Medical Marijuana: The Conflict Between Scientific Evidence and Political Ideology. Part One of Two

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ABSTRACT. Whether “medical marijuana” (Cannabis sativa used to treat a wide variety of pathologic states) should be accorded the status of a legitimate pharmaceutical agent has long been a contentious issue. Is it a truly effective drug that is arbitrarily stigmatized by many and criminalized by the federal government? Or is it without any medical utility, its advocates hiding behind a screen of misplaced (or deliberately misleading) compassion for the ill? Should Congress repeal its declaration that smoked marijuana is without “current medical benefit”? Should cannabis be approved for medical use by a vote of the people as already has been done in 13 states? Or should medical marijuana be scientifically evaluated for safety and efficacy as any other new investigational drug? How do the competing—and sometimes antagonistic—roles of science, politics and prejudice affect society’s attempts to answer this question?

This article examines the legal, political, policy, and ethical problems raised by the recognition of medical marijuana by over one-fourth of our states although its use remains illegal under federal law. Although draconian punishment can be imposed for the “recreational” use of marijuana, I will not address the contentious question of whether to legalize or decriminalize the use of marijuana solely for its psychotropic effects, a fascinating and important area of law and policy that is outside the scope of this paper. Instead, the specific focus of this article will be on the conflict between the development of policies based on evidence obtained through the use of scientific methods and those grounded on ideological and political considerations that have repeatedly entered the longstanding debate regarding the legal status of medical marijuana. I will address a basic question: Should the approval of medical marijuana be governed by the same statute that applies to all other drugs or pharmaceutical agents, the Food, Drug, and Cosmetic Act (FD&C Act), after the appropriate
regulatory agency, the Food and Drug Administration (FDA), has evaluated its safety and efficacy? If not, should medical marijuana be exempted from scientific review and, instead, be evaluated by the Congress, state legislatures, or popular vote? I will argue that advocacy is a poor substitute for dispassionate analysis, and that popular votes should not be allowed to trump scientific evidence in deciding whether or not marijuana is an appropriate pharmaceutical agent to use in modern medical practice.

**KEYWORDS.** Cannabis, law, marijuana, nausea, medical, pain, policy

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**PART I: INTRODUCTION—MEDICAL MARIJUANA: FORBIDDEN FRUIT OR BOON FOR HUMANITY?**

Two plants—*Cannabis sativa* (marijuana) and *Papaver somniferum* (the opium poppy)—which have been cultivated for millennia, have a remarkable ability to alleviate physical and mental pain. Yet both may also cause harm. Opioids have significant addiction liability, and even a small dose causes measurable respiratory depression, whereas larger doses are capable of producing respiratory arrest and death. Even so, their undisputed capability to relieve pain is thought to far outweigh these risks. Consequently, opium and its derivatives are a legal mainstay in today’s medical practice. In contrast, although marijuana is far less addicting than the opioids and there is no documented evidence of death resulting from its use, even in large doses, it is illegal under federal law to cultivate or distribute marijuana in order to treat patients or for a sick individual to use it on the advice of a physician. Indeed, in some jurisdictions, even a physician’s recommendation to patients that marijuana might alleviate their symptoms has been sanctioned. Nonetheless, at this point in time medical marijuana had been legalized by 13 states, either by legislation or direct statewide popular vote in referenda or ballot initiatives. The federal government, however, has asserted that the Controlled Substances Act (CSA) preempts such actions by the individual states, a claim that has been upheld by the Supreme Court.

In this article, I will examine the legal, political, policy, and ethical problems raised by the recognition of medical marijuana by almost one quarter of our states in the face of federal opposition. I will use the term “medical marijuana” to refer to any form of *Cannabis sativa* used (usually by smoking) to treat a wide variety of pathologic states and diseases. Although draconian punishment can be imposed for the “recreational” use of marijuana, I will not address the contentious question of whether to legalize or decriminalize the use of marijuana solely for its psychotropic effects, a fascinating and important area of law and policy that is outside the scope of this paper. Instead, the specific focus of this article will be on the conflict between the development of policies based on evidence obtained through the use of scientific methods and those grounded on ideological and political considerations that have repeatedly entered the longstanding debate regarding the legal status of medical marijuana. I will address a basic question: Should the approval of medical marijuana be governed by the same statute that applies to all other drugs or pharmaceutical agents, the Food, Drug, and Cosmetic Act (FD&C Act), after the appropriate regulatory agency, the Food and Drug Administration (FDA), has evaluated its safety and efficacy? If not, should medical marijuana be exempted from scientific review and, instead, be evaluated by the Congress, state legislatures, or popular vote? I will argue that advocacy is a poor substitute for dispassionate analysis, and that popular votes should not be allowed to trump scientific evidence in deciding whether or not marijuana is an appropriate pharmaceutical agent to use in modern medical practice.

**Part II** will examine the authority of the Food, Drug, and Cosmetic Act and the Controlled Substances Act, focusing on their application to the approval of medical marijuana. I will propose that because those advocating for medical marijuana are proposing its use as a drug, it should be evaluated as a drug according to the statutory requirements of the Food, Drug, and Cosmetic Act.

**Part III** will address the known risks of medical marijuana as documented in the peer-reviewed scientific literature. When possible, I will distinguish between the adverse effects of...
recreational and medical use of marijuana because its pathology may not be identical in both settings.

Part IV will summarize the known benefits of medical marijuana as demonstrated in the peer-reviewed scientific literature.

Part V will examine the battle between investigators who have attempted to obtain scientifically valid data to use as a basis for formulating public policy and those who, apparently for ideological and political reasons, have erected barriers to such studies. I will propose that both disapproval by the Congress and approval by state referenda are equally inappropriate because each bypasses the normal FDA regulatory and evaluation procedure.

Part VI will examine the potential impact of two approved medications that contain at least one active ingredient of marijuana and analyze why their legitimate use does not moot the question of whether medical marijuana should also be accepted.

Part VII will conclude that activists on both sides are responsible for the current state of affairs and that scientific evidence devoid of political considerations should be allowed to guide future decisions regarding the status of Cannabis sativa when used for medical purposes.

PART II: THE AUTHORITY OF THE FOOD, DRUG, AND COSMETIC AND THE CONTROLLED SUBSTANCES ACTS

THE FDA: NEW DRUG EVALUATION AND MEDICAL MARIJUANA

Marijuana is not just a natural remedy, an “herbal cure,” or “Mother Nature’s most precious gift.”20 Marijuana, whether smoked or taken orally as a therapeutic—not recreational—agent, is a drug as defined by the FD&C Act.

The term “drug” means articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and articles (other than food) intended to affect the structure or any function of the body of man or any other animals.21

New drugs (pharmaceuticals) are subject to stringent premarket approval. The FD&C Act requires that all new drugs be scientifically evaluated before they may be allowed to enter the stream of interstate commerce.22 As a result, drugs may not be advertised and sold in the absence of “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved.”23

The Food and Drug Administration is charged with ensuring the safety and efficacy of drugs marketed within the United States. Its authority is based on the government’s responsibility to provide for public safety, a power that may at times be used in ways that abrogate individual rights. The tension between the state’s police power and personal autonomy was set forth exquisitely by the Supreme Court over a century ago in a case pitting an individual’s assertion of the right to refuse vaccination during a smallpox epidemic in Boston against the Commonwealth of Massachusetts, which invoked its police power to enforce this necessary public health measure:

The liberty secured by the Constitution of the United States to every person within its jurisdiction does not import an absolute right in each person to be, at all times and in all circumstances, wholly freed from restraint. There are manifold restraints to which every person is necessarily subject for the common good. On any other basis organized society could not exist with safety to its members... Even liberty itself, the greatest of all rights, is not unrestricted license to act according to one’s own will... [but is] liberty regulated by law.24

The authority and justification for governmental regulation of pharmaceutical agents in order to ensure public safety was reiterated in 1979. In a case involving patients who claimed that an unapproved drug, Laetrile, represented their last hope for survival, the Supreme Court held that public safety must prevail over the rights of both terminally ill patients seeking a cure and “inventive minds” who manufacture and sell unproven panaceas:

To accept the proposition that the safety and efficacy standards of the Act have
no relevance for terminal patients is to deny the Commissioner’s authority over all drugs, however toxic or ineffectual, for such individuals. If history is to be any guide, this new market would not be long overlooked. Since the turn of the century, resourceful entrepreneurs have advertised a wide variety of purportedly simple and painless cures for cancer, including liniments of turpentine, mustard, oil, eggs, and ammonia; peat moss; arrangements of colored floodlamps; pastes made from glycerine and limburger cheese. In citing these examples, we do not, of course, intend to deprecate the sincerity of Laetrile’s current proponents, or to imply any opinion on whether that drug may ultimately prove safe and effective for cancer treatment. But this historical experience does suggest why Congress could reasonably have determined to protect the terminally ill, no less than other patients, from the vast range of self-styled panaceas that inventive minds can devise.

A BRIEF HISTORY OF THE FDA

Today’s FDA was born in response to investigative journalism and developed out of disasters rather than foresight. Much of the impetus behind its origin in 1906 came from the public’s reaction to the revelation of abuses within the food industry. Shocking disclosures of unsanitary conditions in food-processing plants called attention to the need for governmental regulation. Upton Sinclair revealed fraud and abuse in the meat packing industry in the early 1900s in his muckraking novel The Jungle. The novel’s powerful role in precipitating the passage of the first Food and Drug Act is revealed in the following excerpt:

There would be meat that had tumbled out on the floor, in the dirt and sawdust, where the workers had tramped and spit uncounted billions of consumption germs. There would be meat stored in great piles in rooms; and the water from leaky roofs would drip over it, and thousands of rats would race about on it. It was too dark in these storage places to see well, but a man could run his hand over these piles of meat and sweep off handfulls of the dried dung of rats. These rats were nuisances, and the packers would put poisoned bread out for them; they would die, and then rats, bread, and meat would go into the hoppers together. This is no fairy story and no joke; the meat would be shoveled into carts, and the man who did the shoveling would not trouble to lift out a rat even when he saw one.

Congress reacted to these disclosures by passing the original Pure Food and Drug Act in 1906. This Act, the progenitor of today’s FD&C Act, prohibited interstate commerce in misbranded and adulterated food, drinks, and drugs and required accurate listing of contents (including narcotics and marijuana) on labels of patent medicines shipped in interstate commerce. The subsequent evolution of food and drug legislation clearly illustrates what I term “government by crisis.” It took the elixir of sulfanilamide tragedy, in which a mislabeled and adulterated medication killed 107 people, mostly children, to bring about passage of the Food, Drug, and Cosmetic Act of 1938. This act required not only that drugs be correctly labeled but that they be shown to be safe prior to marketing. It was not until 1962, after the use of thalidomide by pregnant women had resulted in the birth of thousands of newborns with major physical disabilities, that the Kefauver-Harris Amendment mandated that drugs be demonstrated effective as well as safe before they could enter interstate commerce. These and other changes in the scope of the FD&C Act were made out of the conviction that only strong governmental action could protect individuals from harm that they had no way of combating on their own.

HOW THE FDA EVALUATES NEW DRUGS

Before a drug is permitted to enter the stream of interstate commerce, the FD&C Act requires that the FDA evaluate its safety and efficacy as demonstrated by “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience.”

The Act does not require that the new drug be proven superior to already approved drugs,
only that its benefits outweigh its risks when used for the purpose for which it has been approved.

That marijuana as a botanical should not, in itself, preclude scientific investigation of the drug and, if warranted, its approval as a legitimate therapeutic agent. Botanicals are the source of the active ingredients in many drugs commonly used in today's medical practice. Digitalis leaf, derived from *Digitalis purpurea* (the foxglove plant), is the source of drugs commonly used to treat congestive heart failure. *Papaver somniferum* (the opium poppy) provides opium from which morphine used to treat pain is derived. Donnatal, a medication used to treat irritable bowel syndrome, contains belladonna alkaloids (originally found in *Atropa belladonna*), the deadly nightshade plane) as one of its active ingredients. Ephedra sinica is used to treat hypertension and aspirin (found in the bark of *Salix alba*, the White Willow tree) is a ubiquitous over-the-counter remedy. Taxol, a potent therapy for breast cancer, is derived from *Taxus brevifolia* (Pacific yew tree). All of these agents are legal and FDA-approved when employed for legitimate therapeutic use.

With this background, I will briefly outline the statutory procedure for conducting adequate testing for safety and efficacy in appropriate animals and then humans. After the initial studies of the pharmacological and physiological effects have been completed in animals, the manufacturer must apply to the FDA for an investigational new drug (IND) exemption, which, if approved, allows the drug to be transported across state lines for extensive testing of safety and efficacy in humans. The IND application must provide the FDA with information regarding proposed clinical investigations, the chemistry, formula, and manufacturing details of the investigational drug, and any pharmacological or physiological data from prior studies. The FDA has 30 days to respond to the IND application; the manufacturer may begin clinical testing if it has not heard from the FDA after the 30-day review period. Of course, the FDA can halt clinical testing at any time if the agency feels that new information indicates the investigational new drug no longer meets safety and efficacy standards.

Clinical testing is not carried out by the FDA itself but is the responsibility of the drug's manufacturer (sponsor). The necessary investigations, conducted by academic institutions or by private contractors, involve three discrete phases designed to document safety and efficacy through "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience." In Phase I, the drug’s toxicity and human tolerance to it are examined usually in fewer than 100 subjects with the primary purpose of evaluating potential toxicity rather than efficacy (although gaining knowledge of effectiveness is not precluded). In Phase II, which begins after dose-response and toxicity data are deemed sufficient to continue the process of clinical investigation, detailed studies are carried out in several hundred humans. This phase, involving "controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication... in patients with the disease or condition under study," is designed to verify the drug’s effectiveness, major side effects, and appropriate dose. In Phase III, which is commenced once the drug under consideration has been deemed sufficiently safe and effective for further testing and evaluation, large-scale (as many as several thousand patient volunteers) studies are conducted to determine complications of low incidence as well as efficacy in a large cohort of the general population with the disease.

Once these three phases of drug evaluation have been completed, the manufacturer of the drug files a New Drug Application (NDA) with the FDA. This document must provide the results of all preclinical and clinical investigations and include the names of all of the clinical investigators; describe all components of the drug; document manufacturing, processing, and packaging methods; and furnish samples of the proposed labeling. If the FDA deems the benefits of using the drug for the purposes proposed in the NDA outweigh its risks, it will grant approval and the drug may then enter the stream of interstate commerce.

The FDA's approval of an NDA does not require that the investigational new drug be superior to, or even as effective as, an already approved medication. The data need only demonstrate that it is safe and effective. Therefore, for medical marijuana, as with any other investigational new drug, only its safety and efficacy need be demonstrated—not its superiority.
An important part of regulatory oversight involves the labeling and advertising of approved drugs. A manufacturer can explicitly advertise or otherwise promote medications only for indications approved by the FDA. Furthermore, all advertising must be based on data that were approved by the FDA for inclusion in the labeling of the drug. A drug may be deemed to be misbranded “because the labeling or advertising is misleading.” Thus, the Act requires both proven safety and efficacy and accurate labeling and advertising of a drug. As a condition of approval, the FDA may require postmarketing surveillance studies (“Phase IV studies”) to gain the additional knowledge that is possible only with observation of even larger numbers of patients. Even after the FDA’s final approval has been gained, the FDA can suspend or revoke the manufacturer’s license based on new evidence that calls into question the drug’s safety and/or efficacy.

Recent events have illuminated major deficiencies in the FDA’s ability to protect the public, including overly hasty and, in the views of some, far too permissive drug approval, real and perceived conflicts of interest, and lack of appropriate post-marketing surveillance. In addition, what some consider to be an intrusive role of politics in the FDA’s decision-making procedures has severely damaged the agency’s reputation. Finally, the Administration and some members of the Congress have proposed changes that some believe will undermine the FDA’s authority to regulate the advertising of off-label use (off-label use, the prescription of drugs for purposes that were not part of the approved NDA, is further discussed in Part VI) and thereby threaten the agency’s ability to protect the public. Even so, these deficiencies in the FDA’s regulation of pharmaceuticals do not provide a rationale for disregarding its major role in protecting the public. Indeed, the FDA, in its “watchdog” function, has successfully served the public far more often than not. Therefore, this analysis considers the FDA in light of its successes and promises rather than these deficiencies.

THE CONTROLLED SUBSTANCES ACT: SCHEDULING AND MEDICAL MARIJUANA

If the FDA finds that a drug’s addiction liability requires additional regulation under authority granted by the Controlled Substances Act (CSA), it petitions the Drug Enforcement Agency (DEA) to place the drug on the list of controlled substances. The scheduling process begins with a scientific review performed by two divisions of the Department of Health and Human Services (DHHS)—the FDA and the National Institute on Drug Abuse (NIDA), the latter of which is an institute of the National Institutes of Health (NIH). Once their analysis is complete, DHHS makes a preliminary binding recommendation that is printed in the Federal Register for public comment. Thereafter, if the scientific experts of the FDA recommend that scientific evidence supports placing the drug on the list of scheduled controlled substances, the actual level of scheduling—as determined by specific factors detailed in the CSA—is assigned by the DEA. In assigning the appropriate schedule, the DEA must ensure that the determination is based on objective and verifiable scientific findings. The level of scheduling is based on the following questions: (1) Does the drug have a “currently accepted medical use” in the United States? (2) What is the drug’s safety under medical supervision? Will it be a hazard to those using it or to others? (3) What is its addiction liability? (4) Is there a potential for (or history of) significant diversion for illegal use? (5) Are individuals using it on their own initiative or only on physician’s prescription? (6) Is the drug similar in its pharmacology to other controlled drugs?

The Controlled Substances Act also provides that the Congress may take any action it wishes regarding scheduling on its own without regard to available scientific evidence. The significance of this authority will be discussed further in Part V.

PART III: POTENTIAL RISKS OF USING MEDICAL MARIJUANA

The decision of whether or not to grant approval of any new drug requires a careful balancing of its potential risks and benefits. All approved medications used in the legitimate practice of medicine are associated with adverse effects; there is no a priori reason why marijuana should be different. Before assessing the potential pathology of marijuana, it is necessary to
distinguish between its recreational and medical use.

When used recreationally, marijuana might be taken in large doses over long periods of time for its psychotropic effects. In contrast, when used as medical therapy, marijuana is administered only in doses sufficient to produce the desired clinical effect and only for as long as is medically necessary. The effects of any pharmaceutical agent, whether beneficial or pathologic, depend on the route of administration (e.g., oral, intravenous, intramuscular, or smoked), the dose administered, the pharmacologically active fraction of the administered dose that reaches the desired site of action, the rate at which the drug is metabolically inactivated, and the frequency and duration of use. Thus, it may be misleading to assume that marijuana’s properties manifested in individuals who have used it frequently, often in large quantities, and over a long period of time, can predict the effects of marijuana in patients who use it only as often as necessary under the advice of a medical professional and who carefully titrate the drug to achieve a desired clinical effect.

Another factor to consider is the significant biological differences between the developing brains of children and adolescents and the more mature brains of adults. These differences in brain structure and function suggest that marijuana’s long-term pathology may be age dependent and that a “universal” policy applying to all age groups is therefore probably unwarranted.

At the present time, only limited data regarding adverse effects of medical marijuana are available. This contrasts sharply with our extensive knowledge of the pathology of both recreational marijuana and cocaine, morphine, and other "hard" drugs.

MARIJUANA AND DEATH

Many legal drugs subject to the CSA are both indispensable to modern medical practice and potentially lethal (e.g., morphine, fentanyl, Demerol, and phenobarbital). Indeed, an appreciation of the possibility that such medications can cause death when used inappropriately is essential to medical training. For instance, the mechanism by which drugs such as morphine can cause death is set forth in a major textbook of pharmacology:

Morphine is a primary and continuous depressant of respiration... The respiratory depression is discernible even with doses too small to disturb consciousness, and increases progressively as the dose is increased. In man, death from morphine poisoning is nearly always due to respiratory arrest.

In contrast, there is no evidence that the recreational use of marijuana is associated with death. In healthy young users, marijuana’s cardiovascular effects are unlikely to be of clinical significance. Documented evidence of death resulting from recreational use, even in large doses, is lacking.

The possibility that marijuana might cause death is not mentioned in a discussion of its pathology in a standard textbook of pharmacology. The author only calls attention to a reversible effect of marijuana on heart rate and blood pressure, suggesting an absence of a relationship between use of marijuana and death:

The most consistent effects on the cardiovascular system are an increase in heart rate [and] an increase in systolic blood pressure... The increase in heart rate is dose related, and its onset and duration correlate well with the concentration of Δ9-tetrahydrocannabinol (THC) in blood... There are no consistent changes in respiratory rate.

Obviously, marijuana can be a factor in causing death when it accompanies the use of other potent drugs such as alcohol or heroin, or is smoked during potentially hazardous activities such as driving.

HARMFUL PROPERTIES OF MARIJUANA

It is not an exaggeration to state that all approved pharmaceuticals are associated with some degree of pathology; although these effects are not necessarily life-threatening. Marijuana
is not an exception. However, risk alone is a poor determinant of whether marijuana should be approved as a legitimate therapeutic agent. Far more important to the analysis of marijuana and, indeed, all investigational new drugs, is the relationship of their inherent risks to their proposed benefits. In this section I will analyze the available evidence concerning the addiction liability of marijuana, its possible association with cognitive impairment, whether its use is either associated with or causes mental illness, the question of marijuana smoking and pulmonary carcinoma (lung cancer), and marijuana’s role as a "gateway drug."

**Marijuana and Addiction Liability**

Although there is little doubt that recreational marijuana is associated with addiction liability, its ability to produce dependence is less significant than that associated with either alcohol or pharmaceutical agents, such as morphine, phenobarbital, and Valium, that are part of the legitimate practice of medicine.

Clinical and epidemiologic evidence indicates that a cannabis dependence syndrome occurs in heavy chronic users, as exhibited by a lack of control over use and continued use of the drug despite adverse personal consequences ... [However, the risk of becoming dependent on cannabis probably is probably more like the risk for alcohol than for ... the opioids, with around 10% of those who ever use cannabis eventually meeting the criteria for dependence.]

Epidemiologic data from a national study indicate that about 10% of regular marijuana users become addicted to it. This incidence is more like that of alcohol use (15% becoming addicted) than either nicotine (32%) or the opioids (23%). These data did not escape public attention. An Op-Ed piece published in the Washington Post emphasized that marijuana’s addiction liability was less than that of either alcohol or nicotine, both of which are legal drugs:

Fewer than one in 10 marijuana smokers become regular users of the drug, and most voluntarily cease their use after 34 years of age. By comparison, 15 percent of alcohol consumers and 32 percent of tobacco smokers exhibit symptoms of drug dependence.

Although the use of recreational marijuana may result in addiction, the relevant question to consider is the possibility of becoming addicted when marijuana is used for medical purposes as directed by a licensed health care professional. However, marijuana has not been used in a medical context for a sufficiently long period to allow the collection of scientific observations and data analysis necessary for a definite answer. Nonetheless, valid information concerning the likelihood that patients will become addicted to marijuana when using it medically may be extrapolated from the medical use of other controlled substances whose ability to produce addiction has been well documented. As Denise Kandel has observed:

There are, unfortunately, no empirical data to guide policy. However, inferences can be made from appropriate medical use of morphine, which does not lead to addiction. This is a curious phenomenon that points out the complexity of drug behavior and the role of psychological and social conditions in shaping its development.

The use of opioids is a significant component of pain therapy; when using these drugs, treating physicians must be aware of the possibility of addiction. Nonetheless, when the benefits and risks of opioid therapy are balanced, these drugs are generally considered to be a legitimate component of treatment. A discussion of pain management by Neil Irick, a specialist in pain management, typifies this view:

Existing evidence suggests that iatrogenic [physician-induced] drug dependence is a real phenomenon but one that occurs infrequently when dependence-producing drugs are prescribed in an appropriate manner. Consistent narcotic use in chronic pain of known etiology that is unable to be relieved by other means, while associated with physical dependence [in contrast to true addiction], may nonetheless allow an individual to function in a productive manner.
Experience with other approved controlled substances used appropriately in the practice of medicine suggests that while the possibility of addiction (in contrast to physical dependence and/or tolerance) cannot be ruled out, it should be balanced with the potential benefits of the drug (infra, Part IV). The basic principle of balancing risk and benefit when deciding whether to approve a drug for medical treatment is equally applicable when evaluating the acceptability of marijuana as a safe and effective medication.

**Marijuana and Cognitive Impairment**

**Recreational Marijuana Use and Cognitive Impairment**

Can the recreational use of marijuana cause cognitive impairment? The most obvious answer is “yes”—after all, this is the basic reason for its recreational use. The consensus of workers in the field is that chronic recreational use of marijuana may be associated with cognitive dysfunction and, indeed, that this significant pathology is related to structural changes in the brain.

Marijuana has an adverse effect on cognitive functions and tests, but the *sine qua non* of use appears to be impairment of the ability to learn... Marijuana intoxication interferes with the formation of new memories... Depersonalization and other behavioral effects also have been associated with marijuana use.81

A recent study demonstrated that smoking four joints or more per week resulted in a decrement in mental test performance; subjects who had smoked regularly for a decade or more did the worst. The investigators found that long-term marijuana users were impaired 70 percent of the time on a decision-making test, compared to 55 percent for short-term users and 8 percent for nonusers.82

More significant than the acute effects of marijuana is that cognitive dysfunction may persist after its use has ceased; this phenomenon was described by Pope and Yurgelon-Todd who measured cognitive function after sufficient abstinence to ensure that the subjects were not acutely intoxicated by the drug:

Heavy marijuana use (daily for at least one month) is associated with residual neuropsychological effects even after a day of supervised abstinence from the drug. However, the question remains open as to whether this impairment is due to a residue of drug in the brain, a withdrawal effect from the drug, or a frank neurotoxic effect of the drug.83

Block and coworkers tested subjects’ memory as demonstrated by memorizing words. Although marijuana users refrained for at least 26 hours prior to testing (in order to obviate any residual acute cognitive effects of marijuana), they required approximately three times the number of word presentations to demonstrate the same degree of recall evidenced by nonusing controls. The authors therefore suggested that marijuana use altered memory-related brain function, an effect that persisted beyond the expected period of acute marijuana-induced pathology.84 These changes in brain function appeared to be related to or associated with anatomic and metabolic alterations in this organ (it is also possible that a longer period of abstinence might have resulted in different findings):

Using positron emission tomography (PET), memory-related regional cerebral blood flow was compared in frequent marijuana users and nonusing control subjects after at least 26 hours of monitored abstinence. Memory-related blood flow in marijuana users, relative to control subjects, showed decreases in prefrontal cortex, increases in memory-relevant regions of cerebellum, and altered laterализation in hippocampus. Marijuana users differed most in brain activity related to episodic memory encoding.85

However, other investigators have been unable to demonstrate that the hippocampus, an area of the brain that plays a significant role in memory, is involved in marijuana’s possible effects on memory. For example, Tzilos and colleagues state:
We used magnetic resonance imaging to investigate these effects in a group of 22 older, long-term cannabis users and 26 comparison subjects with no history of cannabis abuse or dependence. When compared to control subjects, smokers displayed no significant adjusted differences in volumes of gray matter, white matter, cerebrospinal fluid, or left and right hippocampus. Moreover, hippocampal volume in cannabis users was not associated with age of onset of use or total lifetime episodes of use. These findings are consistent with recent literature suggesting that cannabis use is not associated with structural changes within the brain as a whole or the hippocampus in particular.86

This study did not dispute that marijuana could produce long-term cognitive effects. Rather, it suggested that marijuana’s action on brain sites other than the hippocampus might be responsible for these mental changes.

In view of these studies indicating that the use of recreational marijuana impairs mental ability, it should not be surprising that its use may also be associated with a significant decrement in driving ability. A recent study of fatal automobile accidents conducted in France demonstrated the presence of marijuana in 8.8% of drivers found to be at fault compared with only 2.8% of those involved in fatal accidents but deemed to be without fault. Parenthetically, alcohol was associated with a far greater number of such accidents.87

The pathologic effects of chronic recreational marijuana use by a judge (Superior Court Judge Philip Marquardt) who was presiding at a capital murder case have been substantiated in case law.88 In what may be one of the most dramatic illustrations of marijuana’s effect on mental function documented in the legal (as opposed to medical) literature, the Court of Appeals for the Ninth Circuit stated:

It is the raw material from which legal fiction is forged: A vicious murder, an anonymous psychic tip, a romantic encounter that jeopardized a plea agreement, an allegedly incompetent defense, and a death sentence imposed by a purportedly drug-addled judge. But, as Mark Twain observed, “truth is often stranger than fiction because fiction has to make sense.”

Judge Marquardt advised the parties that he would deliberate over the weekend and announce his decision on Monday. Unbeknownst to Summerlin (the defendant), Judge Marquardt was a heavy user of marijuana at the time, a fact that the State conceded in the federal habeas proceedings before the district court in this case.89

The amount of marijuana that Judge Marquardt may have used during the trial or deliberations is unknown because the district court did not allow discovery on this issue, although there is record support for Summerlin’s claim that Judge Marquardt was either having difficulty concentrating or experiencing short-term memory loss.90

There are instances during pre-trial hearings and at trial when Judge Marquardt exhibited confusion over facts that had just been presented to him. He also made some quite perplexing, if not unintelligible, statements at various times during the trial.91

It is important to note that although marijuana’s acute detrimental effects on cognition have been well-documented by some investigators, there is no consensus regarding the long-term sequelae of its chronic use. In a study of 1318 subjects during a 12-year period, Lyketsos and coworkers demonstrated that although the Mini-Mental State Examination had demonstrated a decline in cognitive function of marijuana users during this period, the changes were similar in heavy users, light users, and nonusers of marijuana. The authors, therefore, concluded that “over long time periods, in persons under age 65 years, cognitive decline . . . is closely associated with aging and educational level but does not appear to be associated with marijuana use.”92

Other data support the hypothesis that chronic marijuana use does not produce changes in cognitive function that are irreversible:

U.S. government-sponsored population studies conducted in Jamaica, Greece and Costa Rica found no significant cognitive differences between long-term marijuana smokers and nonsmokers. Similarly, a 1999 study of 1,300 volunteers published in the American Journal of Epidemiology...
reported “no significant differences in cognitive decline between heavy users, light users, and nonusers of cannabis” over a 15-year period. Most recently, a meta-analysis of neuropsychological studies of long-term marijuana smokers by the U.S. National Institute on Drug Abuse reaffirmed this conclusion.\textsuperscript{93}

**Medical Marijuana and Long-Term Cognitive Impairment**

In contrast to the effects of its recreational use, what are the cognitive effects of controlled exposure to marijuana administered to treat symptomatic pathology as recommended by a physician? The basic answer is that at this point in time we do not have a definite answer. Nonetheless, there are a few relevant considerations to keep in mind.

Most important is that medical marijuana is recommended to patients as a bona fide medical treatment to relieve the pathologic symptoms of their disease,\textsuperscript{94} not to enable patients to get “high.” This is analogous to the prescription of opioids, e.g., morphine, for legitimate medical treatment of both acute and chronic pain, not for their psychotropic effects. Morphine, like marijuana, even when used under a physician’s direction, can cause cognitive changes; indeed, this is a reason why some patients reject its use for long-term therapy and seek other modes of alleviating their distress. In most cases, however, this adverse effect is dose-related and therefore can often be controlled by decreasing the dose of either drug.

Finally, physicians are often confronted with the problem of making not the best choice but the least worst choice. In balancing the burdens and potential benefits (infra, Part IV) of marijuana, it is a truism for the practicing physician that many of the conditions for which marijuana has been recommended—pain, spasticity, nausea, lack of appetite, weight loss, and depression—can also produce cognitive impairment.

**Marijuana and Mental Illness**

Perhaps of even greater concern than the effects of marijuana on cognition is its possible association with manifestations of serious psychiatric illness. Available scientific data suggest that there may be a strong association between some forms of psychiatric abnormalities and the recreational use of marijuana. Jaffe has documented the effect of recreational marijuana:

Higher doses of Δ⁹-THC can induce frank hallucinations, delusions, and paranoid feelings. Thinking becomes confused and disorganized; depersonalization and altered time sense are accentuated. Anxiety reaching panic proportions may replace euphoria, often as a result of the feeling that the drug-induced state will never end. With high enough doses, the clinical picture is that of a toxic psychosis with hallucinations, depersonalization, and lost of insight; this can occur acutely or only after months of use.\textsuperscript{95}

A confounding factor is that preexisting psychiatric illness may play a significant role in the development of mental illness in individuals using marijuana. For example, Henquet and colleagues evaluated and compared 2437 individuals 14 to 24 years of age with and without a history of preexisting psychosis:

Psychiatric symptoms were evaluated at the initial interview and during a follow up four years later. After adjustment for age, sex, socioeconomic status, urbanicity, childhood trauma, predisposition for psychosis at baseline, and use of other drugs, tobacco, and alcohol, cannabis use at baseline increased the cumulative incidence of psychotic symptoms at the follow up interview. The effect of cannabis use was much stronger in those with any predisposition for psychosis at baseline. There was a dose-response relation with increasing frequency of cannabis use. The authors concluded that cannabis use moderately increases the risk of psychotic symptoms in young people but has a much stronger effect in those with evidence of predisposition for psychosis.\textsuperscript{96}

Three additional studies have suggested that frequent use of marijuana may lead to (or be associated with) depression and other mental illness. The first study, by doctors in Australia, tracked 1600 teenage girls for 7 years. The research showed that those who used marijuana...
every day were five times more likely to suffer from depression and anxiety than non-users. Teenage girls who used the drug at least once every week were twice as likely to develop depression compared to those who did not use the drug. A study by Swedish researchers provided evidence that marijuana use can significantly increase the risk of schizophrenia. The study found that 30% of the more than 50,000 men who smoked marijuana in the late 1960s developed schizophrenia. A third investigation, by British researchers, found that schizophrenia is more likely in people who start using the drug as teenagers. In a study of 1000 people in their early 20s, 1 in 10 who used marijuana as a teenager had since been diagnosed with schizophrenia.

Whether marijuana caused these phenomena directly or whether it was only associated with them is a significant question that likely could be completely answered only by subjecting randomly selected subjects (without a preexisting history of psychiatric illness) to long-term exposure to the drug and comparing them with a similar and also randomly selected non-exposed cohort. Although such a study might provide a definitive answer to the question, it would clearly be unethical. Moreover, whether controlled medical use will lead to psychiatric illness is another important question to which we do not yet have the answer. Therefore, future studies of medical marijuana should include evaluating possible long-term effects on mental health.

**Marijuana Smoking and the Development of Pulmonary Cancer**

Can smoking marijuana cause lung cancer as does the smoking of tobacco? This is an area of considerable controversy. Several respected researchers have supported the hypothesis that smoking marijuana and lung cancer are causally related. Gold has called attention to the ability of some ingredients found both in marijuana and tobacco smoke to cause pulmonary symptoms:

Marijuana and tobacco smoke are very similar, and the effects of marijuana smoking are similar to the effects of tobacco smoking. Marijuana smoke contains many of the same carcinogenic components identified in tobacco smoke... Chronic marijuana smoking (at least four days a week for six to eight weeks) results in mild airway obstruction, which may not be readily reversible with abstinence. Marijuana smoking also causes decreased exercise tolerance, chronic cough, bronchitis and decreased pulmonary function.

Similarly, Mehra and colleagues advise caution without presenting specific epidemiologic data:

Given the prevalence of marijuana smoking and studies predominantly supporting biological plausibility of an association of marijuana smoking with lung cancer on the basis of molecular, cellular, and histopathologic findings, physicians should advise patients regarding potential adverse health outcomes until further rigorous studies are performed that permit definitive conclusions.

Moir and coworkers measured the concentrations of known carcinogens in tobacco and marijuana smoke and found them to be similar, thereby suggesting that marijuana and tobacco had the same potential to cause lung cancer. However, their data did not examine the actual incidence of lung cancer in marijuana smokers:

The chemical composition of tobacco smoke has been extensively examined, and the presence of known and suspected carcinogens in such smoke has contributed to the link between tobacco smoking and adverse health effects... Although there have been only limited examinations of marijuana smoke... ammonia was found in mainstream marijuana smoke at levels up to 20-fold greater than that found in tobacco. Hydrogen cyanide, NO, NOx [toxic oxides of nitrogen], and some aromatic amines were found in marijuana smoke at concentrations 3–5 times those found in tobacco smoke.

The authors concluded that the presence of known carcinogens and other chemicals implicated in respiratory diseases is important information for public health and communication of the risk related to exposure to such materials.

On the basis of such data, Aldington and coworkers declared that “smoking a single
marijuana joint is equivalent to smoking 2.5 to 5 cigarettes in terms of damage to the lungs.104 However, they also stressed the importance of the mode of using the particular cigarette:

The deep drags taken by marijuana users, along with their penchant for holding smoke in before exhaling, can cause problems like obstructed airways and hyper-inflation of the lungs. The lack of filters on marijuana joints also contributes to lung problems. All of the smokers reported coughing and wheezing as acute manifestations of marijuana smoking.105

Although only tobacco smokers demonstrated signs of emphysema, a chronic pulmonary disease, the authors concluded that “equivalence between cannabis joints and tobacco cigarettes for adverse effects on lung function is of major public health significance.”106 Nevertheless, strong epidemiologic data argue against the hypothesis that cigarette and marijuana smoke are similar in their ability to cause lung cancer. For example, Hashibe and coworkers studied 2252 volunteers, of whom 54% had evidence of pulmonary cancer, to determine whether or not there was an association between marijuana use and the risk of developing lung and upper digestive tract cancer.107 Those with cancer and an approximately equal number of cancer-free controls were matched with respect to age, gender, and the neighborhoods in which they lived. The subjects were interviewed with a standardized questionnaire. On the basis of their data, the authors concluded that “the association of these cancers with marijuana, even long-term or heavy use, is not strong and may be below practically detectable limits,”108 and thereby argued that smoking marijuana (in contrast to tobacco) did not cause lung cancer. It is noteworthy that the considerable media publicity109 that this study received after its publication typified the often bitter conflict between scientific evidence and ideological advocacy that continues to pervade the discussion of medical marijuana.

In summary, the question of whether medically recommended smoked marijuana can cause pulmonary carcinoma is currently unanswered and awaits further epidemiologic studies.

**MARIJUANA AND THE “GATEWAY” HYPOTHESIS**

One of the most controversial claims about the effects of marijuana use is that although marijuana itself may not cause significant harm, it can serve as a “gateway” or “trigger” that predisposes the user to experiment with and become dependent on more harmful drugs. Supporters of the gateway hypothesis acknowledge that many possible mechanisms might contribute to this phenomenon. It is theorized that marijuana may trigger a biochemical craving for other psychoactive substances. It is also proposed that the permissive atmosphere associated with its use is an equally plausible explanation of why marijuana users escalate their use to other drugs. That one’s peers are also using marijuana is yet another possible explanation of marijuana’s capacity to function as a gateway to other drugs.110

Well-founded arguments have been raised against the gateway hypothesis. For example, although a large proportion of our population has used marijuana at some point in time, the majority has eventually stopped, or markedly diminished its use, and has not progressed to using other illegal substances.111 In addition, and relevant to the thrust of this article, data presented in a recent report provide strong support for the view that medical use of a controlled substance will not inevitably progress to dependence on either the same drug or on other drugs with addiction liability. Mannuzza and coworkers concluded that initiation of methylphenidate (Ritalin™) treatment in children with attention deficit hyperactivity disorder (ADHD) at an early age (6 to 12 years) did not increase the risk of later substance abuse disorders and, indeed, had beneficial long-term effects on ameliorating the symptoms of their ADHD.112

Moreover, the observations and data supporting the gateway hypothesis do not permit a distinction between marijuana as a direct cause of later drug use and a simple association of marijuana’s use with later behavior. For example, Lynskey and colleagues sought to determine whether there was an association between early marijuana use and subsequent progression to use of and addiction to other drugs by examining genetic and shared environmental influences. They surveyed an Australian national volunteer sample of 311 young adult identical and dizygotic (nonidentical) same-sex twin pairs who varied in
their early (prior to age 17) marijuana use. Those who had used marijuana by age 17 years had a 2.1 to 5.2 greater incidence of other drug and alcohol abuse or dependence than did their co-twin who had not used marijuana before age 17 years. However, although early marijuana use and later addiction to other drugs appeared to be related, the association did not differ significantly between identical and fraternal (nonidentical) twins. The authors therefore concluded that while genetic factors were unlikely to be a significant factor in marijuana’s acting as a “gateway” to later drug use, the available data did not allow them to distinguish between cause and association:

The association [between early marijuana use and later drug use and abuse or dependence] may arise from the effects of the peer and social context within which cannabis is used and obtained. In particular, early access to and use of cannabis may reduce perceived barriers against the use of other illegal drugs and provide access to these drugs.

Kandel’s perceptive editorial accompanying Lynskey’s article reiterated the problem of differentiating between cause and association in humans:

Whether or not a true causal link exists between the use of marijuana and other drugs, the association between the two has been well established . . . [T]he central question remains: does marijuana use cause the use of other illicit drugs? The search for causes in the absence of direct experimental manipulation may be elusive. Nonetheless, the search for mechanisms is necessary if only to explain the association between the use of different drug classes . . . [Only in human beings] can one explore the many other social, psychological, and contextual factors that are also important in drug use behavior.

In summary, although the gateway drug hypothesis may be attractive to some, it has not been scientifically validated. Moreover, even if this hypothesis were substantiated, marijuana would not be a unique “gateway” to other drugs. For example, although there is an association between tobacco smoking and alcohol use, both remain legal activities unconstrained by the possibility that each might function as a “gateway” to the other. Finally, as with alcohol and tobacco, even if recreational marijuana were a gateway drug, this would not necessarily provide a rationale for public policy barring the use of marijuana for medical therapy.

Although the debate regarding marijuana as a gateway drug has focused mainly on its recreational use, its medical use may have a significantly different spectrum of effects. Although the medical use of other controlled drugs does not lead to experimentation with other drugs, we simply do not know whether the use of marijuana for medical purposes will have this undesired effect. As Kandel concluded: “There are, unfortunately, no empirical data to guide policy. However, inferences can be made from appropriate medical use of morphine, which does not lead to addiction.”

Finally, the risks and benefits of the medical use of marijuana cannot be considered as though they are unique to this drug. Rather, they must be evaluated in light of the knowledge of the risks of all approved, legal, and potentially addicting controlled prescription drugs. Morphine, meperidine, fentanyl, barbiturates, and tranquilizers such as diazepam (Valium™) are among the many FDA-approved and DEA-scheduled controlled substances that play a significant role in legitimate medical practice. Their addicting liability alone has not automatically been allowed to contraindicate their use. It would be contrary to the basic principles of medical ethics to forgo the use of these medications to treat the physical and emotional effects of chronic pain due to metastatic cancer because of fear that they might cause addiction or function as gateway drugs. It would be unfortunate, indeed, if opioid-induced pain relief were denied during or after surgery because of concern about its possible risks, while ignoring its known benefits. The linchpin for medical decisionmaking is not risk—for no treatment is without risk—but the balancing of risks and benefits. Both must be carefully and scientifically evaluated; available scientific evidence should be dispositive.

REFERENCES AND NOTES

1. Morphine and some other opioids may be extracted from the opium poppy. Additional opioids possessing similar pharmacologic effects, but not found in the opium poppy, are the products of synthesis.

Morphine is a primary and continuous depressant of respiration . . . The respiratory depression is discernible even with doses too small to disturb consciousness, and increases progressively as the dose is increased. In man, death from morphine poisoning is nearly always due to respiratory arrest.


In man, morphine [derived from opium] produces analgesia, drowsiness, changes in mood, and mental clouding . . . When therapeutic doses of morphine are given to patients with pain, they report that the pain is less intense, less disconforting, or entirely gone . . . In addition to relief of distress, some patients experience euphoria.

4. Although “marijuana” and “cannabis” refer to the same compound, I will refer to “marijuana” rather than “cannabis” unless “cannabis” was used in a quotation.


A new study by researchers at Johns Hopkins University (FA Wagner and JC Anthony, From the First Drug Use to Drug Dependence: Developmental Periods of Risk for Dependence upon Marijuana, Cocaine, and Alcohol, 26 Neuropharmacology 479 (2002)) gives us some useful numbers. Based upon data from the National Comorbidity Survey with 8,100 people (men and women ages 15 to 54) who were interviewed for when they first used drugs and for when they became dependent, it was found that 12 to 13 percent became dependent on alcohol in a 10-year period. About 15 to 16 percent of people who used cocaine became dependent in the 10-year period [5-6% during their first year of use], and about 8 percent of marijuana users became dependent during the same period . . .

[These data] are very close to previously published incidence numbers for dependence: alcohol (10 percent of users); cocaine (17 to 18 percent of users); marijuana (4 percent of users) . . . nicotine (40 percent); heroin (40 percent).


Clinical and epidemiologic evidence indicates that a cannabis dependence syndrome occurs in heavy chronic users, as exhibited by a lack of control over use and continued use of the drug despite adverse personal consequences . . . The risk of becoming dependent on cannabis probably is more like the risk for alcohol than for nicotine or the opioids, with around 10% of those who ever use cannabis eventually meeting the criteria for dependence.

6. Sandra P. Welch, Billy R. Martin. The pharmacology of marijuana. In Principles of Addiction Medicine, 249, 261–263. While cannabis is not devoid of harm, there are no data suggesting that it can cause death. (“In healthy young users, [its] cardiovascular effects are unlikely to be of clinical significance.”)

See also Jerome H. Jaffe. Drug addiction and drug abuse. In Goodman and Gilman, 535, 561. Jaffe suggests that marijuana’s effects on circulation and respiration are not lethal in nature:

The most consistent effects on the cardiovascular system are an increase in heart rate [and] an increase in systolic blood pressure . . . The increase in heart rate is dose related, and its onset and duration correlate well with the concentration of Δ9-THC in blood . . . There are no consistent changes in respiratory rate.


8. Physicians may prescribe only those drugs that have been approved by the Food and Drug Administration.


4, 2009], apparently rejecting arguments that doing so would increase crime and juvenile drug use. The marijuana measure, Proposal 1, led 63% to 37%, with half of all precincts tallied . . . When it goes into effect—10 days after the vote is certified later this month—patients suffering from cancer, glaucoma, HIV/AIDS and other conditions can be authorized to cultivate, possess and use marijuana without fear of prosecution under state law. Michigan becomes the 13th state to approve medical marijuana, meaning that one in four Americans will live in a place where the use of the herb for medical purposes will be legal, according to advocates for legalization.


12. Gonzales v. Raich, 545 U.S. 1, 17 (2005):

Our case law firmly establishes Congress’ power to regulate purely local activities that are part of an economic “class of activities” that have a substantial effect on interstate commerce. . . As we stated in Wickard (317 U.S. 111, 125 (1942)), “even if appellee’s activity be local and though it may not be regarded as commerce, it may still, whatever its nature, be reached by Congress if it exerts a substantial economic effect on interstate commerce.” . . . We have never required Congress to legislate with scientific exactitude. When Congress decides that the “total incidence” of a practice poses a threat to a national market, it may regulate the entire class. (Some citations omitted.)

13. Advocates of medical marijuana claim (with some pharmacologic justification) that smoking allows easy titration and rapid onset of its therapeutic effects, thereby allowing its users to inhale the minimal dose necessary to achieve the desired medical effects while avoiding the frequently undesired psychological attributes of marijuana.

14. Weldon Angelos, a first-time offender, was convicted in federal court of selling marijuana in 2004 and received a mandatory minimum sentence of 55 years in prison. Although this harsh sentence was based on Weldon’s possession of a gun during the drug deals (although the weapon was never used), a sentence of 6 to 8 years would have been required even in the absence of a gun. On December 4, 2005, the Supreme Court refused to hear Angelos’ appeal. Angelos v. United States, 127 S. Ct. 723 (2006, cert. denied). Although this may be an extreme example, the imposition of significant incarceration is by no means an isolated phenomenon: conviction of possession of more than 1 kg of marijuana in Rhode Island carries a mandatory minimum sentence of 10 years. Possession of larger amounts may result in a maximum sentence of life in prison, whereas the highest mandatory minimum sentences imposed by Connecticut and Massachusetts is 5 years. See Elizabeth Gudrais, State May Revise Guidelines for Drug Sentences, Rhode Island News June 14, 2007. (Last accessed July 22, 2008 at http://www.projo.com/news/content/mandatory_minimums_06-14-07_9H60LMB.34c74a9.html.)

However, even a short period of incarceration can have an extraordinary impact. Jonathan Magbie received a sentence of only 10 days in prison for marijuana possession although he was a quadriplegic and first-time offender. Unfortunately, failure of the prison to provide essential medical care resulted in his death during his incarceration. See Henri E. Cauvin, Care Provided by Hospital, Corrections Dept. in Question, Washington Post, October 1, 2004, B1.

15. Recreational marijuana has not always been a drug subject to opprobrium. For the history of federal marijuana control, see David F. Musto. Opium, cocaine and marijuana in American history. Sci Am. 1991;265:40.

Unlike opiates and cocaine, marijuana was introduced during a period of drug intolerance. Consequently, it was not until the 1960s, 40 years after marijuana cigarettes had arrived in America, that it was widely used. The practice of smoking cannabis leaves came to the U.S. with Mexican immigrants, who had come North during the 1920s to work in agriculture, and it soon extended to white and black musicians.

As the Great Depression of the 1930s settled over America, the immigrants became an unwelcome minority linked with violence and with growing and smoking marijuana. Western states pressured the federal government to control marijuana use. The first official response was to urge adoption of a uniform state Narcotics law. Then a new approach became feasible in 1937, when the Supreme Court upheld the National Firearms Act. This act prohibited the transfer of machine guns between private citizens without purchase of a transfer tax stamp—and the government would not issue the necessary stamp. Prohibition was implemented through the taxing power of the federal government.

Within a month of the Supreme Court’s decision, the Treasury Department testified before Congress for a bill to establish a marijuana transfer tax. The bill became law, and until the Comprehensive Drug Abuse Act of 1970, marijuana was legally controlled through a transfer tax for which no stamps or licenses were available to private citizens.

16. Ismail Serageldin. Science in Muslim Countries. Science. 2008;321:745 (quoting Ibn Al-Haytham [10th century]. The scientific method should operate through observation, measurement, experiment, and conclusion, the purpose being to “search for truth, not support of opinions.”)

17. Note, however, that the “recreational” use [I will not use quotations to distinguish between “recreational” and “medical” marijuana in the remainder of this article] of marijuana far exceeds its legal (under state law) incorporation into the practice of medicine, the focus
of the remainder of this article. For example, although 11.1 million individuals (80% of those reporting any illicit drug use) used marijuana during a 1-month survey period in 1997 (National Household Survey on Drug Abuse for 1997; America’s Drug Use Profile, in National Drug Control Strategy, Office of National Drug Control Policy, The White House, 1999), a 2005 report estimated that only 115,000 people had made use of medical marijuana in the 10 states in which the cultivation, possession, and use of marijuana for medical purposes was legal at the time (Susan Okie. Medical marijuana and the Supreme Court. New Engl J Med. 2005;353:648).

Although this number probably increased as legalization was extended to a total of 13 states by 2009 (supra note 10), it is clear that the number of people using marijuana for therapeutic purposes will continue to be miniscule in comparison to its recreational use.


19. Safety and efficacy must be demonstrated by “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience.” 21 U.S.C. §355(d)(7).


This book is dedicated to: The Sun and Mother Nature for conspiracy to cultivate medical marijuana… Those being sought after and prosecuted while utilizing and cultivating this planet’s most valuable natural resource. Some day understanding will come about, laws will change and Mother Nature’s most precious gift and its users will be released from tyranny.

21. 21 U.S.C. §§ 301(g)(1)(B) and (C).

22. 21 U.S.C. § 355(a). “No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application . . . is effective with respect to such drug.”

23. Supra note 19.


28. Id. at 121-22.


35. Beckford, supra note 34, at 530 (describing market failures that demonstrate the need for consumer protection in the pharmaceutical industry).

36. The Commerce Clause encompasses virtually all aspects of drug marketing and advertising, as they are “part of an economic ‘class of activities’ that have a substantial effect on interstate commerce:” Gonzales v. Raich, 545 U.S. 1 (2005). Supra note 14.

37. Beckford, supra note 34, at 530 (describing market failures that demonstrate the need for consumer protection in the pharmaceutical industry).

38. Supra note 19.


40. Jerome H. Jaffe, William R. Martin. Opioid analgesics and antagonists. In Goodman and Gilman, 494, 509: “Powdered opium is a light brown powder. The official morphine content of opium is 10.0 to 10.5% by weight. Pparegoric, U.S.P. (camphorated opium tincture) is a hydroalcoholic preparation in which there is also benzoic acid, camphor, and anise oil. The usual adult dose is 5 to 10 ml, which corresponds to 2 to 4 mg of morphine.”


44. Parenthetically, the multibillion dollar “dietary supplement” industry depends on the use of a wide variety of botanical agents that are exempt from the strict FDA premarket review demanded for pharmaceutical agents. Dietary Supplement Health and Education Act of 1994, Pub. L. No. 103-417, 108 Stat. 4325 (codified as amended in scattered sections of 21 U.S.C. §§ 301-399 (2000)). See, e.g., David M. Eisenberg, Roger B. Davis, Susan L. Ettner, Scott Appel, Sonja Wilkey, Maria van Rompay, Ronald C. Kessler. Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national Study. JAMA. 1998;280:1569, 1575. (“Use of at least 1 of 16 alternative therapies during the previous year increased from 33.8% [of those surveyed] in 1990 to 42.1% in 1997. The therapies increasing the most included herbal medicines . . . [and] megavitamins. . . [A]lternative therapies were used most frequently for chronic conditions, including back problems, anxiety, depression, and headaches.”)

I have previously proposed (Cohen and DSHEA) that the majority of these dietary supplements should be subject to premarket review identical to that required for new pharmaceutical agents. In this article, I suggest that a similar approach to the evaluation of medical marijuana would be both good science and rational policy.

45. In setting forth the FDA’s review process, I have made use of a recent excellent review. See James L. Zelenay, Jr. The prescription drug user fee act: is a faster food and drug administration always a better Food and Drug Administration? Food Drug L.J. 2005;60:261.

46. Supra note 19.

47. 21 C.F.R. § 312.21(a).

48. 21 C.F.R. § 312.21(b).

49. 21 C.F.R. § 312.21(c).


52. Hutt, Supra note 39.


Acquisition of information concerning drug action does not stop at the time of FDA approval. Invaluable information, not available during the limited phase of clinical investigation, is gleaned only through postmarket surveillance. Newly approved drugs are administered to patients with a variety of diseases, and who may be taking a panoply of other medications. Adverse effects occurring with extremely low frequency, unlikely to have been noted during the phase of clinical investigation, may only become manifest after approval. Often, clinical studies designed to gather data to support the NDA do not include members of every group who will eventually receive the medication.

57. 21 U.S.C. § 355(e).

58. See, e.g., Cohen and DSHEA at 211-213.

59. Id.

60. See infra notes 180, 196, 197, 198

61. See, e.g., Cohen and DSHEA, 179. (The FDA’s oversight was responsible for averting a major disaster by prohibiting the use of thalidomide in the United States after its widespread distribution in Europe had led to the catastrophe of malformed infants born after maternal use of the compound.)


63. Petitions may also be filed by any other interested parties such as the pharmaceutical sponsor, public interest group, or concerned physicians.


65. Once the FDA recommends that the drug be scheduled, the DEA is responsible for assigning the level of scheduling. In doing so, however, the scientific findings presented by the FDA and NIDA are binding on the DEA.


Title 21, § 812. Schedules of controlled substances

(a) Establishment

There are established five schedules of controlled substances, to be known as schedules I, II, III, IV, and V. Such schedules shall initially consist of the substances listed in this section. The schedules established by this section shall be updated and republished on a semiannual basis during the 2-year period beginning one year after October 27, 1970, and shall be updated and republished on an annual basis thereafter.

(b) Placement on schedules; findings required

Except where control is required by United States obligations under an international treaty, convention, or protocol, in effect on October 27, 1970, and except in the case of an immediate precursor, a drug or other substance may not be placed in any schedule unless the findings required for such schedule are made with respect to such drug or other substance. The findings required for each of the schedules are as follows:

(1) Schedule I—

(A) The drug or other substance has a high potential for abuse.
(B) The drug or other substance has no currently accepted medical use in treatment in the United States.

(C) There is a lack of accepted safety for use of the drug or other substance under medical supervision.

(2) Schedule II.—

(A) The drug or other substance has a high potential for abuse.

(B) The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions.

(C) Abuse of the drug or other substances may lead to severe psychological or physical dependence.

(3) Schedule III.—

(A) The drug or other substance has a potential for abuse less than the drugs or other substances in schedules I and II.

(B) The drug or other substance has a currently accepted medical use in treatment in the United States.

(C) Abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.

(4) Schedule IV.—

(A) The drug or other substance has a low potential for abuse relative to the drugs or other substances in schedule III.

(B) The drug or other substance has a currently accepted medical use in treatment in the United States.

(C) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule III.

(5) Schedule V.—

(A) The drug or other substance has a low potential for abuse relative to the drugs or other substances in schedule IV.

(B) The drug or other substance has a currently accepted medical use in treatment in the United States.

(C) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule IV.

68. See, e.g., Gonzales v. Raich, 545 U.S. 1, 14 (2005). “In enacting the CSA, Congress classified marijuana as a Schedule I drug.” (Emphasis added.)

69. See Cruel and Unusual Punishment: The Juvenile Death Penalty, Adolescence, Brain Development and Legal Culpability (Juvenile Justice Center, American Bar Association January 2004). (Last accessed on July 22, 2008 at http://www.abanet.org/crimjust/just/juvjus/Adolescence.pdf): Scientists are now utilizing advances in magnetic resonance imaging (MRI) to create and study three-dimensional images of the brain without the use of radiation (as in an x-ray). This breakthrough allows scientists to safely scan children over many years, tracking the development of their brains.

Researchers at Harvard Medical School, the National Institute of Mental Health, UCLA, and others, are collaborating to “map” the development of the brain from childhood to adulthood and examine its implications . . .

This discovery gives us a new understanding into juvenile delinquency. The frontal lobe is “involved in behavioral facets germane to many aspects of criminal culpability,” explains Dr. Ruben C. Gur, neuropsychologist and Director of the Brain Behavior Laboratory at the University of Pennsylvania. “Perhaps most relevant is the involvement of these brain regions in the control of aggression and other impulses . . . If the neural substrates of these behaviors have not reached maturity before adulthood, it is unreasonable to expect the behaviors themselves to reflect mature thought processes.

The evidence now is strong that the brain does not cease to mature until the early 20s in those relevant parts that govern impulsivity, judgment, planning for the future, foresight of consequences, and other characteristics that make people morally culpable . . . Indeed, age 21 or 22 would be closer to the ‘biological’ age of maturity.”

See also Roper v. Simmons, 543 U.S. 551, 569-70; 125 S. Ct. 1183 (2005) (citations omitted):

Three general differences between juveniles under 18 and adults [are recognized under our laws]. First, as any parent knows and as the scientific and sociological studies respondent and his amici cite tend to confirm, “[a] lack of maturity and an underdeveloped sense of responsibility are found in youth more often than in adults and are more understandable among the young. These qualities often result in impetuous and ill-considered actions and decisions.” It has been noted that “adolescents are overrepresented statistically in virtually every category of reckless behavior.” In recognition of the comparative immaturity and irresponsible of juveniles, almost every State prohibits those under 18 years of age from voting, serving on juries, or marrying without parental consent.

The second area of difference is that juveniles are more vulnerable or susceptible to negative
influences and outside pressures, including peer pressure. This is explained in part by the prevailing circumstance that juveniles have less control, or less experience with control, over their own environment. (“[A]s legal minors, [juveniles] lack the freedom that adults have to extricate themselves from a criminogenic setting”).

The third broad difference is that the character of a juvenile is not as well formed as that of an adult. The personality traits of juveniles are more transitory, less fixed.

70. Adults are more likely candidates for medical marijuana than patients in the pediatric age group.
79. Physical dependence and tolerance, a normal consequence of opioid administration, differs significantly from addiction. See, e.g., Charles P. O’Brien. A 50-year-old woman addicted to heroin: review of treatment from addiction. See, e.g., Charles P. O’Brien. A 50-year-old woman addicted to heroin: review of treatment from addiction. JAMA. 2008;300:314, 315: “[I]t is essential to distinguish between addiction, which involves a [pathologic] compulsion to take drugs, and simple tolerance with physical dependence, which is a normal phenomenon seen in everyone treated with opiates over the long term. In fact, tolerance begins with the first dose of opiates…”
85. Id.
87. Bernard Laurenon, B. Gadegbeku, JL Martin, MB Biechler, S.A.M. Group. Cannabis intoxication and fatal road crashes in france: population based case-control study. BMJ. 2005;331:1371. (While 2.5% of fatal crashes were attributed to the use of marijuana, at least 28.6% were caused by the use of alcohol.)
88. Summerlin v. Stewart, 341 F.3d 1082, 1084 (9th Cir. 2003).
89. 341 F.3d at 1087.
90. Id. at 1090.
91. Id. at 1090.
The largest study of its kind has unexpectedly concluded that smoking marijuana, even regularly and heavily, does not lead to lung cancer. The new findings “were against our expectations,” said Donald Tashkin [the senior author] of the University of California at Los Angeles, a pulmonologist who has studied marijuana for 30 years. “We hypothesized that there would be a positive association between marijuana use and lung cancer, and that the association would be more positive with heavier use,” he said. “What we found instead was no association at all, and even a suggestion of some protective effect.” . . . While no association between marijuana smoking and cancer was found, the study findings, presented to the American Thoracic Society International Conference this week, did find a 20-fold increase in lung cancer among people who smoked two or more packs of cigarettes a day.

103. Id.
105. Id.
106. Id.
108. Id.
arresting adults who responsibly engage in these activities in order to dissuade our children from doing so. Nor can we justify arresting adult marijuana smokers at the pace of some 734,000 per year on the grounds of sending a message to children.

118. Supra note 115.

119. See, e.g., Peter J. Cohen. Medical marijuana, compassionate use, and public policy: expert opinion or vox populi? Hastings Center Report. 2006;36:19, 20. (“As an anesthesiologist, I have legally administered more narcotics (in the course of providing medical care) than many low-level illegal drug dealers.”)