Trial and Error:
Medical marijuana, the absence of evidence, and the allure of anecdote

by

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ABSTRACT

For the past four years, Christy Shake has given her son marijuana extract six times a day to ease his childhood epilepsy. Hers is a compelling story that highlights the potential benefits of medical cannabis. But in the wake of antiquated and inflexible federal legislation, anecdotal reports like these are essentially all we have. More than half the states in the U.S. have voted to legalize medical marijuana, as thousands contend it's a viable treatment for a growing list of conditions. Nevertheless, as more and more patients gain access to cannabis, neither they nor their physicians understand exactly what they're receiving from local dispensaries. Patients, caregivers, scientists, physicians, pharmaceutical companies, and dispensary growers alike are calling for changes to government policies that restrict research. It's high time to separate politics from science.

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Christy Shake gets her marijuana from a local dispensary. Since the blossoms contain most of the plant's medicine, she crushes them, soaks them in sugar cane alcohol, strains them twice, freezes them, strains them yet again, and evaporates the alcohol. Once the remaining resin has become thick and dark like molasses—but far more bitter—she dissolves it in coconut oil and feeds it to her 13-year-old son, Calvin.

Christy and her husband, Michael, learned something wasn't right thirty-two weeks into her pregnancy. A fetal ultrasound showed that the lateral "ventricle" spaces in his brain, containing the cerebrospinal fluid, were abnormally large, threatening healthy development. Calvin came six weeks early, missing more than half his brain's white matter—the fatty connections that allow nerve cells to conduct electrical signals—according to one doctor.

Today, Calvin suffers from epilepsy as well as a set of developmental disorders impairing his ability to walk, talk, and speak. The neurologist predicted he might never even crawl, but Christy refused to accept the prognosis and spent a year physically moving Calvin's hands and knees along the floor. As a teenager, he is now relatively mobile, but his balance and coordination are poor, and he depends on Christy's assistance to get from place to place.

Once a year, she goes to his grade school in Brunswick, Maine, to tell his classmates about his condition. Lacking so much white matter, she explains, his brain is like a one-lane street with a hundred cars; there's a traffic jam of information.

Four years ago, Christy began researching cannabis treatment online. After consulting with an experienced herbalist and fellow parents, she began treating Calvin daily with homemade cannabis oil to assuage the four daytime grand mal seizures he was experiencing roughly each month. (These seizures cause a loss of consciousness and violent muscle contractions, which can be especially dangerous if the patient is awake and mobile when the episode occurs.) Christy has perfected her recipe over time—culling bits and pieces of information from various parents on the Internet.

After all this, Calvin's condition seems to be improving. "He's only had three daytime grand mal seizures since about six months after we started using the cannabis oil," Christy said.

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This is not another story about the miracles of medical marijuana. Yes, Calvin's seizures have eased remarkably since he started the regimen. But even in light of thousands of other cases emphasizing the plant's many therapeutic benefits, it's not enough. Lacking rigorous, "scientific" studies, these anecdotes are essentially all we have.

Even as the pro-marijuana movement continues to unfold one state at a time (29 have legalized medical use and eight permit recreational), the strict federal laws have stood unrevised for decades, labeling cannabis a Schedule I substance and thus illegal. The most highly regulated of the five possible scheduling categories, this designation is reserved for drugs that currently have no approved medical use and a high potential for abuse. It places cannabis in the same tier as heroin and ecstasy. It also means many clinical researchers—interested in investigating the therapeutic aspects of the drug—must jump through numerous hoops to secure federal approval and financial support.

The result is a Catch-22 of epic proportions: more than half the states in the U.S. have voted to legalize medical marijuana, as thousands contend it's the only viable treatment for a

growing list of conditions. Yet as more and more patients gain access to cannabis, neither they nor their physicians understand exactly what they're receiving from local dispensaries.

Although the U.S. government has gradually begun permitting more research to this end, there remains a maze of state and federal laws that renders this endeavor forbiddingly difficult. Marijuana must stay in Schedule I until the Food and Drug Administration (FDA) determines it has medicinal use, but its tangled legal status continues to hinder that process.

Dr. Donald Abrams[1] was livid. Despite his best efforts, the federal government remained apathetic towards his research interests; his message continued to fall on deaf ears. As the assistant director of the HIV/AIDS Program at San Francisco General Hospital during the height of the epidemic, Abrams had witnessed firsthand the antiemetic and appetite-enhancing effects of marijuana. But to convert theory to fact, he required study approval and funding from the National Institute on Drug Abuse (NIDA)—which flatly refused to comply.

By April of 1995, Abrams had enough. He wrote a scathing letter[2] to NIDA's director, ending with a flourish:

You had an opportunity to do a service to the community of people living with AIDS. You and your Institute failed. In the words of the AIDS activist community: SHAME!

After enduring years of protocol submissions and resubmissions, Abrams ultimately switched the focus of his experiment from treating AIDS wasting syndrome to an analysis of the interaction between cannabis and the protease inhibitors widely prescribed to treat HIV. "Now *that* NIDA was able to fund," Abrams recalled. "It's a congressional mandate that they can only study substances of abuse *as* substances of abuse—looking at harm and risk as opposed to therapeutic effect."

Five different federal institutes were ultimately involved in the review process and offered to aid NIDA with the financial support—$1 million in total. NIDA also agreed to supply the 1,400 marijuana cigarettes required to conduct the study.

Now the chief of hematology-oncology at Zuckerberg San Francisco General Hospital, Abrams finally published his HIV study in *Annals of Internal Medicine*[3] in 2003. Yet, even today the fight to streamline the cannabis research approval process is far from over. "It hasn't changed since the 1990s," Abrams said.

Six years before he aided Abrams' HIV study, Boston-based therapist Dr. Rick Doblin[4] established the Multidisciplinary Association for Psychedelic Studies[5] (MAPS), an organization that designs and funds experiments to probe the safety and effectiveness of controlled substances like marijuana.

Of the myriad of agencies and their acronyms, Doblin affirms that NIDA and the Drug Enforcement Administration (DEA) present the greatest research hurdles. NIDA holds what

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[1] https://www.ucsfhealth.org/donald.abrams
[2] http://www.maps.org/research-archive/mmj/abrams.html
[3] http://files.iowamedicalmarijuana.org/science/hiv/Abrams Annals Intl Med 2003.pdf
[4] http://www.maps.org/about/staff
[5] http://www.maps.org

Doblin refers to as a "monopoly" on DEA-licensed marijuana—the only herbal cannabis permitted for FDA-approved research.

During the 60s, in an effort to combat drug abuse globally, the U.S. signed an international treaty requiring a single government agency to control research marijuana distribution. Since then, NIDA has maintained ultimate jurisdiction[6] and licensed only one institution to cultivate the plant for research purposes: the School of Pharmacy[7] at the University of Mississippi. (Every three to five years, NIDA permits other institutions to apply for this contract, but it has been awarded to the University of Mississippi every year since cannabis research truly began in 1968.)

The crop here is not one-size-fits-all—the University does allow researchers like Doblin to request certain strains containing specific chemical ratios—but scientists are often left unsatisfied.

"I'm sure on paper the University of Mississippi product looks fantastic," said Brian Piper,[8] assistant professor of neuroscience at the Geisinger Commonwealth School of Medicine, located in Pennsylvania. "But the general commentary among the research community is that it's crap. Maybe it standardizes very nicely, but it doesn't have any correspondence to what patients currently use, and the patients who have used it are extremely underwhelmed."

Doblin himself asked for a strain containing a particular ratio of chemical compounds for his most recent cannabis study,[9] focused on treating posttraumatic stress disorder (PTSD) in veterans. Instead, he received a plant that was extremely low in tetrahydrocannabinol, or THC. (As one of the hundreds of chemicals in cannabis, THC induces a high while cannabidiol, or CBD, has recently gained a reputation for similar "therapeutic" potential sans intoxication—addressing epilepsy, neuropathic pain, nausea, and more.)

"The NIDA supply has limited quality and availability," Doblin said. "They simply are not providing the material that researchers are asking for."

In 1999, a special committee known as the Public Health Service Review was established by the Department of Health and Human Services to evaluate research applications and purchase NIDA-sanctioned marijuana for privately funded studies. "They blocked many of our studies that had already been approved by FDA," Doblin said. "They simply refused to sell us the marijuana."

Almost two decades later, things may be looking up; Health and Human Services eliminated the committee in August of 2015. This past August, the DEA announced its "intention" to grant licenses to additional marijuana growers for research—perhaps finally dissolving NIDA's monopoly after nearly 50 years. In anticipation, MAPS allied with Dr. Lyle Craker at the University of Massachusetts Amherst, who has worked for 18 years to convince NIDA to accept his petition to grow marijuana for study.

Doblin says a fundamental issue with NIDA's drug supply program (besides the caliber of the product) is that the University of Mississippi plant could never be developed into a prescription medicine.

"FDA requires that Phase III studies be conducted using the exact same drug that you want to market," Doblin explained, and NIDA is authorized to provide marijuana only for

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[6] https://www.drugabuse.gov/researchers/research-resources/nida-drug-supply-program-dsp/marijuana-plant-material-available-nida-drug-supply-program

[7] https://pharmacy.olemiss.edu/ncnpr/research-programs/cannabis-research/

[8] https://tcmc.edu/facultymember/brian-j-piper-phd-ms/

[9] http://www.maps.org/research/mmj/marijuana-us

academic research—as opposed to prescription sales. "As long as NIDA has a monopoly on federally-licensed marijuana for FDA research, cannabis can never become a medicine in the U.S.," Doblin added. While whole-plant marijuana might one day be imported from a foreign producer, currently none have registered with the FDA to do so.

After seven years of submissions and resubmissions, the MAPS Phase II PTSD study finally began screening potential participants in January 2017. According to Doblin, it is one of only a handful of whole-plant clinical trials being conducted in patients in the country at the moment. Doblin's experiment, funded by the state of Colorado, is slated to span three years.

"We're hoping that over the next few years while we complete the study—if we get good results—we'll manage to break the government monopoly," Doblin explained. "Then we can have production underway for DEA-licensed, FDA-accepted marijuana to use in a Phase III study."

How much will things change in the coming months? "I don't know," Abrams said. "I'm just a simple oncologist."

Getting federal approval for such trials is only half the battle these days; scientists must also abide by the government's many persnickety rules. Aron Lichtman[10] of Virginia Commonwealth University, who examines the behavioral and pharmacological effects of cannabis in mice, noted that the DEA seems to be tightening its hold on the research realm as the pro-marijuana movement unfurls state-by-state.

"I had to have a 500-pound safe bolted to the floor in my office," Lichtman said. "I thought that was good place for the THC solution because my office is locked and the safe is bolted. But to get to the lab from there, you have to go through a divider to a different building. Turns out you can't have a license for one street address and use the drug at another. So now I have colleagues who have labs in three different buildings and need three different DEA licenses."

According to Lichtman, this recent crackdown on the regulation of scheduled drugs has also increased the expense of conducting research with these substances, and slowed the DEA approval process.

Many scientists like Lichtman—probing cannabis in animal models—tend to focus on the ramifications of single, purified chemicals (called cannabinoids) rather than the whole plant. This is partially because the relative percentages of cannabinoids vary by strain and growing conditions, making it difficult to identify which are the "active" ingredients responsible for the side effects and therapeutic properties.

Daniel Morgan,[11] an assistant professor of Anesthesiology and Perioperative Medicine at Penn State, said the advantage to this approach is that scientists can better understand the independent effects of each cannabinoid. "Knowing the basic mechanics helps facilitate therapeutic development," he said. "The disadvantage is that it's not necessarily what people are using."

In the states where marijuana is legal, scientists could theoretically purchase an array of intriguing recreational or medical products, but bringing those materials through lab doors to test

[10] http://www.people.vcu.edu/~alichtma/

[11] https://profiles.psu.edu/profiles/display/112774

their properties would constitute a felony under the same law that categorizes cannabis as a Schedule I substance. "We can't study the things people are using recreationally, and that's a bad thing," Morgan said.

When Pennsylvania voters passed the medical marijuana referendum in 2016, the law was written to encourage dispensaries to forge academic partnerships with medical schools—diverting a subset of the marijuana sales revenue back towards the research domain to better understand the drug. Such a collaboration could prove rewarding for both parties, but there remains a disconnect between theory and practice.

State dispensaries are free to sell their extract oils without a DEA license. Yet scientists like Morgan and Lichtman are not permitted to accept Schedule I substances from any organization lacking DEA authorization. It's yet another Catch-22, since there's little incentive for a dispensary to initiate the arduous licensing process. "It becomes really difficult, if not impossible, to exchange materials for scientific use," Morgan said. "It's a logistical nightmare."

The universities, too, remain wary about accepting money through this mechanism, since it could jeopardize the millions of dollars in government funding they receive. Technically, they would be in violation of federal law, given that the dispensary extract is a Schedule I substance. Once again, that leaves a single option: the University of Mississippi.

Back in Brunswick, Maine, Christy supports Calvin as they make the trek from the kitchen to the living room. Although he'll be 14 next February, Calvin is just over four feet tall and doesn't quite reach her shoulder. They make their way as one unit towards the large hanging swing in the center of the living room, one of Calvin's favorite pastimes.

His missing brain cells slow the transfer of information between his eyes and his brain; his eyeballs are shaped slightly oblong and his pupils sometimes drift inwards towards his nose. Calvin also suffers from low muscle tone throughout his entire body, both inside and out, which slows his digestion.

Although Calvin can't follow a conversation, he gets the gist of certain phrases. He knows when it's time to take his medicine, when the bus is coming, and when it's time to go to bed. "He knows when I'm proud. I say, 'Momma's so proud of you,' and he gets this big smile," Christy said. "Maybe he just likes the way my voice sounds when I say that. But I like to think he understands."

To communicate, Calvin uses the four sign language signals he's learned: hug, eat, more, all done. Those gestures came slowly, and Christy hopes he'll eventually master "yes" and "no."

Yet, of all Calvin's afflictions, his epilepsy is the most distressing. Christy and Michael witnessed Calvin's first grand mal seizure when he was 18 months old, as the three of them lay together on their futon one Sunday morning.

"I was calling the hospital to tell them Calvin had a 102-degree fever, and they said it was no big deal," Christy recalled. "I hung up the phone and I swear a minute later he began seizing. Michael was rocking him and Calvin's eyes were bulging out, and I was calling 911. Then I looked out the window and saw the ambulance coming. They came so fast."

Medical marijuana hadn't occurred to Christy until five years ago, when she heard the story of Charlotte Figi,[12] a young girl from Colorado, whose story popularized a special cannabis

[12] http://www.cnn.com/2013/08/07/health/charlotte-child-medical-marijuana/

strain to treat her rare form of epilepsy called Dravet syndrome. That hybrid plant—known as Charlotte's Web and now supplied to thousands of patients—is high in CBD but low in THC. However, when Christy requested that Calvin's neurologists recommend it they refused, citing the lack of clinical data.

After much back and forth, Christy was finally able to convince Calvin's doctors to authorize the certificate allowing her to purchase medical marijuana in Maine. Since the Maine facilities lacked high-CBD strains at the time—and it's illegal to ship marijuana across state borders—Christy initially began treating Calvin with a different product, mainly comprised of the non-psychoactive compound, tetrahydrocannabinolic acid (THCA).

She receives two ounces of flower, dried and cured, every six to eight weeks from the dispensary. After the crushing, soaking, straining, and evaporation process is finished and the residual resin has been dissolved into an oil, Calvin receives four doses of THCA and two of CBD each day. "The oil is mostly non-psychoactive," Christy said. "There may be a tiny bit of THC still in it, but I get it tested at a lab, and Calvin never appears high."

She turned to address Calvin. "All right, kid, it's 2:30. Time for your cannabis."

In 1976, Robert Randall, a man in his 20s from Washington, D.C., became the first legal pot smoker in the U.S. since its federal prohibition in 1937. The FDA provided Randall with marijuana grown and harvested at the University of Mississippi, once a federal judge ruled it was the most effective treatment for Randall's glaucoma. Two years later, the FDA established the Compassionate Investigational New Drug Program—which ultimately provided monthly marijuana rations to 15 patients, including Randall, suffering from a myriad of afflictions from AIDS to bone tumors. Although President George H.W. Bush barred new patients beginning in 1992, four of those grandfathered into the program still receive marijuana from the government today.

Randall's eyesight was preserved until the day he died in June of 2001. But it wasn't easy being the first federally condoned medical marijuana patient, and the situation hasn't changed much since Randall's time. Given that cannabis was used as a medicine across cultures for thousands of years, this modern-day stigma is rooted in the relatively recent past.

In fact, between the 1600s and 1890s, the presiding government openly condoned marijuana crops. In 1619, due to the high demand for rope, sails, and clothing, the Virginia General Assembly passed a law requiring all farmers to cultivate hemp—the name for cannabis when grown for fiber. At the time it was even considered legal tender in Pennsylvania, Virginia, and Maryland. Production soared until after the Civil War, when other domestic and imported materials became more lucrative.

The late 19th century saw a national rise in cannabis-based pharmaceuticals to treat rabies, cholera, infantile convulsions, and more—but it soon became clear just how difficult it would be to determine a set composition and dose. As a result, marijuana fell out of favor with the medical community and was replaced by opioids. There was little pushback in 1906 when the Pure Food and Drug Act required that any drug or food containing cannabis be explicitly labeled.

With cannabis advocacy steadily declining, the influx of Mexican immigrants into the U.S. following the 1910 Mexican Revolution was the final straw. Many newcomers brought with them their own traditional means of intoxication in the form of marijuana (illegal in Mexico at

the time). Xenophobia ensued, associating the people with the drug, and fear of the "Marijuana Menace" further escalated during the Great Depression.

In 1930, the Federal Bureau of Narcotics (FBN) was initiated, later merging with a branch of the FDA and eventually becoming the DEA. As luck would have it, propaganda underscored that marijuana engendered crime and violence, usually stemming from the lower tiers of society. Harry Anslinger, the FBN's first commissioner, maintained that[13] "reefer makes darkies think they're as good as white men," and "causes white women to seek sexual relations with Negroes, entertainers and any others."

By 1931, nearly 30 states had outlawed the drug. Under the Uniform State Narcotic Act, approved in 1932, the FBN urged individual states to limit marijuana within their own borders, but it wasn't until 1937 that the federal government stepped in. That year Congress passed the Marijuana Tax Act, essentially criminalizing what was once a mainstream pharmaceutical, permitting only those who could pay a pretty penny to possess marijuana for medical or industrial purposes. In 1941, cannabis was officially dropped from the Pharmacopeia-National Formulary, despite the vehement opposition of the American Medical Association, which asserted that the plant had substantial medicinal potential.

When the Second World War erupted, the U.S. government harkened back to earlier days, encouraging farmers to cultivate hemp to augment the war effort, producing parachutes, rope, and the like. But by the 1950s, the government cracked down on marijuana once again. New federal laws mandated that first-offense possession be punishable by a minimum of two to ten years in prison, and fines up to $20,000.

Nonetheless, the drug gained popularity, at least recreationally, within the white upper middle class during the early 60s and eventually among young hippies. Although aspects of the plant's therapeutic capabilities as an antidote to headaches, menstrual cramps, and more were inadvertently rediscovered thereafter, the spike in drug-related arrests and street crime during the 60s re-branded the use of marijuana and other drugs as a serious national threat. THC had just been identified as the primary psychoactive ingredient and synthesized in a laboratory, but these revelations catalyzed very little scientific follow-up.

President Richard Nixon eagerly exploited the cultural divisions of the early 70s and spearheaded the Controlled Substances Act, which divided drugs into classes based on potential harm and likelihood of abuse. Marijuana was temporarily placed in Schedule I, a provision to be reviewed by a Presidential Commission. However, Nixon refused to change that designation and cannabis has stayed in this category ever since. (In August of 2016, the DEA denied two more petitions to reschedule the drug.)

The 1961 Single Convention on Narcotic Drugs international agreement decreed that a single government agency be named to oversee marijuana cultivation, importation, and distribution for any purpose, including research—the same rule that applied to highly addictive substances like opium. NIDA assumed the role of this single agency in the U.S., still serving as the primary source of funding to investigate the abuse potential of Schedule I drugs today.

During the mid-70s, a nationwide movement of alarmed parents campaigned for more stringent marijuana statutes, gaining support from DEA and NIDA. These efforts swayed public perceptions at the time, contributing to the War on Drugs during the 1980s.

As closet use continued to suggest marijuana's possible benefits, the drug garnered more attention throughout the scientific community after the discovery of its two chemical receptors within the body. These milestones began to reveal the drug's mysterious function, while reports

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[13] http://www.cbsnews.com/news/column-war-on-drugs-merely-fights-the-symptoms-of-a-faulty-system/

indicating its therapeutic properties regarding HIV/AIDS, neuropathic pain, and more continued to accumulate. Yet the bulk of evidence regarding marijuana's therapeutic benefit still remains purely anecdotal. Voters have become impatient as they await more rigorous facts indicating where and how the drug exerts its medicinal effects, and in many states policy has preceded science.

In 1996, California approved Proposition 215, legalizing the sale and distribution of medical marijuana to treat AIDS, cancer, chronic pain, and various other serious conditions. This was the first state-level legislation to permit medical marijuana, and it stood in opposition to the federal laws barring possession. Oregon was next, then Alaska, Washington, Maine, and 24 others. (Florida, Montana, North Dakota, and Arkansas are the most recent additions.) Colorado and Washington were the first to legalize recreational use in 2012, and Alaska, Oregon, California, Nevada, Maine, and Massachusetts have followed suit.

The destigmatization has begun, even though many of today's policies continue to reflect the antiquated "War on Drugs" mentality. As for the four remaining patients from the Compassionate Investigational New Drug Program, according to a report[14] by CBS News they've received a total of 584 pounds of government-sanctioned marijuana—which would be worth over $500,000 on the street.

The cannabis plant consists of more than 500 naturally occurring chemicals, and just over 100 have been classified as cannabinoids. Not all marijuana strains contain each cannabinoid, and in fact most have been bred to primarily include one in particular: the psychoactive THC that induces a high. However, the ideal therapeutic combination of these compounds may vary depending on the ailment in question; one strain may effectively remedy neuropathic pain, while another could counteract nausea induced by chemotherapy.

And yet, without decades of legally condoned research, cannabis treatment remains more art than science. At Virginia Commonwealth University, Lichtman emphasizes the need for large, rigorous studies examining the relationship between plant composition and therapeutic effect. "Right now these are not evidence-based conclusions, and very much based on people's perceptions and case reports," he said. "Dispensaries don't have a strong incentive to spend millions of dollars on clinical trials to prove how well certain cannabis strains work. But it's the time of personalized medicine, and a lot of medicines don't work in all patients."

Cannabinoids are effective in treating a variety of conditions because they regulate a group of naturally occurring chemicals, known as endocannabinoids, which are involved in everything from pain sensation and appetite to memory. This is also why they hold such promise. Unlike opioids, cannabinoids don't affect respiratory function, meaning it's virtually impossible to overdose on marijuana alone. What's more, most short-term effects associated with cannabis intoxication (including lapses in memory, judgment, and motor abilities) wear off. That is not to say that use of the drug is without risk: the correlation between marijuana and schizophrenia or depression is as yet unclear. It also remains unknown whether chronic cannabis administration has more severe repercussions in the young, developing brain.

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[14] http://www.cbsnews.com/news/4-americans-get-medical-pot-from-the-feds/

While marijuana is generally not considered physically addictive, cannabis does produce physical dependence and elicits mild withdrawal symptoms, including anxiety, increased dreaming, nervousness, sleep disturbances, and in some extreme cases, mild flu-like reactions.

Instead, the real dangers of cannabis stem from excessive doses of THC, which can trigger panic, hallucinations, paranoia, and a severe drop in blood pressure. Whether heavy users develop tolerance to the drug—requiring greater doses or entirely new strains to get the same therapeutic benefits and high—is still up for debate.

"I've had grants reviewed where the reviewer basically said, 'There's no such thing as cannabinoid tolerance, why the hell are you doing this work?'" Morgan from Penn State recalled. "It's an aggressive way to ask the question, but it's valid. The level of tolerance for THC is more modest than you would see for opioids like morphine or oxycodone."

Morgan estimates it might take a daily, heavy cannabis user only a few weeks to begin developing tolerance (although the exact timeframe depends on dose, route of administration, strain, and more). He suspects one reason marijuana tolerance remains so controversial is the dearth of adequate research. "Right now there are really only small clinical studies and a lot of anecdotal reporting," he said.

At the Geisinger Commonwealth School of Medicine, Piper depends on such anecdotal reporting to conduct his own survey-centered studies, which rely on responses from medical cannabis patients at dispensaries throughout Maine, Vermont, and Rhode Island.

"Individual strains certainly don't have the same degree of standardization that you see for other agricultural products," Piper said. "That may be the reason patients are bouncing between five to six strains a year."

Piper sifted through the literature, but was unable to pinpoint previous work citing the exact number of cannabis strains in existence. So he took it upon himself to devise a list. He ultimately put his finger on almost 2,000, deducing that the strains available at one dispensary could be completely different from those at another, irrespective of proximity.

On the up side, Piper's soon-to-be-published survey data corroborate prior studies indicating that those using medical cannabis often quit their other prescription pain drugs, including opioids. That said, he found an appreciable portion of patients felt uncomfortable communicating with their healthcare providers due to the stigma. Insurance companies, for their part, are leaving individuals to pay out-of-pocket for their medical cannabis. Of the 1,500 participants who responded to Piper's questionnaire, the average person spent $3,000 a year on cannabis treatment, although some cashed out close to $50,000.

After one twenty-minute seizure at age two, Calvin began his first antiepileptic, Trileptal®. Today, he's tried exactly nine (up to four simultaneously). After Trileptal® came Keppra®, Depakote®, Lamictal®, Zonegran®, Klonopin®, Neurontin®, Onfi®, Banzel®, and then Keppra® once again. Calvin has also attempted various diets, one "ketogenic" regimen that's high in fat but low in carbs and mimics fasting—which seems to help control epileptic fits—and another "low-glycemic index treatment" that's slightly less strict.

"The ketogenic diet is nutso," Christy recalled. "You need a certain ratio of fat to carbs and protein. And the portions are tiny; you have to weigh the food on a jeweler's scale to a tenth of a gram. It was so stressful."

Once it became clear the diets weren't working, Christy removed gluten and casein from Calvin's meals instead to abate the extreme agitation triggered by the high doses of his many medications. His tantrums and hyperactivity lessened somewhat, but his chronic constipation persists. Christy sprawled him on the living room floor to inspect his diaper and facilitate a bowel movement as we spoke.

Given the litany of treatments Christy has tried in order to manage Calvin's epilepsy, she was intrigued to hear about the new cannabis-based antiepileptic, Epidiolex®,[15] currently being developed by a company called GW Pharmaceuticals[16] in the U.K. This medication, projected to go to market in about a year and a half, is primarily composed of isolated, plant-derived CBD—which stands in stark contrast to the two cannabinoid drugs currently available in the U.S. Marinol®[17] and Cesamet®[18] are instead akin to synthetic forms of THC, and treat nausea and vomiting in those undergoing cancer treatment. (Marinol® also stimulates appetite in AIDS patients.)

CBD is not only gaining traction as the therapeutic cannabinoid of choice at GW; this component and others like it have piqued the interest of the federal government as well. The U.S. Department of Health and Human Services has held a patent[19] on a class of non-psychoactive cannabinoids, including CBD, since 2003. The National Institutes of Health has since granted an exclusive license[20] to the American pharmaceutical company KannaLife Sciences, Inc.[21] to explore using a CBD-like chemical to treat two conditions that cause loss of brain function.

"This highlights a scientific discrepancy," said Dr. Ethan Russo,[22] medical research director at Phytecs. "How can the government hold this patent for years on substances that are considered Schedule I, yet claim that there's no scientific basis for their medical efficacy? That's just an irreconcilable situation." (An NIH spokeswoman told *The Denver Post*[23] last August that the government's patent was for "compounds that are structurally similar to THC, but without its psychoactive properties" and "adverse side effects.")

Christy noted that Calvin's doctors, too, seem reluctant to accept the benefits of cannabis-based medications. When she phoned Calvin's neurologist to discuss Epidiolex® treatment, he'd never heard of it. "Parents are so connected that they know more than the neurologists sometimes," Christy said.

From her seat on the living room floor, Christy paused her explanation and removed Calvin's fingers from his eyes. "It's day seven without a partial seizure," she said. "He has a fever and a cold, and you can tell by the eye-poking and the not-pooping that he's due for another seizure. He usually goes about five to nine days between them." Though these partial seizures still come with teeth gnashing, post-cannabis Calvin doesn't convulse. He's still

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[15] https://www.gwpharm.com/epilepsy-patients-caregivers/patients
[16] https://www.gwpharm.com
[17] http://www.marinol.com
[18] https://www.cesamet.com/patient-home.asp
[19] http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=6630507.PN.&OS=PN/6630507&RS=PN/6630507
[20] https://www.kannalife.com/kannalife-mention-in-vox-marijuanas-medical-use-is-illegal-under-federal-law-its-also-patented-by-the-feds/
[21] https://www.kannalife.com
[22] http://www.phytecs.com/about-us/team/ethan-russo/
[23] http://www.denverpost.com/2016/08/28/what-is-marijuana-patent-6630507/

averaging the same number of grand mal seizures each month—about four—but they almost exclusively occur at night when he's safe in bed. After years of trial and error, Christy is finally beginning to see signs of improvement in Calvin as she tweaks her cannabis recipe and continues to lower his other medications.

Dr. Ben Daitz,[24] a professor emeritus of Family and Community Medicine at the University of New Mexico School of Medicine, does not often waltz around the exam room with his patients. But he made an exception in the case of one 70-year-old woman suffering from neuropathic leg pain—since she began taking cannabis, the endless discomfort has finally ceased.

In 2007 New Mexico became one of the first states to pass a Compassionate Care Act, currently stipulating roughly 20 conditions for which medical cannabis can be recommended—"recommended" being the operative word, since physicians in the U.S. can't prescribe it. Prescriptions are dispensed through pharmacies, and no pharmacy can distribute cannabis—with the exception of Marinol® and Cesamet®—until the plant is legal federally.

Instead, doctors complete a patient evaluation and determine whether the individual meets the criteria listed. (In Massachusetts, these "debilitating medical conditions"[25] include cancer, glaucoma, HIV, AIDS, hepatitis C, ALS, Crohn's disease, Parkinson's disease, multiple sclerosis, and "other debilitating conditions as determined in writing by a qualifying patient's certifying physician.") If the New Mexico Department of Health approves, the patient receives a card, valid at any dispensary in the state.

"After that it's all a mystery," Daitz said. "The patient doesn't know what they're getting and usually neither do I. The only person who knows is at the dispensary."

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As his last name suggests, Fred Green of Fred Green Consulting[26] in Princeton, Massachusetts, has always had the metaphorical thumbs for horticulture. He's had almost no hands-on experience growing marijuana, but 35 years as a commercial flower grower taught him the tricks of the trade regarding plant production on a mass scale—expertise many dispensary cultivators lack at the moment.

"From a commercial grower's perspective, the marijuana industry is prehistoric," Green said. "There's no consistency. That's because the industry is so young, and each state has its own requirements."

Green left flower sales in favor of marijuana to inject his own expertise into the floundering industry. "Marijuana is just a plant—it's got roots, a stem, leaves, and flowers; it's not rocket science," he said. But today's growers who oversee massive cannabis crops have only just emerged from their once illicit "closet" practices. These aficionados understand what it takes to raise five or ten plants, but production on the order of five to ten thousand leaves no margin for trial and error.

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[24] https://findadoc.health.unm.edu/Home/ProviderDetail/739

[25] http://www.mass.gov/eohhs/docs/dph/quality/medical-marijuana/physician-guidance-2015-06-09.pdf

[26] http://www.fredgreenconsulting.com/home.html

To a commercial grower, this system (or lack thereof) seems ludicrous. "As a patient, you can go to CVS and get your prescription filled, knowing each tablet is 50 milligrams; it's exactly the same, no matter the state," Green said. "But with this industry, nothing is the same."

To make matters worse, Mother Nature introduces inherent variability into her offspring (without a few disparities here and there, species would never diverge from one another and evolve). So despite a good many overlapping characteristics, when it comes down to it, five seeds will beget five distinct plants. Several generations later, the progeny are far afield from the original specimen.

In the commercial flower business, breeders often patent products. They place a genetic marker in the plant, and if others wish to propagate it they must pay a royalty of several cents. The Canadian Food Inspection Agency has issued at least one such copyright regarding a cannabis strain known as Big C. Patenting cannabis products and services is possible in the U.S. as well, but Green maintains that very few companies will seek patents on their specific strains until marijuana is federally legal—it won't be worth the expense until growers can supply patented strains throughout the entire country.

In most instances, patented plants stem (literally) from a small group of cells isolated in a test tube. This process of tissue culturing can engender hundreds or thousands of genetically identical descendants. Such a rigorous and "scientific" growing method permits breeders to concoct "hybrid" cannabis varieties that present the best characteristics of each contributing strain—just as one might breed a docile dog with long hair and a snub nose. And yet, to date, only one company, THC BioMed[27] in British Columbia, leverages tissue culturing to systematize marijuana production.

But as long as cannabis remains a Schedule I substance, transporting seeds across state lines will qualify as drug trafficking, punishable under federal law. "You could get marijuana seeds from Colorado, but bringing them into Massachusetts is illegal," Green said. "You go to the state house in Boston or the DPH [Department of Public Health] and they just look the other way and tell you to do what you have to do."

Here, Green has recently teamed with Jane Heatley of the William Noyes Webster Foundation.[28] Green is designing Heatley's three dispensaries, two amid construction in Dennis and North Dartmouth, respectively, and another to be placed somewhere in the greater Boston area. "About 1.8 million people voted in favor of marijuana in Massachusetts this past November, but nobody wants it in their backyard," he said.

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"When I was told I would be the one to implement the medical marijuana program in Maine I was like, 'You've got to be kidding me,'" recalled Cathy Cobb,[29] former director for Maine's Division of Licensing and Regulatory Services. "I thought the new legislation was just an excuse to get high. But then patients started calling me, and their stories were really compelling."

When the medical marijuana law was passed almost two decades ago, the legislature licensed only a few dispensaries (one in each of the eight public health districts). No additional applications have been reviewed since, because individual caregivers—authorized to grow product for up to five patients—constitute the larger faction of the industry, which Cobb affirms has "exploded out of control."

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[27] http://thcbiomed.com

[28] http://www.wnwfoundation.org

[29] http://wellnessleadership.org

Massachusetts and Maine legalized adult use at the same time, and while both states specify that medical dispensaries be nonprofit, recreational facilities will likely not be held to the same injunction. Whether or not this business model will inspire similar changes within the medical marijuana dispensary system is anyone's guess.

Mark Kleiman,[30] a professor of Public Policy at NYU, advocates taxation based on THC content rather than price—meaning the higher the THC content, the greater the cost. Otherwise, he reasons, as price falls over time, so will tax revenue.

In theory, this could also discourage users from purchasing and consuming high THC content, which could be beneficial given that THC triggers intoxication.

In California, where recreational use became legal in 2016, a portion of the tax revenue will be allocated towards marijuana research once sales commence in 2018. The University of California Center for Medicinal Cannabis Research,[31] established in 2000, was fully endowed by the state and served as a clearing house for cannabis studies until recently when funds ran low. Director Igor Grant[32] anticipates it may take a few years before the center has the financial backing to initiate more studies than the two now in progress.

Grant is optimistic that annual infusions from the state (not to exceed two million dollars) will facilitate more clinical studies. "As far as I know, there are only a couple states that have started moving in the direction of funding research in that area," he said. "California, of course, has been doing that for a long time."

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Despite the cracks emerging in NIDA's monopoly, until cannabis is removed from Schedule I status the convoluted federal system will remain fundamentally intact. In fact, researchers suspect that the Trump administration will impede further progress on this front. While the President himself may be pro-states' rights, Attorney General Jeff Sessions vehemently opposes state-level cannabis legalization efforts. After all, "Good people don't smoke marijuana."[33]

On October 8, 2010, Christy began her personal blog.[34] Called "Calvin's Story," it's exactly that. For the first three and a half years she posted at least once a day, from short vignettes to words of wisdom for her peers. She has a substantial following, and many readers comment on her entries, sometimes offering support but most often seeking advice. "Technically I could get in trouble—I'm all over the internet using cannabis," she admitted. "But I hope I can give other parents confidence, because there's a fear factor involved when you're dealing with a substance that's not legal, and hasn't really been tested like it should be."

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[30] http://wagner.nyu.edu/community/faculty/mark-r-kleiman

[31] http://www.cmcr.ucsd.edu

[32] http://grant.hivresearch.ucsd.edu

[33] https://www.washingtonpost.com/news/wonk/wp/2016/11/18/trumps-pick-for-attorney-general-good-people-dont-smoke-marijuana/?utm_term=.19cf5993b64f

[34] http://www.calvinsstory.com