

Do Marijuana and Psychedelics Merit Greater Scientific Study?

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Health care and legal landscapes are rapidly changing when it comes to numerous compounds recently thought of as street drugs. Cannabis, or marijuana, products are becoming more commonplace, and some “psychedelic” drugs are being researched as potentially effective therapies for a variety of resistant neurological and psychological disorders.

The U.S. Food and Drug Administration approved the first cannabis-derived pharmaceutical Epidiolex for certain rare childhood seizure disorders in 2018. It is a formulation of cannabidiol, commonly called CBD. The FDA also approved Spravato, which is esketamine — a compound similar to the psychedelic and anesthetic, ketamine — for treatment-resistant depression. These treatments may be the first of more such drugs to hit the U.S. market in coming years, prompting greater re-examination of what constitutes a therapeutic drug versus a drug of abuse.

Cannabis and most of the psychedelic compounds under investigation have been assigned Schedule I controlled substance status by the U.S. Drug Enforcement Administration (DEA). Because use and possession of any Schedule I drug is considered to be a crime, that status has complicated both research and clinical practice. Now, many researchers argue that placement of these drugs onto Schedule I has been arbitrary and not evidence-based,¹ while others remain concerned about potentially dangerous effects from these drugs.

A CLOSER LOOK AT SCHEDULE I

Under the U.S. Controlled Substances Act (CSA)

of 1970, federal controls are placed on prescribing, distributing and using certain drugs. The drug schedules of the CSA sort controlled substances into classifications from Schedule I to Schedule V, with Schedule I being the most restricted, reserved for drugs “with no currently accepted medical use and a high potential for abuse.”² Because of the definition of Schedule I, these drugs are not available with a prescription. The U.S. law fits into a larger context; it was being developed at a time when some international consistency on drug policy and importing was sought, the same time as the Psychotropic Convention of the United Nations of 1971.³

Schedule I includes drugs like heroin and phencyclidine, more commonly called PCP, but also drugs used ceremonially like psilocybin from “magic mushrooms;” mescaline from the peyote cactus; and ayahuasca, a psychoactive brew. Schedule I also includes some 20th-century psychedelic drugs that were undergoing research before being placed onto Schedule I, like LSD (“acid”) and MDMA (“ecstasy”). Cannabis (marijuana) is also a Schedule I controlled substance.

Schedule II includes highly addictive substances that have been approved by the FDA; they have an accepted medical use and are available



by prescription throughout the United States, such as oxycodone, fentanyl and cocaine. Schedule III includes ketamine, along with Tylenol with codeine and a man-made form of cannabis, dronabinol (Marinol). Schedule IV includes Xanax and Valium, and Schedule V includes cough medicines with small amounts of codeine, like Robitussin AC.

MARIJUANA'S COMPLICATED HISTORY

Cannabis has consistent medical documentation of being used for pain and convulsions, going back to around 4,000 B.C.⁴ It had been used in U.S. patient medications starting in the 1800s, but its use as an explicitly recreational drug in the United States is traced to Mexican immigration to the southwestern United States in the early 1900s. Sailors also reportedly brought cannabis back from the Caribbean region to the port of New Orleans, where it became a popular recreational drug in the emerging New Orleans jazz music scene. Historians have noted that there were racist and xenophobic elements driving the fear of cannabis.⁵ By 1937, cannabis was controlled nationwide by the Marijuana Tax Act, and it has been ever since.

Later, with the advent of the Controlled Substances Act of 1970, psychedelics also were placed on the CSA's Schedule I. Much like with cannabis, some researchers believe that the move to place psychedelics on Schedule I had more to do with cultural backlash than with real harms from the drugs themselves. In the late 1960s and early 1970s, cannabis and psychedelic drugs were being used by a youth counterculture that was attempting to "tune in, turn on and drop out," to protest the Vietnam War and to rebel against authority in general.⁶

A LEGAL PATCHWORK

Even though cannabis has been federally illegal since the 1930s, the late 20th and early 21st centuries have seen a patchwork of disparate laws emerge across the United States, as states and municipalities have adopted their own legislation.⁷

Currently, the majority of U.S. states have passed new laws showing disagreement with the assessment that cannabis has "no currently

accepted medical use," as stated in Schedule I. In 33 states, medical marijuana, or MMJ, is legal, allowing patients to register to use marijuana for certain pre-approved medical conditions, with a doctor's prescription. The health care provider writing MMJ prescriptions often is not the patient's primary care provider, and the fact that a patient has a cannabis prescription may not be information available to providers on state databases in the same way that opioids are tracked. In states where MMJ is available, patients often obtain these prescriptions from a provider who specializes in writing them, working for a business whose sole purpose is cannabis prescriptions, education and registration

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of MMJ patients within their state of residence. (For example, a cannabis prescription business up the street from my house in Arizona is called "Dr. Reeferalz.") Registration as an MMJ patient gains statewide access to cannabis dispensaries, where an incredible number and types of cannabis products are sold.

Another 11 states allow cannabis to be used medicinally as well as recreationally by adults. It can be purchased much like alcohol or over-the-counter medications, but only from particular state-regulated sites available to adults.

Even more states have not legalized cannabis, but they have "decriminalized" it, and are not prosecuting people who have small amounts for personal use. Other states have allowed hemp to be grown as a crop, and almost all states have allowed people to use medical cannabidiol (CBD), the component of cannabis that is associated with the alleviation of pain and management of seizures, without the "high" associated with cannabis' other main component, tetrahydrocannabinol (THC).

According to the map at NORML.org, at the time of this writing, of all of the 50 states and the District of Columbia, only Idaho criminalizes

every form of cannabis, including hemp and CBD.

In February 2019, the World Health Organization (WHO) recommended to the United Nations that cannabis be reclassified to a less restrictive category of controlled substance than reflected in the United Nations' current treaties. Much like the legal patchwork that has emerged with the United States, the UN member states have also had disparate laws emerge, causing difficulties

in trade and international drug law enforcement. Because WHO is the health arm of the United Nations, this recommendation has led many to wonder if the UN may re-examine the scheduling of cannabis under its multiple treaties, but this has not happened yet. In the same letter to the UN, WHO also recommended that cannabis-derived CBD not be treated as a controlled substance.⁸

VAPE-RELATED ILLNESS OUTBREAK

In mid-August of 2019, the U.S. Centers for Disease Control and Prevention (CDC) began sounding the alarm that some people were getting sudden, severe lung damage from vaping products.¹

Vaping products are used as a 21st Century alternative to smoking. For a “vape,” a liquid is transformed into a vapor that contains nicotine, the cannabis compound THC, flavorings or some combination of the above.

By November 5, 2019, there had been 2,051 cases of lung injury and 39 deaths in this outbreak, throughout the United States. The cause of these severe illnesses is still undetermined, but consistent patterns have emerged, allowing the CDC to clarify its messages to health care providers and the public. A name for the lung-injury syndrome has also emerged—“e-cigarette, or vaping, product use associated lung injury” (EVALI).²

The main pattern that has emerged as of this writing is that most of the people who have suffered from EVALI reported using vapes containing THC. At this time, it seems that most of these vapes have been obtained from black market suppliers or over the internet, not through legal channels or through prescription dispensaries. Although some people with EVALI have claimed to use only nicotine vapes, researchers suspect that fear of criminal charges (in areas where THC is illegal) may be

leading to data being misreported or underreported. The other main element to emerge is that 29/29 (100%) of the bronchial lab samples from 10 states have contained Vitamin E acetate, supporting the symptom picture of an aspiration pneumonia. Vitamin E acetate is harmless when taken orally or used topically, but has a “stickiness” like honey when inhaled.³

Recommendations for health care providers include:

1. Assess for and discourage vaping among patients, especially vaping of products that contain THC.

2. Discourage patients from using black-market THC vapes from illegal channels such as drug dealers, friends or family, or the internet.

3. Be familiar with the symptom picture of EVALI, including the fact that some people have presented with gastrointestinal symptoms first, before respiratory symptoms. Low oxygen saturation readings in the blood seem to be a significant measure in EVALI patients, although their breath sounds may sound unremarkable by stethoscope.

4. Be familiar with treatments that appear to have helped EVALI patients, including corticosteroids.

5. If providers have suspect cases, it is important to gather proper samples from living or dead patients, and to gather any available information about products consumed. Guidance is avail-

able on the CDC website, below.

6. Report suspect cases to public health authorities. As with most public health reporting, each state's Department of Public Health can help to facilitate testing, reporting and shipment of samples to the proper federal investigators.

The CDC's website for the investigation is at: https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease/healthcare-providers/index.html. Data are updated each Thursday.

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WHAT CHANGES MEAN FOR HEALTH CARE PRACTICES

Depending on where a health care practice is located, cannabis in some form may show up on patients' medication lists, either as a prescription for MMJ or as an over-the-counter medication. Cannabis physicians⁹ and cannabis nurses¹⁰ have emerged as roles to assist patients using cannabis as medicine.

For people who work in human resources, they also may need to address the fact that their staff has legal or medical access to cannabis. For example, if THC shows up on a potential employee's pre-employment drug screen, having an existing prescription may offer protections against discrimination in hiring, even though it doesn't offer protections about being impaired at work.¹¹ Because THC is still regarded as illegal by the U.S. government, federal employees and some federal contractors are still barred from using any cannabis products.

Increased cannabis availability also may impact use of other prescriptions by patients. A 2016 study published in *Health Affairs* showed a significant reduction in Medicare Part D pharmaceutical use when MMJ was available, particularly a reduction in pain medications. The authors found that the Medicare program and its enrollees spent around \$165.2 million less in 2013 in the 17 states and the District of Columbia that had legalized medical marijuana by then. They projected that increased availability of MMJ could potentially cut spending by the Medicare Part D population by approximately a half billion dollars per year, and significantly decrease the use of prescription pain medications, which are usually opioids.¹²

CURRENT MARIJUANA RESEARCH

Meanwhile, researchers trying to better understand the effects of cannabis say that such studies are bogged down by federal regulations. In addition to being on Schedule I, extra restrictions apply to cannabis researchers that do not apply to researchers of other Schedule I drugs. Since 1968, the National Institute on Drug Abuse and the University of Mississippi have had a contract to grow and distribute all marijuana allowed for scientific research in the United States. Unlike any other Schedule I research drug, for instance LSD, which can be sourced from qualified private manufacturers, cannabis researchers are required to use

the University of Mississippi product, which is reportedly of a very low quality, very low in THC and not indicative of the potency of the products being consumed by the public.¹³

A quick perusal of a dispensary advertising website like Leafly.com reveals a wide variety of products and extraction methods that do not remotely resemble what we thought of as cannabis in 1970. Some of the concentrated "dabs" look like earwax, like crystals ("kief"), or like glass ("shatter"). There are gummy candies, dosed popcorn, soda pop and fancy chocolate bars—all

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with cannabis. Concentrated THC cartridges can be loaded into vape "batteries" for a portable and easily concealed puff. Some of these new cannabis products have levels of up to 80% THC, the component of cannabis that gets a person high.¹⁴

Just as there are discrepancies between federal laws and state laws for cannabis, there are also discrepancies between what the federal research laws state and how they are being implemented. Rulings in 2007 and in 2016 allowed for more legal research growers than the University of Mississippi, but the DEA has apparently refused to review the applications. The DEA cites concerns about violating international treaties, such as the 1961 Single Convention on Narcotic Drugs, the 1971 Convention on Psychotropic Substances, and the 1988 Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, but it's not clear if there would truly be any penalties. Canada has been cultivating MMJ in potential violation of these treaties since 2001, with no apparent repercussions. Researchers would like the freedom to do so in the United States.

LEGITIMATE CONCERNS REMAIN ABOUT CANNABIS

The American Medical Association does not support legalization of cannabis through legislatures or ballot measures. It would like to see more research on cannabis products, particularly into effects it may have on young people and pregnant women. The association also is interested in research on the unintended consequences of legalization. Regardless, it also supports physi-

cians who think that writing a cannabis prescription is appropriate, and they believe free conversation about treatment options between patients and providers should not be criminalized.¹⁵

Currently there is very little non-commercial information about the short-term or long-term effects of some cannabis-derived products like new forms of edibles and vapes that allow for consumption in nontraditional ways, due in great part to their recent development and the restrictions on cannabis research in the United States. Public health officials and research scientists lack research access to many of the products available to consumers, even if the researchers reside in a state where the products are being legally consumed by the public, causing many scientists to cry foul.

In the absence of randomized controlled trials that have become the “gold standard” for pharmaceutical research, so much remains unknown about how cannabis affects different populations, different health disorders and how these drugs may interact with other medications. All of these questions can have providers legitimately wondering whether these drugs are helping or harming their patients, and they leave providers to have those conversations with their patients and to form their own conclusions without adequate research. These issues are further complicated by the rapidly changing social, commercial and legal landscapes, and by the potency of the drugs themselves.

Research conducted on DEA-seized marijuana shows that the average THC potency nearly doubled between 2008 and 2017, from 8.9% to 17.1%. This is concerning, because some research has shown that use of THC high-potency cannabis (over 10% THC) correlates with an increased risk of having a psychotic episode. Although researchers admit that there is not evidence to prove causation, the use of high-potency cannabis on a daily basis correlated with quadruple the risk of developing psychosis.¹⁶

There are also concerns that cannabis use can lead to addiction and impaired brain development, especially for young people. The Substance Abuse and Mental Health Services Administration reports that young people who use cannabis may lose up to eight IQ points, and that 1 in 6

people who use marijuana under the age of 18 can become addicted. For adults who try marijuana, they report that 1 in 10 can become addicted.¹⁷

Depending on how the cannabis products are consumed, there can also be serious physical effects. Most recently, there has been an outbreak of cases of acute, severe lung injury in the United States, linked to using black market THC vapes containing Vitamin E acetate. (See sidebar.)

RECENT STRIDES IN PSYCHEDELIC-GUIDED THERAPY

In the 1950s and 1960s, extensive research was being conducted on psychedelics for everything from helping cure addiction to aiding military interrogations. In recent years, we are seeing a revival of this research, including investigations into novel prescription drugs.¹⁸

In September 2019, Johns Hopkins Medicine announced that it is opening a Center for Psychedelic and Consciousness Research. In the absence of federal funding, the center’s operational expenses for the first five years have been pledged by private donors.

For the last 20 years, Hopkins’ psilocybin/“magic mushrooms” research has shown benefit for nicotine addiction and also for the depression

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and anxiety that can come with terminal diagnoses. Now, Hopkins hopes to continue its research to develop targeted therapeutics for opioid addiction, post-treatment Lyme disease syndrome (formerly known as chronic Lyme disease), anorexia nervosa and alcohol use in people with chronic depression.¹⁹ Its research also has shown that psilocybin has very low abuse potential, possibly showing a path forward for taking psilocybin off of Schedule I.²⁰ The city of Denver has been the first to decriminalize possession of psilocybin, though its distribution is not legal.²¹



Because therapeutic psychedelics are not self-administered, not taken on an ongoing basis and may take several hours to wear off, specialized therapy visits may look very different in the context of these compounds.

Researchers of the psychedelic compound MDMA (“ecstasy”) have earned “breakthrough drug” status for large Phase 3 clinical trials, based on earlier studies that showed significant results for post-traumatic stress disorder, results that continued to improve over time. The Multidisciplinary Association for Psychedelic Studies (MAPS) Phase 2 trial results showed that of 107 participants with chronic, treatment-resistant PTSD, 56% no longer qualified for a PTSD diagnosis at the end of the study. At the 12-month follow-up, 68% no longer qualified for a PTSD diagnosis. The study involved preparatory psychotherapy and then sessions with MDMA in a controlled clinic setting with therapy teams present for study participants. Most of the subjects received 2-3 sessions of MDMA-assisted psychotherapy, and they had suffered from PTSD for an average of 17.8 years.²²

A recent letter published in *Nature* discussed that MDMA seems to work in the brain by re-opening developmental pathways that have closed, specifically as regards oxytocin. This re-opening seems to allow for a brain “reset” for people with social disorders like PTSD, allowing for a greater sense of connection with others.²³

In addition to researching MDMA itself, the Multidisciplinary Association for Psychedelic Studies has developed extensive treatment protocols and training programs for licensed psychotherapists. Only these trained therapists, along with a physician and some trained unlicensed therapists would be allowed to work as a team to administer MDMA to patients.²⁴ They hope to have a product to market by 2021, as part of a therapist-assisted protocol for PTSD.²⁵

CONCLUSION

Medical researchers are continuing to debate

whether cannabis and psychedelics require the tight legal controls of being on Schedule I. How addictive are these substances? Do they have medical utility? Many scientists and clinicians argue that the Schedule I status of these drugs is hampering research into the creation and distribution of potentially life-saving medications and medication-assisted therapies. Other people argue that these drugs can be dangerous, especially for people prone to psychosis.

In the case of neurological and psychological disorders, we may see more research and treatments in coming years utilizing cannabis and psychedelics, challenging our current definitions of what constitutes a recreational drug versus a therapy. Cannabis use is becoming more prevalent, and psychedelic drug administration may need a very different treatment model altogether. Because therapeutic psychedelics are not self-administered, not taken on an ongoing basis and may take several hours to wear off, specialized therapy visits may look very different in the context of these compounds. For those of us who work in health care, we can only hope that we will soon have research that may help to inform treatment decisions and the advice that we give to patients.

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