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Piomelli, D

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Scientifically Speaking, This Drug's on the Wrong List

BYLINE: Daniele Piomelli

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When the Supreme Court ruled last week that federal authorities have the power to prosecute individuals for the possession and use of medical marijuana, even in the 11 states that permit it, the news reopened longstanding questions. What kind of scientific data exist to clarify just how useful -- or harmful -- marijuana actually is? And why does the Drug Enforcement Administration assign it to the same class of controlled substances as heroin and LSD?

As director of a laboratory funded by the National Institutes of Health to study how drugs act on the brain, I am committed to answering that first question -- which could, in turn, help with the second. When my colleagues and I look dispassionately at the available data on marijuana, we see a Janus-faced drug that has many adverse or even dangerous properties, even as it presents an exciting and largely untapped therapeutic potential. But science's ability to tap marijuana's potential is inhibited by the DEA's inappropriate classification of it as a Schedule I controlled substance.

It is true that marijuana and its active ingredient -- a chemical in the tetrahydrocannabinol (THC) family of compounds -- can produce a variety of undesirable effects in both experimental animals and human subjects. A single marijuana cigarette has been shown to impair the judgment of a professional pilot in a flight simulator, and one injection of THC significantly reduces the ability of a rat to navigate a maze. Long-term use of these drugs may also have adverse consequences.

Most importantly, perhaps, and contrary to common misconceptions, a growing number of studies show that prolonged exposure to marijuana or THC can cause addiction. This is best seen in lab experiments with monkeys, who learn to self-administer THC by pressing a lever that allows the drug to be delivered directly into a vein. The animals will work hard to get that fix -- though not as hard as they would for cocaine or other more addictive drugs. What's more, a marijuana withdrawal syndrome has been demonstrated in frequent long-term users of this drug: It is characterized by mild but distinctive symptoms, including loss of appetite, irritability and depression.

Despite these negative points, marijuana and THC also appear to have significant medical benefits. As drugs go, THC is a very safe compound: It would take about 70 pure grams of it -- about the weight of a chocolate bar -- to seriously harm a 150-pound adult. Indeed, it has satisfied the strict requirements of the Food and Drug Administration for approval as a human medicine and is currently used in the United States, under the trade name of Marinol (manufactured by Unimed), to reduce nausea and stimulate appetite in patients suffering from HIV/AIDS, or undergoing chemotherapy for cancer. A manmade derivative of THC called Cesamet (manufactured by Eli Lilly) is prescribed in Europe for the same conditions.

Recent tests suggest that these drugs may have much broader medical uses. For example, clinical trials have shown that Marinol can reduce the physical and vocal tics caused by Tourette's syndrome -- a neurological disorder that still lacks a satisfactory drug treatment. Another report published in 2004 suggests that oral sprays of a marijuana extract marketed under the name of Sativex might reduce muscle spasms in patients with multiple sclerosis, though additional work is needed to confirm the efficacy and safety of this approach. Various animal experiments have confirmed the therapeutic significance of THC and its derivatives, revealing novel potential applications in such areas as neuropathic pain, cancer, glaucoma and atherosclerosis.

Nevertheless, ever since the Controlled Substances Act (CSA) became law in 1970, both marijuana and THC have been listed on Schedule I -- the list of drugs "with a high potential for abuse" and with "no currently accepted medical use."

The data obviously contradict that assessment. The error was highlighted by a DEA decision made in 1999 to move Marinol -- but not THC -- to Schedule III, which includes much less dangerous compounds, such as the anti-hyperactivity drug Ritalin. As a result of this puzzling move, the very same chemical, THC, is now assigned to two different CSA schedules. This is patently absurd.

Marijuana, the smokable leaf, may well belong in Schedule I -- I am a neuroscientist and a pharmacologist, not a medical doctor or sociologist, and I am not going to address this issue. But THC, the chemical compound, does not belong there.

A somewhat larger problem is raised by lumping marijuana and THC together with far more hazardous drugs: If we fail to identify the varying degree of danger posed by different substances, we undermine the credibility of our legislation and hinder its effectiveness at preventing drug abuse. Any young person who has smoked marijuana and seen a friend ravaged by heroin can tell the difference between these drugs. Why can't we?

Actually we can -- at least at a scientific level. During the past decade the properties of marijuana have been studied in great detail and its actions are now well understood. When marijuana smoke enters the lungs, its THC component dissolves into the blood and

spreads rapidly throughout the body. It then combines with protein molecules present on the surface of many cells in the brain. These molecules selectively recognize THC, much as a lock fits a key. They are called cannabinoid receptors (after the Latin name for the marijuana plant, Cannabis).

Heroin binds to a different class of protein molecules, called opiate receptors -- just as lock-and-key specific as the cannabinoids, but with different effects. The two receptors are not interchangeable.

Take, for example, the question of addiction. Research indicates that when THC stimulates cannabinoid receptors in the brain, it engages a complex circuit of neural cells and transmitters that are normally involved in the response to rewarding stimuli, such as tasty foods. A brief burst of activity in this circuit produces only a pleasant sensation, but if the stimulus persists for a long time (as it does with frequent and heavy marijuana use) it can eventually cause changes in the neural circuit that result in tolerance -- the need to take larger amounts of drug to produce the same effect -- and dependence -- the feelings of unease and craving experienced when prolonged drug use is suddenly stopped.

Heroin's interaction with its opiate receptors triggers a much more intense sensation of pleasure than does marijuana -- so intense, indeed, that heroin addicts are at a loss to put it into words. But heroin's withdrawal is far more severe emotionally than marijuana's, and unlike the latter, it causes a myriad of physical symptoms including shivering and pain. It's not a higher degree of the same response -- it's a different response to a different chemical reaction.

All potential benefits of marijuana, such as its ability to increase appetite and ease nausea, are also caused by the binding of THC to its brain receptors. This is one of the main sources of trouble with developing medicinal uses for marijuana: If a single receptor is responsible for all actions of the drug, how can we tease apart the good from the bad? One way to do this may be to forgo smoked marijuana and find better methods to deliver THC -- for example, metered aerosols such as those used in asthma -- which would allow patients to take just enough drug to control their symptoms, minimizing unwanted side effects. This strategy would also avoid inhaling the dangerous mixture of toxic and cancer-promoting chemicals present in marijuana smoke.

Another way to offset marijuana's risks may be to take advantage of the fact that cannabinoid receptors did not evolve in the human brain to give us the opportunity to experience a high. Rather, their original role is to combine with a set of THC-like chemicals produced by brain cells, whose functions include the control of pain and anxiety. If we could design chemicals that tweak the levels of these transmitter substances in the brain, we might be able to boost their normal effects. Our lab and others throughout the world are now working in this direction with the goal of creating new classes of painkiller, anti-anxiety and antidepressant drugs.

Because of THC's Schedule I status, that research sometimes faces extra bureaucratic hurdles. But preventing a few months of paperwork to a scientific project is not the main reason the drug and its derivatives should be reclassified to a schedule that is in accord with their medical utility. Far more important is the goal of having realistic drug laws in this country that penalize drug abuse but also encourage medical progress.

Ever since the enactment of the CSA, advocates have been pressing for THC to be reclassified. These pleas have gone unheeded so far. Perhaps the Supreme Court decision will inspire citizens and medical organizations to take a fresh look at the scientific evid

ence without being blinded by prejudice. This evidence suggests that, while marijuana is an addictive drug that requires careful monitoring, its active constituents can be useful in medicine when appropriately employed. But it's hard to get this message across: All too often, the voice of science and reason is lost in a polarized shouting match.

Daniele **Piomelli** is professor of pharmacology and director of the Center for Drug Discovery at the University of California, Irvine.