Whither Medical Marijuana

Lester Grinspoon

The medical marijuana problem is a Janus-like conundrum. One face represents the growing number of suffering patients who are denied medical marijuana yet find it less toxic, more useful, and cheaper than legally available medications. From this perspective, the problem is how to acquire and to use this medicine without swelling the ranks (more than 800,000 annually) of those who are arrested for using this illegal substance, and how to avoid jeopardizing job security through random urine testing. The other face represents that of an obdurate government, which defensively and inconsistently insists that "marijuana is not a medicine" while buttressing this ill-informed position with the full force of its legal power.

Marijuana is less toxic than almost any medicine in the pharmacopoeia; it is, like aspirin, remarkably versatile, and it is less expensive than the conventional medicines it replaces. One of humanity's oldest medicines, it has been used for thousands of years by millions of people with little evidence of significant toxic effects. Furthermore, the medical community knows more about marijuana's few adverse effects than about those of most prescription drugs. This is due, in part, to the work of the U.S. government. It has conducted

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a decades-long, multi-million dollar research program through its National Institute of Drug Abuse (NIDA) in an attempt to demonstrate significant toxic effects that would justify the prohibition of cannabis as a non-medical drug. This extensive government-supported effort has instead provided a record of safety that is more compelling than that of most approved medicines.

There are many thousands of patients who currently use cannabis as a medicine; three are allowed to use it legally. They are the only survivors among the several dozen patients who were awarded Compassionate Use Investigational Use Drugs (INDs) between 1976 and 1991, when the government halfheartedly acknowledged that marijuana has medicinal properties. This program was eventually discontinued because of the exponentially growing number of Compassionate IND applications. Each of the surviving IND recipients receives a tin each month that contains enough rolled marijuana joints to treat his or her symptoms. Because the quality of the cannabis is poor, it requires more inhalation than would a superior quality medicinal cannabis. In fact, some of Compassionate IND recipients have been known to supplement this government-issued cannabis with better quality street marijuana.

Patients who use marijuana as a medicine appreciate its therapeutic properties and general lack of adverse side effects. Most, however, use the drug illegally and therefore face a number of serious repercussions, including prosecution and imprisonment. Given the long-established sanative benefits that marijuana provides, as well as the monetary and societal burdens its prohibition creates, the U.S. federal government should lift current restrictions on marijuana use and make the drug available to those who could benefit from its unique, therapeutic properties.

Pharmaceuticalization of Marijuana. The current legal alternative to medical herbal marijuana was introduced in 1985, when the Food and Drug Administration (FDA) approved dronabinol (Marinol) for the treatment of nausea and vomiting associated with chemotherapy. Marinol is a solution of synthetic tetrahydrocannabinol in sesame oil; the oil is meant to prevent users from smoking the contents of the capsule. It was developed by Unimed Pharmaceuticals Inc. with a great deal of financial support from the U.S. government. This was the first indication that the pharmaceuticalization of marijuana might serve as the solution to the government's problem with marijuana as medicine, addressing how to make the medicinal properties of cannabis—in so far as the government believes such properties exist—widely available, while at the same time prohibiting its use for any other purpose.

Marinol did not displace marijuana as "the treatment of choice," however; most patients found the herb itself much more useful than Marinol in the treatment of the nausea and vomiting that resulted from chemotherapy. In 1992 the treatment of the AIDS wasting syndrome was added to Marinol's labeled uses; again, patients reported that it was inferior to smoked marijuana. Marinol has not solved the medical marijuana problem because patients favor the therapeutic usefulness of plant marijuana to Marinol. In general, they

find Marinol less effective than smoked marijuana. One cannot titrate it but rather must take it orally, and use in this manner requires at least an hour and a half for the therapeutic effect to manifest itself. In addition, even with the exorbitant prohibition tariff on street marijuana, Marinol is still more expensive. Thus, the first attempt at pharmaceuticalization proved unworkable.

One can separate the cannabinoids in whole marijuana from the burnt plant products—which comprise the smoke—by vaporization devices which would be inexpensive when manufactured in large numbers. A vaporizer, which heats—but does not burn—the herb to release the plant's cannabinoids, causes finely chopped marijuana to release these active compounds when air flowing through it is held within a fairly large temperature window, just below the ignition temperature of the plant material. Inhalation is a highly effective means of delivery. Faster means will not be available, except for the possibility that injectable analogs will be developed and will make it possible to deliver cannabinoids to a patient who is unconscious or suffering from pulmonary impairment. It is the rapid response to inhaled marijuana that makes it possible for patients to titrate the dose so precisely.

Furthermore, any new analog like Marinol would have to possess an acceptable therapeutic ratio. The therapeutic ratio—an index of a drug's safety—of marijuana is unknown because there is no documented evidence that it has ever caused an overdose death. However, on the basis of extrapolation from animal data, it is estimated to have an unheard of therapeutic ratio—lethal dose divided by effective dose—of 20,000 to 40,000; alcohol, by comparison, has a therapeutic ratio of four to ten. While it is unlikely that a new analog would possess a higher therapeutic ratio, it might prove far less safe than smoked marijuana, because it would remain physically possible to ingest more of them. In addition, there is a problem of classification under the Comprehensive Drug Abuse and Control Act for analogs with psychoactive effects. The more restrictive the classification of a drug, the less likely drug companies are to develop it and physicians to prescribe it. Recognizing this economic determinant, the government, in an attempt to increase physician interest in Marinol, moved it from Schedule 2 to Schedule 3, despite the fact that naturally occurring THC—the same 21 carbon molecule as the synthetic THC in Marinol—remains in Schedule 1.

The great advantage of the administration of cannabis through the pulmonary system is the rapidity with which one experiences its effects. This in turn allows for the self-titration of dosage, the best way of adjusting individual dosage. With other routes of delivery, the response time is longer and self-titration grows more difficult. Thus, precise self-titration is not possible with oral ingestion of cannabis. While the response time for sublingual or oral mucosal administration of cannabis is shorter than it is with oral ingestion, it is significantly longer than the response time for absorption through the lungs and, therefore a considerably less useful route of administration for self-titration. Given that these products

will prove considerably more expensive than natural marijuana, they will succeed only if patients are intimidated by the legal risks, and if patients and physicians consider the health risks of smoking marijuana—with and without a vaporizer—much more compelling than is justified by either the medical or epidemiological literature.

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Regulatory Constraints. What options are available to the many thousands of patients who find cannabis of great importance, even essential, to the maintenance of their health? They can either use one of the government approved pharmaceutical products, such as Marinol or Sativex (a British pharmaceutical), which most patients find less satisfactory than plant marijuana, or they can break the law and use herbal form. Let us consider what might be involved in establishing and maintaining such a legal arrangement in the United States.

The first requirement at this time is that the Food and Drug Administration (FDA) approve marijuana as a medicine. One can argue, however, that FDA approval is superfluous where cannabis as a medicine is concerned. Drugs must undergo rigorous, expensive, and time-consuming tests before granted FDA approval for marketing as medicines. The purpose is to protect the consumer by establishing safety and efficacy. This system is designed to regulate the commercial distribution of drug company products and to protect the public against false or misleading claims about their efficacy and safety. The drug is generally a single synthetic chemical that a pharmaceutical company has acquired or developed and patented. It submits an application to the FDA and tests it, first for safety in animals and then for clinical safety and efficacy. The company must present evidence from double-blind controlled studies demonstrating that the drug is more effective than a placebo. Case reports, expert opinion, and clinical experience are not considered sufficient.

I have come to doubt whether the FDA rules should apply to cannabis, as there is no question regarding its safety. Thousands of years have demonstrated its medical value, and government efforts to establish a level of toxicity sufficient to support its prohibition have instead provided a record of its safety. Should the government waste time and resources to demonstrate for the FDA what is already so obvious?

Even if it were legally and practically possible to conduct the various phased studies to win FDA approval, where

would the money to finance these studies come from? New medicines are almost invariably introduced by drug companies that spend many millions of dollars on the development of each product. They are willing to undertake these costs only because of the large profits they anticipate during the 20 years they own the patent, and marijuana cannot be patented. For this and other reasons, it is unlikely that the pharmaceutical industry will ever develop herbal marijuana as an officially recognized medicine via this route.

It is not even necessary to establish this kind of certification. The modern FDA protocol is not needed to establish a risk-benefit estimate for a drug with a history like marijuana—one in use for thousands of years and unproven to have any significant toxic effects. To impose this protocol on cannabis would be like making the same demand of aspirin, which was accepted as a medicine more than 60 years before the advent of the double-blind controlled study. Many years of experience have demonstrated that aspirin has many uses and limited toxicity, yet today one could not marshal it through the FDA approval process. The patent has long since expired, and with it the incentive to underwrite the substantial cost of this modern seal of approval. Other reasons for doubting the possibility of official approval include today's anti-smoking climate and, most importantly, the widespread use of cannabis for purposes that lack government approbation.

Marijuana as a Prescription Medication. To understand some of the obstacles to this approach, consider the effects of granting marijuana legitimacy as a medicine while prohibiting it for any other use. How would one determine the appropriate "labeled" uses and how would one monitor "off-label" uses? Let one suppose that studies satisfactory to the FDA are somehow completed, affirming that marijuana is safe and effective as a treatment for the AIDS wasting syndrome and/or AIDS-related neuropathy, and physicians may prescribe it for those conditions. This would present unique problems. When a drug is approved for one medical purpose, physicians are generally free to write off-label prescriptions—that is, to prescribe it for other conditions as well. If marijuana was approved as a medicine, how would it be prescribed off-label? Knowledgeable physicians would want to prescribe it for some patients with multiple sclerosis, Crohn's disease, migraines, convulsive disorders, spastic symptoms, and many other conditions for which the use of cannabis is well established by a plethora of anecdotal evidence.

Generally speaking, the more dangerous the drug, the more serious or debilitating the symptom or illness for which it is approved. Conversely, the more serious the health problem, the more risk is tolerated. If the benefit is very large and the risk very small, the medicine is distributed "over the counter" (OTC). These drugs are considered so useful and safe that patients are allowed to use their own judgment without a doctor's permission or advice. Thus, today anyone can buy and use aspirin for any purpose at all. This is permissible because aspirin is considered extremely safe; it takes "only" 1,000 to 2,000 lives a year in the United States. One can also purchase

remarkably versatile drugs such as ibuprofen (Advil) and other non-steroidal anti-inflammatory drugs (NSAIDs) OTC as well, because they, too, are considered very safe; "only" about 10,000 Americans lose their lives to these drugs annually. Acetaminophen (Tylenol), another useful OTC drug, is responsible for about 10 percent of cases of end-stage renal disease. The public is also allowed to purchase many herbal remedies whose dangers and efficacies remain underassessed. Compare these drugs with marijuana. Today, there is no doubt that it is, as Drug Enforcement Agency Administrative Judge Francis L. Young stated, "among the safest therapeutic substances known to man." If included in the official pharmacopoeia, it would rank as a serious contender for the title of least toxic substance in that compendium.

Practical Considerations for Legalization. Then there is the question of who will provide the cannabis. The federal government now provides marijuana from its farm in Mississippi to the three surviving patients covered by the now-discontinued Compassionate IND program. Surely the government could not or would not produce marijuana for the many thousands of patients who need it, any more than it does for other prescription drugs. If production is contracted out, will the farmers have to enclose their fields with security fences and protect them with security guards? How would the marijuana be distributed? If through pharmacies, how would they provide secure facilities capable of keeping fresh supplies? Would the government need to control the price of pharmaceutical marijuana: not too high, lest patients are tempted to buy it on the street or grow their own; not too low, lest people with marginal or fictitious "medical" conditions besiege their doctors for prescriptions? What about the parallel problems with potency? When urine tests are demanded of workers, what would emerge as the bureaucratic and other costs of identifying those who use marijuana legally as a medicine, as distinguished from those who use it for other purposes?

To realize the full potential of cannabis as a medicine within the setting of the present prohibition system, one would have to address all these problems and more. A delivery system that would successfully navigate this minefield would prove cumbersome, inefficient, and bureaucratically top-heavy. Government and medical licensing boards would insist on tight restrictions, challenging physicians as though cannabis was a dangerous drug every time it is used for any new patient or purpose. Constant conflict would exist, with one of two outcomes: patients would not receive all the benefits they should, or they would obtain the benefits by abandoning the legal system for the black market or their own gardens and closets.

Meanwhile, a number of drug companies, attracted by the obvious medicinal properties of marijuana, are pursuing what one might refer to as the "pharmaceuticalization" of marijuana, the development of synthetic prescription drugs derived from cannabis: isolated individual cannabinoids; synthetic cannabinoids; and cannabinoid analogs. The question is whether these developments will make marijuana itself

medically obsolete. Many of these new products would prove useful and safe enough for commercial development. It is uncertain, however, whether pharmaceutical companies will find them worth the enormous development costs. Some may prove worthwhile—for example, a cannabinoid inverse agonist that reduces appetite might be highly lucrative—but for most specific symptoms, analogs or combinations of analogs are unlikely to emerge as more useful than natural cannabis. It also seems unlikely that they would possess a significantly wider spectrum of therapeutic uses, since the natural product contains the compounds—and synergistic combinations of compounds—from which they are derived.

In the end, the commercial success of any psychoactive cannabinoid product will depend on how vigorously the prohibition against marijuana is enforced. It is safe to predict that new analogs and extracts would cost much more than whole smoked or ingested marijuana, even at the inflated prices imposed by the prohibition tariff. It is doubtful that pharmaceutical companies would seem interested in developing cannabinoid products if they have to compete with natural marijuana on a level playing field. The most common reason for using Marinol or Sativex is the illegality of marijuana, and many patients choose to ignore the law for reasons of efficacy and cost. The number of arrests on marijuana charges has steadily increased, yet patients continue to use smoked cannabis as a medicine. One wonders whether any level of enforcement would compel enough compliance with the law to embolden drug companies to commit the many millions of dollars it would take to develop new cannabinoid products. Pharmaceutical companies may develop useful cannabinoid products, some of which may not be subject to the constraints of the Comprehensive Drug Abuse and Control Act. But it is unlikely that this pharmaceuticalization will displace natural marijuana for most medical purposes.

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The Lasting Dilemma of Marijuana Legalization. It is also clear that the realities of human need are incompatible with the demand for a legally enforceable distinction between medicine and all other uses of cannabis. Marijuana use simply does not conform to the conceptual boundaries established by twentieth century institutions. It enhances many pleasures and it has many potential medical uses, but even these two categories are not the only relevant ones. The kind of therapy often used to ease everyday discomforts does not fit any such scheme. In many cases, what lay people do in prescribing marijuana for themselves is not very different from what physicians do when

they provide prescriptions for psychoactive or other drugs. The only workable way of realizing the full potential of this remarkable substance, including its full medical potential, is to free it from the present dual set of regulations—those which control prescription drugs in general, and the special criminal laws that control psychoactive substances. These mutually reinforcing laws establish a set of social categories that strangle marijuana's uniquely multifaceted potential. The only way out is to cut the knot by giving marijuana the same status as alcohol—legalizing it for adults for all uses, and removing it entirely from both the medical and criminal control systems.

Two powerful forces are now colliding: the growing acceptance of medical cannabis and the proscription against any use of the plant marijuana, medical or non-medical. As a result, two distribution systems will emerge for medical cannabis: the conventional model of pharmacy-filled prescriptions for FDA-approved cannabinoid medicines, and a model closer to the distribution of alternative and herbal medicines. The only difference, albeit an enormous one, will be the continued illegality of whole smoked or ingested cannabis. In any case, increasing medical use by either distribution pathway will inevitably make a greater number of people familiar with cannabis and its derivatives. As they learn that its harmfulness has been greatly exaggerated and its usefulness underestimated, the pressure will increase for drastic change in the way that we as a society deal with this drug.