC levels are indeed increasing and continue to increase, there will likely be a growing number of users who find themselves dependent on marijuana. Furthermore, as the National Institute on Drug Abuse's (70) definition of addiction focuses on the "uncontrollable, compulsive craving, seeking and use of drugs", the physical effects of dependency and withdrawal may be only part of the problem, as addiction can occur without physical signs of dependency. This may prove more problematic if future research establishes additional negative health consequences of long-term use as users may experience more difficulty abstaining from use even in the face of exacerbating social and health problems.

Marijuana Use and Mental Health

In addition to some potentially serious physical health problems, marijuana use has also been associated with mental health problems. The link between marijuana use and psychosis or later schizophrenia has possibly received the most attention in the research literature. This body of research focuses on the role of marijuana in triggering psychosis (71 - 75), the risk of developing schizophrenia among those who suffered marijuana-induced psychoses (76, 77), the dangers of marijuana use for those already suffering from psychosis (78), and a number of hypotheses on whether marijuana use contributes to the presence

of psychoses or schizophrenia or whether mental health issues contribute to the onset of marijuana use (69, 79 – 81). To a lesser degree, researchers have also investigated the relationship between marijuana use and depression (30, 82) and anxiety (83).

Marijuana-Precipitated Psychosis and Schizophrenia

An association between marijuana use and the onset of psychosis recently emerged as a serious concern. Given this, it is necessary to understand the potential for marijuana to contribute to psychosis and what proportion of marijuana users are at risk for developing psychosis. Research suggests that 8% to 10% of all cases of psychosis may be triggered by the use of marijuana (71, 75). Others (74) concluded that marijuana use was linked to psychosis independent of any previous mental pathology. Given this, there is a growing consensus that, although it is relatively rare, marijuana induced psychosis is a potential threat to users, specifically to those who are already vulnerable for this type of mental affliction (71, 73, 75). In order to explain this relationship, Caspi et al. (72) reported that there may be an interaction between the chemicals typically present in marijuana and a number of 'susceptible' genes in the user that contributes to the onset of marijuana-induced psychosis and schizophrenia.

Research findings suggested that if marijuana use triggered psychosis, it might be a risk factor for schizophrenia (71, 72, 76). In determining whether those who suffered from an episode of marijuana-induced psychosis were at risk of developing later schizophrenia, a group of such individuals was compared to a group of people referred for schizophrenia-spectrum disorders for the first time who had no history of marijuana psychosis (76). Although suffering from some recognized methodological problems, this study (76) found that marijuana-induced psychosis was an important risk factor for developing schizophrenia and that it often had an earlier age of onset compared to those who self-reported no marijuana use. In partial support, Solowij and Michie (77) found similarities between the cognitive effects of marijuana use and the cognitive endophenotypes of schizophrenia. This suggested that there was little reason to believe that marijuana is a direct cause of schizophrenia, but that marijuana likely aggravates pre-existing susceptibilities to schizophrenia (77). This hypothesis may explain why those prone to suffering from marijuana-related psychosis are also more susceptible to later schizophrenia.

One of the complications for fully understanding marijuana's association with psychosis and later schizophrenia is that people with mental illness may continue to use the drug. The effects of marijuana use in patients who had recently suffered from psychosis were studied to determine whether symptoms were prolonged and worsened by the drug (78). Findings suggested that those who continued to use marijuana were at a greater risk of having more symptoms and a continuous course of mental illness (78). It could not be confirmed from the study, however, if marijuana caused the symptoms to worsen or the degree to which marijuana directly contributed to the symptoms.

There were a number of relational hypotheses tested in the research literature (69, 79 - 81). The most common hypotheses were that: marijuana use caused psychosis and schizophrenia without any existing predisposition; marijuana use triggered the onset of these symptoms in people who were previously vulnerable; marijuana use exacerbated the symptoms in those already suffering; and those already suffering from these symptoms were more likely to self-medicate with marijuana. Although the current state of the research does not support the hypothesis that the relationship between marijuana and psychotic symptoms is one of self-medication (81), other hypotheses found more support.

The strongest support was for the second and third hypotheses. However, the causal hypothesis remains debatable. Degenhardt and Hall (79) found that cases of schizophrenia in the general population did not rise with an increase in reported marijuana use, thus weakening the case for the causal hypothesis. Although further research is needed to more fully understand the causal association between marijuana use and psychosis, based on the research to date, psychosis and later schizophrenia as a result of marijuana use is a risk for a small portion of the marijuana using population.

Depression and Anxiety Among Marijuana Users

Although psychosis and schizophrenia were researched more than other mental health issues associated with marijuana use, there is a body of research on other issues such as depression, anxiety, and violence. Research (30) found that increased marijuana use among high school students was associated with increased self-reports of depression.(96) However, others (82) found that past-year marijuana use was not a significant predictor of future development of depression. Similarly, research by Bonn-Miller et al. (83) found that marijuana use was a predictor of anxiety symptoms, but not of depression. Again, it remains a challenge to determine whether marijuana use is a cause of these symptoms or if the symptoms play a contributing role in marijuana use.

Marijuana's Role in Continuing Drug Use

The discussion of potential harms of marijuana use presented thus far indicated that marijuana poses a number of potential risks to the general population of users and some specific negative outcomes for a relatively small subgroup. The risk or actual harms associated with marijuana use can be seriously compounded by the use of other drugs and can become overshadowed by the dangers associated with becoming addicted to 'harder drugs'. Moreover, there has long been the suggestion that marijuana can act as a 'gateway' for much harder drug use. It would appear that the probability that marijuana acts as a gateway to other illicit drugs is much higher than the other way around (84). According to Fergusson and Horwood (84), when adjusting for other common covariate factors such as childhood, family, and life-style factors, regular marijuana use (fifty or more times in a year) was strongly related to the onset of further illicit drug use. However, others (85) found that the opportunities presented by the lifestyle accompanying marijuana use were just as likely as the actual use of marijuana to predict the use of other illicit drugs.

Currently, there is no evidence to prove or disprove that any biological effects of marijuana use increases the likelihood of using other illicit drugs, although researchers continue to test this hypothesis (86, 87). Based on twin studies, it is well established that marijuana use is a strong predictor of future illicit drug use regardless of the familial and environmental similarities between twins (88).

Still, since the majority of marijuana users do not continue on to other illicit drugs (84), it is important to understand what factors distinguish between those who do and those who do not go on to use harder drugs. The appropriate policy and control responses may be very different depending on whether the relationship was based on the biological effects of marijuana use or on the lifestyles that accompanied marijuana and other illicit drug use. Currently, it can be concluded that, for those who use marijuana, there is a risk of using other illicit drugs. However, without a better understanding of what causes or correlates with an increased risk, it is impossible to determine what effects changes to marijuana's current legal status would have on patterns and rates of drug use.

Conclusions

The debate over the most appropriate policy to have with respect to the personal use of marijuana has generally been polarized because of differing positions on the drug's harms. In addition to the unknown extent of the potential for harm caused by existence and interaction of over 800 natural chemical components of marijuana, including 70 cannabinoids, it can be concluded that marijuana does pose some considerable confirmed risks to users. Some concern over marijuana is merited by findings regarding its ability to create short-term impairment, specifically on driving ability. Academic performance and social development appear to be negatively affected by marijuana use, but the causal role that the drug plays in the lack of future success of young people remains unconfirmed. As expected, smoking the drug contributes to considerable harm to the lungs and airways. Even though the use of vaporizers removes the contaminants of combustion and reduces some major respiratory problems, THC exposure to the lungs appears to be unhealthy. The immune system is also compromised by the use of marijuana, specifically the ability of the lungs to defend against foreign pathogens. Although cancers, heart problems, and threats to human reproduction are not common among marijuana users, most experts contend that further investigation is required, and the potential for risk should not be dismissed. The development of psychosis and later schizophrenia should also remain a concern for a small proportion of those who use marijuana. Dependency and regular, long-term use of the drug are also factors that likely exacerbate the potential for the majority of the harms previously identified in this review. Of course, these harms are often compounded by the fact the marijuana users have an increased likelihood of continuing on to other illicit drugs.

It is important to remain cognizant of the fact that the harms associated with marijuana use, though very serious in some cases, are not experienced by the majority of users, although prolonged regular use will generally put a person at a greater risk than occasional use. The debate over marijuana use requires advocates of both decriminalization and prohibition to concede that marijuana is neither harmless, nor is it particularly dangerous to the majority of users. It should be acknowledged by all that the lives of a small proportion of the population will be seriously disrupted by marijuana use.

With an understanding of the potential harms associated to marijuana use forming the basis of the debate, politicians, policymakers, and citizens can begin to answer the important questions that will form the basis for discussing policy options. For example, what can be learned from other jurisdictions about ways to respond to the social and personal harms associated with marijuana use? What lessons can be learned from the experiences with alcohol that might apply to marijuana? Are there other or better approaches than prohibition to manage the problems that marijuana use creates? Further research will also be required to better understand whether decriminalization promotes increased use. In other words, would the decriminalization of marijuana create better opportunities to regulate the drug, or would it result in greater social harm?

To date, the research evidence shows that marijuana has a number of associated harms. In some cases, these harms are worse than those associated with regulated substances such as alcohol or tobacco. Based on the course of research, it is likely that future studies will further refine our understanding of the harms of marijuana use. However, because marijuana continues to be a popular recreational drug, it is necessary that researchers disseminate their latest findings in a wide range of ways in order for the public to have the best information at their disposal about the harms and risks associated with using marijuana.

The authors wish to acknowledge the support of the Drug Awareness Branch, "E" Division, Royal Canadian Mounted Police.

Author Information

Jordan Diplock

Jordan Diplock is a Research Assistant in the Centre for Criminal Justice Research at the University of the Fraser Valley.

Irwin Cohen